

Unilateral Symptomatic Intracranial Arterial Stenosis and Myopathy in an Adolescent with Graves Disease: A Case Report of an High-resolution Magnetic Resonance Imaging Study

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Vascular and muscular involvements in Graves disease (GD) are rare. Here, we report a case of a 17-year-old patient with unilateral symptomatic middle cerebral artery stenosis concurrent with GD and myopathy. He presented with a 1-day history of acute severe right-sided hemiparesis and aphasia and a 3-week history of high metabolic syndrome. The pathogenesis of the stenosis is most likely vasculitis rather than atherosclerosis, based on contrast-enhanced high-resolution magnetic resonance imaging showing concentric wall enhancement. We suggest that lipid storage myopathy is secondary to GD, and it is likely mitochondrial dysfunction or immune dysfunction induced by GD responsible for the myopathy and that magnetic resonance spectroscopy (MRS) is capable of establishing the diagnosis of myopathy. Thus, MRS can be used for follow-up evaluations of the myopathy along with the pathology biopsy. **Key Words:** Adolescent—infarction—middle cerebral artery—Graves disease—muscular diseases—magnetic resonance imaging.

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Graves disease (GD), a common autoimmune disorder of the thyroid with genetic susceptibility, is mainly induced by infection and trauma and often results in hyperthyroidism. During the past few years, an increasing

number of case reports concerning hyperthyroidism, together with intracranial arterial disease, cerebral infarction, or transient ischemic attack, have been published, suggesting a growing interest in GD and vascular diseases.¹⁻³ To the best of our knowledge, there has been no report of a youth suffering from an ischemic stroke, GD, and myopathy simultaneously. The present work is likely the first case with these complicated issues and provides an initial exploration of the potential etiology and pathogenesis of the disease.

Case Report

A 17-year-old Asian boy without apparent vascular risk factors initially presented with a 1-day history of acute severe right-sided hemiparesis and aphasia. Previously, the patient had experienced bilateral lower extremity weakness early in the morning 3 times during March and April 2012, which was resolved in approximately 10 minutes after receiving traditional Chinese medical treatment.

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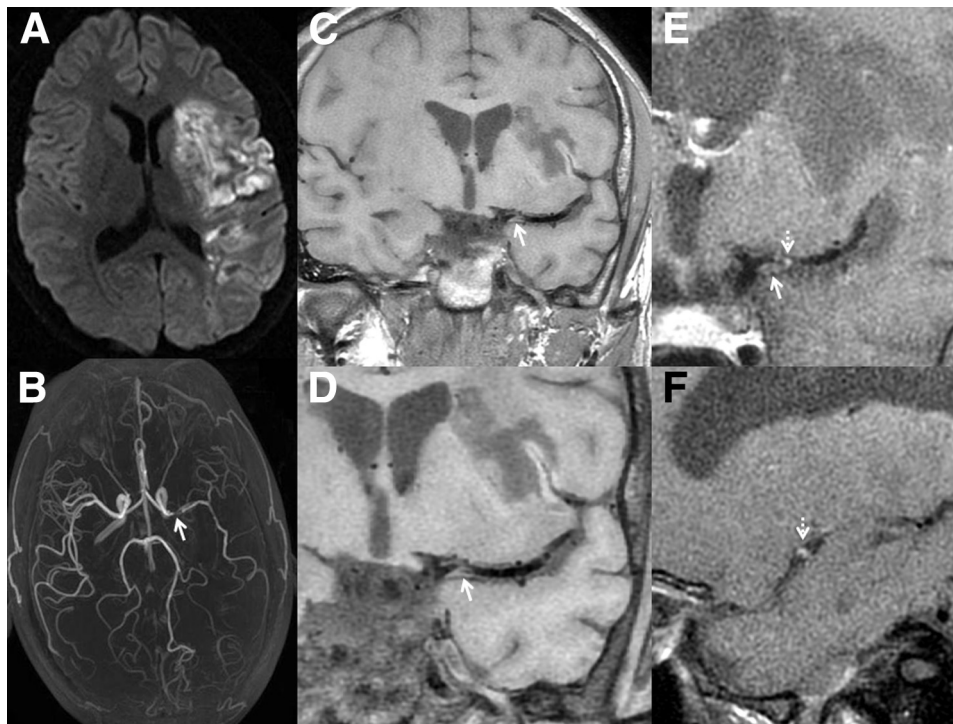
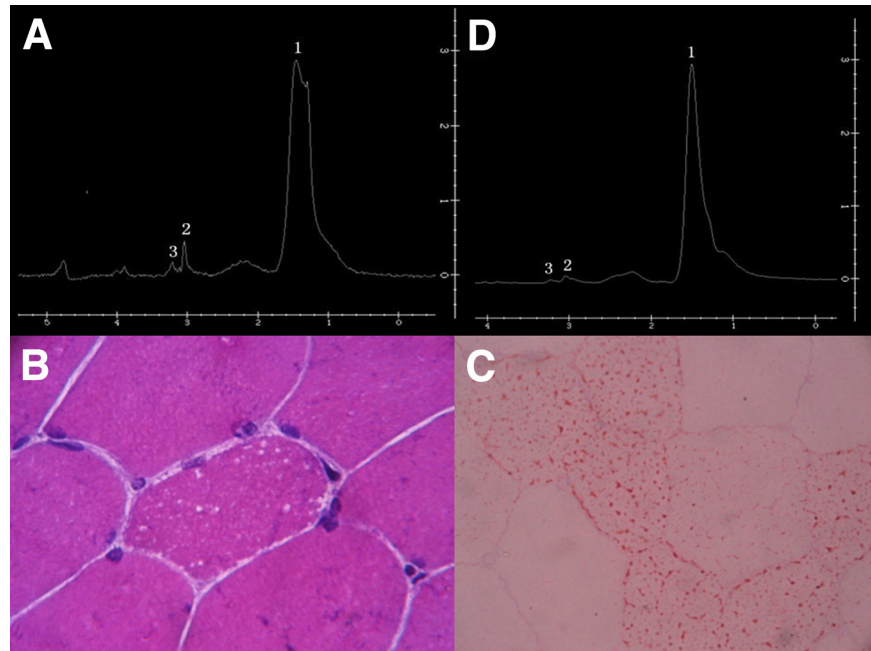


Figure 1. (A) Multiple infarcts are observed in the distribution of the left middle cerebral artery (MCA) on magnetic resonance (MR) diffusion-weighted imaging. (B) MR angiography shows the obvious severe stenosis located at the M1 segment of the left MCA (arrow). (C) Coronal T1WI high-resolution magnetic resonance imaging shows smooth, concentric wall thickening in the MCA at the onset of the attack (solid arrow). (D) Coronal T1WI with fat suppression demonstrates neither atherosclerosis plaques nor lipid storage existed in the vessel wall (solid arrow). (E) One year later, coronal Magnevist-enhanced T1WI demonstrates concentric wall enhancement (dotted arrow) and the expansion of the lesion (solid arrow) after treatment with methimazole, aspirin, and Lipitor. (F) Sagittal contrast-enhanced T1WI shows concentric wall enhancement more clearly (dotted arrow).

The patient had been experiencing heat intolerance, sweating, insomnia, and weight loss for 3 weeks. Except for the symptoms listed previously, his prior medical history was unremarkable, and he has no history of inherited disease. The physical examination revealed slight proptosis and a basal metabolic rate increase of .37. In the neurologic examination, he showed mixed aphasia and spastic paralysis. The patient scored 14 points on the National Institute of Health stroke scale. The initial laboratory examination showed hyperthyroidism (serum free thyroxine, 42.25 pmol/L; free triiodothyronine, 13.706 pmol/L; and thyroid-stimulating hormone [TSH], 0.003 mIU/L), and the TSH receptor antibody and antithyroid peroxidase antibody levels were also elevated (5.66 IU/L and 54.44 IU/mL, respectively). Ultrasound imaging of the thyroid displayed a thickened echo and heterogeneous distribution in both lobes. Routine magnetic resonance imaging revealed a massive left middle cerebral artery (MCA) territory infarction, and time-of-flight magnetic resonance angiography and angiography confirmed an identical severe stenosis of the left M1 segment of approximately 1 cm in length (Fig 1, A,B). The vessel wall images of high-resolution magnetic resonance imaging (HRMRI) with fat suppression delineated the stenotic portion of the artery with smooth, concentric wall thickening and without lipid storage (Fig 1, C,D). The patient

was diagnosed with an acute cerebral infarction concurrent with GD. In addition to the traditional treatment for the infarction, he received methimazole for the treatment of hyperthyroidism at that time. The patient recovered quickly, and his National Institute of Health stroke scale score decreased to 0 after being hospitalized for a month. Approximately 1 year later, a follow-up HRMRI with black-blood contrast-enhancement T1-weighted sequences showed the expansion of the lesion and concentric wall enhancement in the MCA wall (Fig 1, D,F), despite almost normal clinical and serum examinations. In addition, the patient's initial imaging showed multiple cortical necroses; as a result, we decided to perform a muscle biopsy to determine whether mitochondrial encephalopathy was present. Surprisingly, a suspected diagnosis of lipid storage myopathy (LSM) was proposed. Moreover, the findings from the magnetic resonance spectroscopy (MRS; Fig 2, A) were consistent with the muscle biopsy (Fig 2, B,C). Interestingly, however, no abnormalities were observed in the blood tests (acylcarnitine and amino acids), urine tests (organic acids), electromyography, and genetic detection tests (CPT2, CPT1A, ACADVL, ETFDH, ETFA, ETFB, ACADS, ACADM, SLC25A20, ABHD5, and SLC22A5). Our patient received a repeat MRS examination in 2014, which showed that the myopathy had significantly worsened (Fig 2, D).

Figure 2. (A) Magnetic resonance spectroscopy showed the quantitative measurement of lipids in 2013. (B) Hematoxylin-eosin–stained paraffin section of the muscle biopsy showing multiple small vacuoles inside parts of the muscle fibers. (C) The Oil Red O method shows that the amount of red-stained droplets of lipids among the muscle fibers is higher than normal. (D) The quantitative measurement of lipids in 2014 was much higher than that in 2013 (A). The first marked peak represents lipid content, the second peak represents creatine, and the third peak represents choline.



Discussion

To the best of our knowledge, this is the first case report of an adolescent suffering from unilateral symptomatic MCA stenosis, GD, and myopathy simultaneously. In this case, 3T-HRMRI was performed twice, including at the onset of the stroke and 1-year follow-up examinations, to visualize the vessel wall pathology and differentiate the etiology and pathogenesis. We inferred from the HRMRI that neither atherosclerosis plaques nor lipid storage existed in the vessel wall. Concentric wall enhancement and thickening suggested that the attack could likely be attributed to vasculitis rather than atherosclerosis or other causes.⁴ We noted that only most of the circle showed on Fig 1, F with contrast-enhancement in the layer. The reason could be that a small part of the vessel wall is not undergoing active period of vascular inflammation all the time.

Hyperthyroidism has been confirmed to be closely related to intracranial arterial stenosis.^{2,3} However, the pathogenesis involved in this relationship has not been elucidated, and several hypotheses have been proposed. At first, sympathetic activity increases. Excessive thyroid hormones may augment the intracranial vascular sensitivity to the sympathetic nervous system, leading to pathologic changes in the vascular walls.⁵ Second, an immune-mediated inflammatory mechanism may play an important role in the pathogenesis of these diseases.⁶ There are only a few case reports in the literature of GD occurring together with antiphospholipid antibody syndrome, hyperthyroidism concurrent with Takayasu arteritis, hyperthyroidism with giant cell arteritis,^{7,8} or drug-induced vasculitis caused by antithyroid drugs⁹ that facilitate the development of pathologic blood ves-

sels. Third, the low hemodynamics induced by hyperthyroidism induces susceptibility to cerebral ischemic events. High levels of thyroid hormone production are thought to increase the cerebral metabolism and oxygen consumption, gradually impairing cerebral perfusion. Moreover, ischemic stroke is more likely to occur in the case of intracranial arterial stenosis. In addition, thyrotoxicosis-induced hypercoagulability may raise the incidence of ischemic stroke.¹⁰ In our case, the cerebral ischemic event occurred after heavy drinking and sweating. Indeed, we propose that low hemodynamics were responsible for the cerebral ischemic event. In the literature, intracranial arterial stenosis in patients with GD usually manifests as moyamoya syndrome, characterized by progressive stenosis of the bilateral terminal portion of the internal carotid artery.² Shigeo et al² reviewed 32 patients with GD and concurrent intracranial arterial stenosis, including 28 cases of bilateral carotid artery terminus stenosis and 3 cases of unilateral lesions. In addition, similar to a patient in another case report, our patient completely recovered from his illness, but a follow-up HRMRI showed no radiological improvement.¹¹ Therefore, in our case, a reasonable hypothesis is that the clinical manifestation of intracranial arterial stenosis caused by hyperthyroidism may be unilateral MCA stenosis in the early stages, which may develop into a classic case of moyamoya syndrome in a few years.^{2,12}

As the disease progresses, the amount of intramuscular lipids increase, and the mechanism underlying this drawback remains elusive. We consider that LSM is secondary to GD because of the negative genetic tests of primary LSM. Here, we propose 2 possible explanations for this issue. One possibility is that mitochondrial dysfunction

induced by hyperthyroidism may lead to secondary muscle carnitine deficiency.¹³⁻¹⁵ Evidences proved that a decrease in muscle carnitine, but not in serum carnitine, in hyperthyroidism potentially contributes to fatty acid metabolism disorders, resulting in thyroid myopathy.^{16,17} The other possibility might be that the same immune dysfunction mechanism induced by GD is responsible for both intracranial arterial stenosis and thyroid myopathy, because they continue to constantly and gradually develop despite normalization of the T3, T4, and TSH levels, with only the antibody against the thyroid remaining elevated. This is similar to another 2 cases that LSM was secondary to Behcet disease¹⁸ and that polymyositis was associated with GD.¹⁹ Therefore, this case suggested that pathologic manifestations of chronic hyperthyroidism myopathy might have been presented with pure intramuscular lipid deposition at disease onset.

Further research and follow-up evaluations are needed to confirm our views. This case also illustrates the necessity of imaging technologies, such as HRMRI and MRS, for patients with intracranial arterial stenosis or GD.

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