

Original Article

A Case of Graves' Disease Diagnosed in the Course of Bilateral Carotid Artery Stenoses (Moyamoya Disease); A Case Report and Review of the Literature

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Abstract. A 14-year-old boy was admitted to our hospital after being diagnosed at a local clinic with bilateral carotid artery stenoses (Moyamoya disease) and mild thyrotoxicosis. A blood examination showed suppressed TSH and elevated triiodothyronine and thyroxine levels; however, he was negative for anti-thyrotropin receptor antibody (TRAB) and thyroid stimulating antibody (TSAB). Concern about a possible thyroid crisis led us to administer thiamazole (MMI) and potassium iodide (KI), following which encephalo-duro-arterio-synangiosis (EDAS) of the left side was performed successfully. After about 1 mo, he became positive for TRAB and TSAB. He was thought to have Graves' disease and Moyamoya disease coincidentally. Several factors are considered to be involved in the coincidental onset of these two diseases.

Key words: Graves' disease, Moyamoya disease, anti-thyrotropin receptor antibody

Introduction

Moyamoya disease is a cerebrovascular disorder characterized by bilateral stenoses or occlusion of the terminal portions of the internal carotid arteries accompanied by typical net-like collateral vessels at the base of the brain. Moyamoya means mist or smoke in Japanese and describes the shapes of these collaterals. Its incidence is considered to be higher in Asian populations (1). In contrast, Graves' disease is

an autoimmune antibody-mediated disease of the thyroid gland, one of the characteristics of which is the development of anti-thyrotropin receptor antibody (TRAB) (2). Although rare, there have been several cases described who suffered Moyamoya disease and Graves' disease simultaneously.

We report an adolescent boy who developed Graves' disease and Moyamoya disease simultaneously, although elevation of autoantibodies was delayed. We also review some of the literature and discuss the pathogenic relationship between Graves' disease and carotid stenosis.

Case Report

A 14-yr-boy went to a local clinic complaining

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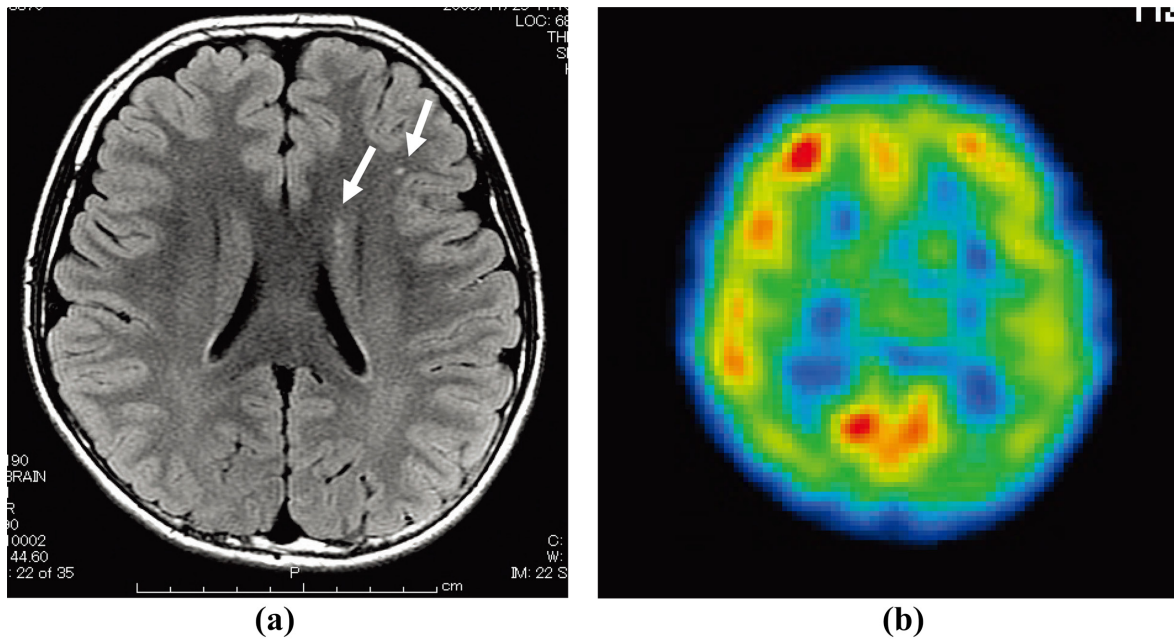


Fig. 1 Brain MRI (FLAIR) (a) and SPECT (b). (a) Small infarctions (white arrows) were found in the white matter of the left lobe. (b) Decreased blood flow was found in the left anterior lobe.

of progressive weakness of his right arm, which had been getting worse for the last 12 mo. A brain magnetic resonance imaging (MRI) scan showed small infarctions in the left anterior white matter (Fig. 1a), and single-photon emission computed tomography (SPECT) revealed decreased blood flow in the left anterior lobe (Fig. 1b). A magnetic resonance angiogram (MRA) revealed bilateral carotid stenoses and the presence of collaterals (Fig. 2). He was diagnosed as having Moyamoya disease. In addition, he had upper limb tremor, and so a physician investigated the possibility of hyperthyroidism. Laboratory data showed low TSH (less than 0.1 μ IU/ml, reference range: 0.1–4.5) and elevation of free T₄ (FT₄, 3.41 ng/dl; 0.8–2.2). He was referred to our hospital and admitted.

On admission, he had a slight fever, and an elevated heart rate (120–150 beats/min) and systolic blood pressure (130–160 mmHg) were detected. The results of a physical examination were as follows. His BMI was 15.1 kg/m². He had mild exophthalmos and a soft goiter (Grade 2, according to WHO differentiation) with no

nodules, pain or redness of the neck. He also had tremor of both hands. Soft bruits over the cervical vessels were detected. No abnormality was found in his electrocardiogram, and ultrasound investigation of the thyroid gland revealed a heterogenous echotexture suggesting Graves' disease. It also showed no tumors or nodules.

Blood examination revealed more elevation of thyroid hormones (FT₄, 4.31 ng/dl; freeT₃ (FT₃), 10.08 pg/ml, reference range: 5.1–2.6) and suppression of TSH (less than 0.1 μ IU/ml). His anti-thyroglobulin antibody (TGAB) level was in the normal range (33.6 IU/ml (0–40.6)) and he was positive for anti-thyroid peroxidase antibody (TPOAB, 33.6 IU/ml (0–5.2)). However, he was negative for TRAB (13.3% (–15.0 to +15.5)) and anti-thyroid stimulating antibody (TSAB, 135% (less than 180)) (Table 1). Concern about a possible thyroid crisis led to the early administration of thiamazole (MMI, 20 mg/day), potassium iodide (KI, 200 mg/day) and bisoprolol fumarate (5 mg/day). Encephalo-duro-arterio-synangiosis (EDAS) was successfully performed on his left side the next day.

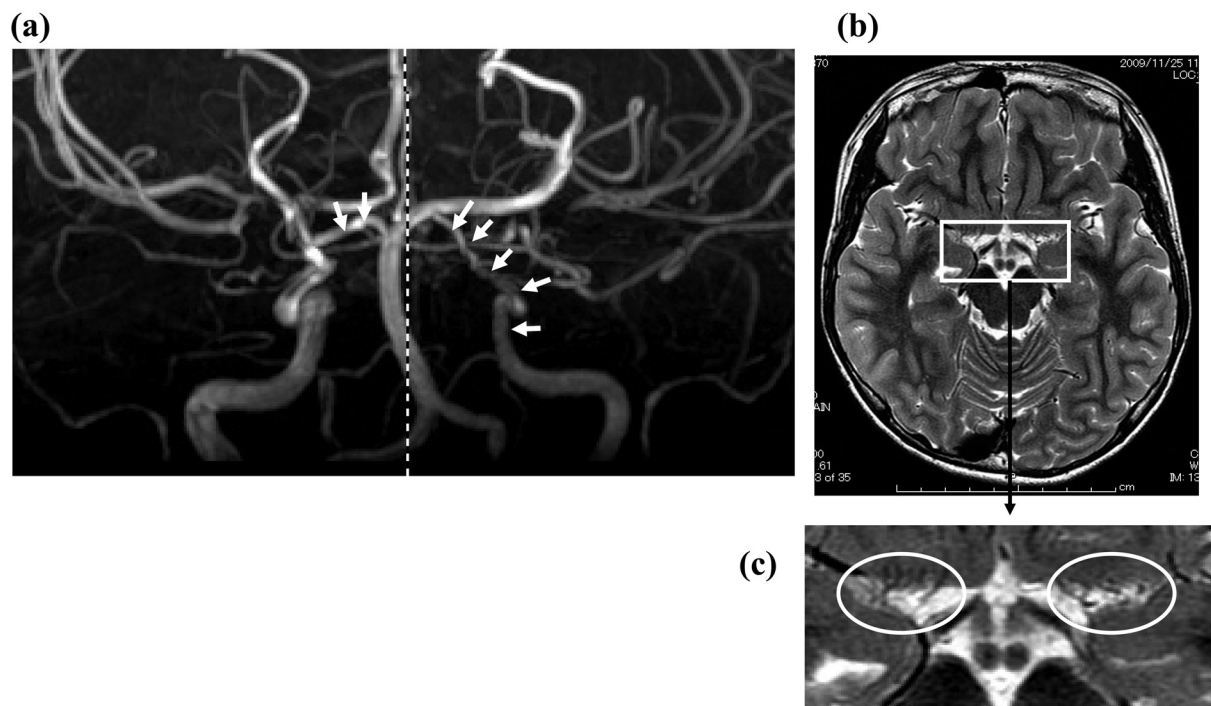


Fig. 2 MRA (a) and magnetic resonance T2-imaging (b, c). (a) Stenoses (white arrows) of carotid arteries were detected. (b, c) The collaterals were found in the Sylvian fissure (white circles).

Table 1 Laboratory data

WBC	10200/ μ l	AST	18 IU/l	IgG	1500 mg/dl
RBC	456 \times 10 ⁴ / μ l	ALT	24 IU/l	IgA	217 mg/dl
Hb	12.3 g/dl	LDH	164 IU/l	IgM	76 mg/dl
Ht	36.70%	ALP	960 IU/l	ANA	40 \times
Plt	30.8 \times 10 ⁴ / μ l	CPK	106 IU/l	Anti CL β 2GPIAB	<1.2 IU/ml
		BUN	5.0 mg/dl	Anti CL IgG	<8.0 IU/ml
TSH	<0.01 μ IU/ml	Cr	0.4 mg/dl	MPO-ANCA	<10 EU
FT3	10.08 pg/ml	Na	140 mEq/l		
FT4	4.31 ng/dl	K	4.2 mEq/l		
TGAB	33.16 IU/ml	Cl	105 mEq/l		
TPOAB	33.16 IU/ml	Ca	9.1 mg/dl		
TRAB	13.30%	CRP	<0.1 mg/dl		
TSAB	135%				
Thyroglobulin	134 ng/ml (0–30)				

After this treatment, his thyrotoxic symptoms remitted within about a wk; however, we could not clarify whether his thyrotoxicosis was related to Graves' disease or silent thyroiditis because of his negative results for TRAB and TSAB. With the intent of making a differential diagnosis of his thyrotoxic state, we discontinued MMI and KI once and followed his thyroid function carefully

every week in our outpatient clinic. On the 8th day after stopping MMI, his thyroid function was almost in the normal range (FT4, 1.90 ng/dl, FT3 6.83 pg/ml, TSH 0.06 μ IU/ml). Two weeks later, he came to our hospital with palpitation and fatigue. His FT4 level was elevated to 7.16 ng/dl, and he was positive for anti-TSH receptor antibodies (TRAB 20.6%, TSAB 182%) (Fig. 3).

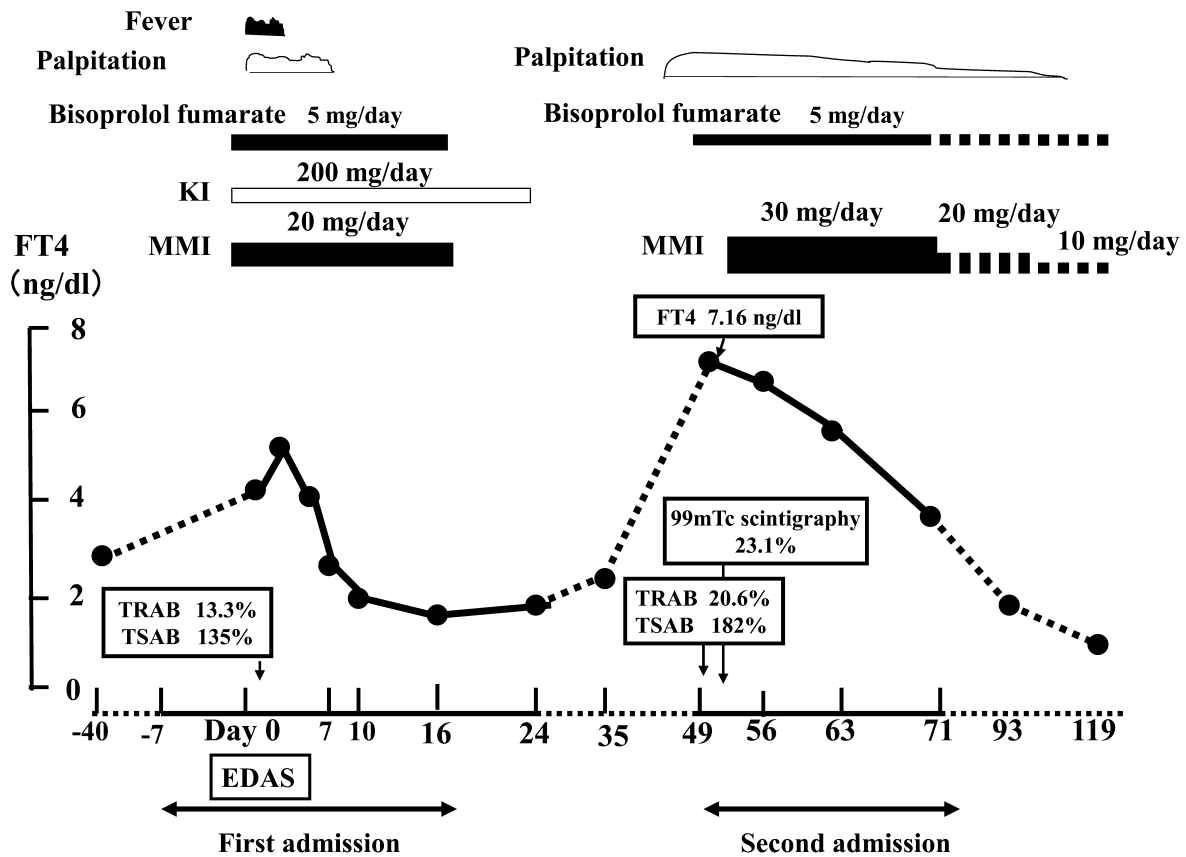


Fig. 3 Clinical course

High, homogeneous uptake of 99mTc was found on thyroid scintigraphy (Fig. 4). We diagnosed his thyrotoxicosis as Graves' disease. Retreatment with antithyroid drugs brought about remission of his thyroid function again, and he has a good prognosis.

Discussion

Although it has previously been reported, coexistence of Moyamoya disease and Graves' disease is rare, especially in children and adolescents. We could identify only eight cases (including our own) younger than twenty years old (Table 2) (1-7). Most of them were girls and were diagnosed with Moyamoya disease in their thyrotoxic states. Brain MRI revealed infarction in six of them. Younger individuals with Moyamoya disease may tend to present

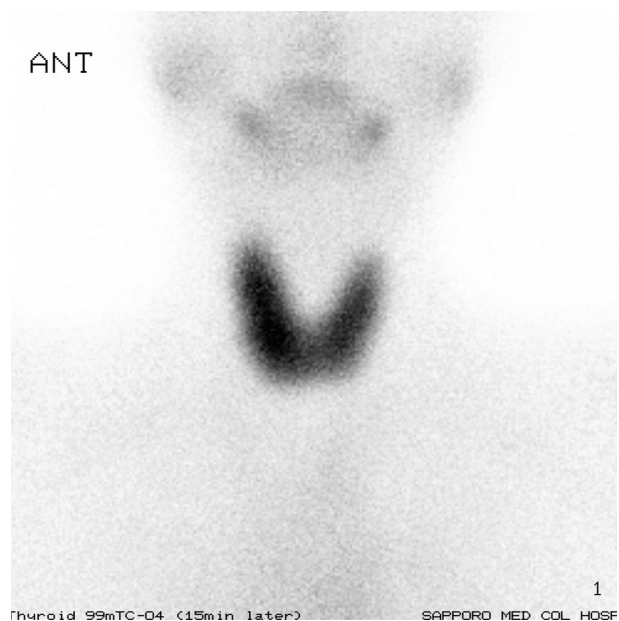


Fig. 4 99mTc scintigraphy (day 50). Diffuse and high uptake (23.1%) were detected.

Table 2 Cases with coexistence of Graves' disease and Moyamoya disease (younger than 20 yr old)

Authors	Age, sex	First symptom	Brain infarction	TRAB	Treatment
Sumikoshi (3)	14, M	Hemiparesis, palpitation, sweats	–	+	MMI/brain vessels reconstruction
Wakamoto (4)	19, F	Goiter	+	+	MMI
Golomb (2)	10, F	Hemiparesis, tachycardia	+	–	Radio isotope/brain vessel reconstruction
Im (5)	8, F	Faint	+	Unknown	Antithyroid drug/brain vessel reconstruction
Sasaki (6)	16, F	Faint, hemiparesis	+	Unknown	Antithyroid drugs/brain vessel reconstruction
Lee (1)	19, F	Diarrhea, goiter	+	+	PTU*/brain vessel reconstruction
Tokimura (7)	19, F	Palpitation, dysesthesia	+	+	Thyroidectomy/brain vessel reconstruction
Our case	14, M	Fatigue, sweats, weakness of the right arm	+	– to +	MMI/brain vessel reconstruction

* Prophylthiouracil.

with ischemic cerebrovascular disease, whereas older individuals may present with cerebral hemorrhage (8). Treatments with antithyroid drugs or radioactive iodine are usually carried out before reconstruction surgery of brain vessels. In two cases, ischemic symptoms improved with antithyroid drug administration alone (3, 4).

There is some debate about the relationship of these two diseases. Panegyres *et al.* (9) and Tendler *et al.* (10) reported autopsy cases of Moyamoya disease and found that there was a prominent lymphocytic infiltration, the majority of cells within which were T-cell marker-positive lymphocytes, in the media of a terminal left internal carotid wall. They concluded that autoimmune mechanisms that worked for the development of Graves' disease might also play an important role in the onset of Moyamoya disease. Tokimura *et al.* (7) reported one pair of a mother and a daughter who both developed Moyamoya disease and Grave's disease, and implicated genetic factors because one gene locus of Moyamoya disease (chromosome 8q23, MYMY3) is very close to that of autoimmune thyroid disease (8q23-24). Furthermore, patients with Moyamoya disease

may be more likely to have elevated thyroid autoantibodies than those with non-Moyamoya disease strokes (11). Finally, sympathetic nervous system stimulation caused by hyperthyroidism might contribute to the development of stenosis of the intracranial arteries. Thyrotoxic states might accelerate the progressive occlusive disease of the intracranial arteries (12).

Our case had no family history of Graves' disease or brain ischemia. He had bilateral stenoses of the carotid arteries, but brain infarction was found only on the left side when he was in a thyrotoxic state. He had EDAS surgery on the left side at almost the same time that he began taking antithyroid drugs, and therefore, we could not estimate the correlation between the recovery of his ischemic symptoms and thyroid function. However, brain infarction in the right hemisphere did not develop after the administration of MMI, which might imply that the remission of thyrotoxicosis prevented further stenosis and occlusion the brain vessels of his right side. However, we were unable to ultimately conclude which phenomena, hyperdynamic state or autoimmune system played a more important

role.

At first admission due to Moyamoya disease, he was negative for both TRAB and TSAB, although his thyrotoxicosis was apparent. In interviews with him and his parents, suspicious symptoms of thyrotoxicosis (fatigue, excess food consumption, diarrhea, sweating, etc.) were found beginning about two years previously. If this was the start of hyperthyroidism, he might have been in a chronic thyrotoxic state for more than one year. Although a few cases of patients being TRAB negative at the beginning of clinical symptoms have been reported (13–15), the mechanism of late TRAB elevation and its correlation with development of Moyamoya disease remain to be elucidated.

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