Co-morbidity of Moyamoya Disease with Graves' Disease. Report of Three Cases and a Review of the Literature

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Abstract

Moyamoya disease is a cerebrovascular disorder characterized by bilateral stenosis or occlusion of the terminal portions of the internal carotid arteries accompanied by typical net-like collateral vessels in the basal ganglia. Although the etiology of moyamoya disease remains unknown, hereditary and immunogenic as well as hemodynamic factors have been implicated in the underlying mechanism of moyamoya disease. We report two patients with confirmed moyamoya disease and a patient with probable moyamoya disease complicated with Graves' disease. We reviewed the literature and summarized 23 cases of moyamoya disease or probable moyamoya, coexisting with Graves' disease.

Key words: Graves' disease, moyamoya, thyrotoxicosis, cerebral ischemia, TIA

(DOI: 10.2169/internalmedicine.45.1543)

Introduction

Moyamoya disease, first reported in Japan in 1963 (1), is a cerebrovascular disorder characterized by bilateral stenosis or occlusion of the terminal portions of the internal carotid arteries accompanied by typical net-like collateral vessels in the basal ganglia (2, 3). Although its incidence is relatively higher and substantial cases have been accumulated in Japan, it is also reported in Western countries (4, 5). Following the diagnostic guidelines, the etiology of moyamoya disease is unknown and any history of causative systemic diseases should be ruled out as having moyamoya disease (6). The term 'probable or angiographic moyamoya' is proposed for the condition associated with angiographic findings similar to those of moyamoya disease (7).

Here, we report two patients with confirmed moyamoya disease and a patient with probable moyamoya disease complicated with Graves' disease. We also review the literature and propose an association between these two conditions.

Case Reports

Case 1

A 27-year-old Japanese woman had been found to have

high blood pressure six months prior to admission. Two months later, she experienced transient attacks of dizziness and left hemiparesis several times. However, a brain CT scan performed at a local hospital revealed no abnormalities. During the same period, she noticed that her thyroid glands were swollen, and consulted an endocrinologist. She was diagnosed with Graves' disease with goiter and bilateral exophthalmos. She was then maintained on regular antithyroid medication and the attacks subsided. Three months later, she again experienced left-arm flaccidity, as well as dysarthria and headache, and was then admitted to our hospital. She had no other past history of disease and denied past head injury and previous oral contraceptive use. She was irregularly on antithyroid medication at that time. A physical examination revealed bilateral carotid bruits in the neck. Her thyroid gland showed symmetric enlargement. Her blood pressure was 150/80 mmHg, and heart rate 116 /min. On neurological examination, she had hemiparesis of the left upper limb and exaggerated deep tendon reflexes in the left extremities with a dorsiflexed plantar response on the left. Laboratory studies, including blood tests, urine analysis, coagulatory parameters, including prothrombin time, fibrinogen, antithrombin III activity, protein C and S antigens were within normal limits except for high alkaline phosphatase (ALP 613; AL₂ 6%, AL₃ 94%). A thyroid function test using radioimmunoassay confirmed hyperthyroidism (TSH

Figure 1. Case 1. Magnetic resonance imaging scans (A and C, T1-weighted scan; B, T2-weighted scan), showing cerebral infarction in the left frontal region and hemorrhagic infarction in the right frontal region. SPECT scan (D), showing decreased blood flow in the right frontal region.

Figure 2. Case 1. Cerebral angiograms (A, right carotid artery angiogram; B, left carotid artery angiogram; C, left vertebral artery angiogram), showing severe focal stenosis of the bilateral distal portions of internal carotid artery, the bilateral M1 portions of middle carotid artery, and the bilateral A1 portions of the anterior carotid artery. Net-like moyamoya vessels are seen. No stenosis is found in left vertebral artery and basilar artery (C).

0.08 μ U/ml; fT₃ 5.5 ng/dl; fT₄ 1.4 ng/dl; TSH receptor antibody, TRAb 56.4%). Immunologically, the patient was negative for antinuclear antibody, anti-double-stranded DNA antibody, anti-cardiolipin antibody, p-ANCA and c-ANCA. A T2-weighted image (T2WI) of brain magnetic resonance imaging (MRI) revealed multiple ischemic lesions in the right upper frontal lobe and in the left paraventricular region. The latter also showed a high intensity area on T1WI, consistent with a hemorrhagic infarction (Fig. 1A-C). Single photon emission computed tomography (SPECT) using ^{99m}Tc-HM-

Figure 3. Case 2. Magnetic resonance imaging scans (A, T1-weighted scan; B, T2-weighted scan), showing cerebral infarction in the right frontal region.

Figure 4. Case 2. Cerebral angiograms (A, right carotid artery angiogram; B, left carotid artery angiogram; C, right vertebral artery angiogram), showing stenosis of the bilateral distal portions of internal carotid artery, the right A1 portions of the anterior carotid artery. Net-like moyamoya vessels are seen. Vertebral artery angiogram demonstrates perfusion of both cerebral hemispheres via posterior communicating arteries (C).

PAO) showed decreased regional cerebral blood flow in the right MCA region (Fig. 1D). An electroencephalogram (EEG) documented both build up and rebuild up phenomena during and after hyperventilation. Four-vessel cerebral angiography showed long narrowed segments at the cervical portions of both internal carotid arteries. A severe focal stenosis of bilateral M1 portion of the right middle cerebral artery (MCA) and typical net-like moyamoya vessels were also seen (Fig. 2). No retrograde anastomosis from the external carotid arteries was detected. After anti-thyroid hormone medication, the hemiparesis abated. Ischemic attacks were suppressed under euthyroid state through the course. In order to prevent further attacks, encephalo-duro-arterio-synangiosis (EDAS) was performed later.

Figure 5. Case 3. Magnetic resonance imaging scans (A, T1-weighted scan; B, T2-weighted scan), showing cerebral infarction in the left frontal region. SPECT scan (C), demonstrating decreased blood flow in the left frontal region. Left external carotid artery angiogram (D), showing abundant collateral circulation by superficial temporal artery via a trans-dural anastomosis.

Case 2

The patient was a 16-year-old Japanese female student. She had suffered transient ischemic attacks (TIAs) consisting of left hemiparesis and faintness, several times during the 6 months before admission. MRI and MR angiography showed a cerebral infarction in the right frontal lobe and stenosis of the distal portion of bilateral ICAs (Fig. 3). She was admitted to our hospital suspected of having moyamoya disease. A physical examination revealed no goiter. Blood pressure was 132/64 mmHg, and heart rate 80 /min. She had no neurological deficits. However, laboratory studies revealed a low total cholesterol level (100 mg/dl) and hyperthyroidism (TSH 0.01 μ U/ml; fT₃ 9.4 ng/dl; fT₄ 3.1 ng/dl). Antinuclear antibody, anti-double-stranded DNA antibody, anti-cardiolipin antibody, p-ANCA and c-ANCA were all negative. She was diagnosed as Graves' disease. Four-vessel cerebral angiography showed long narrowed segments at the cervical portions of both ICAs and occlusion of the right anterior cerebral artery. Typical net-like moyamoya vessels were seen (Fig. 4). In order to prevent further attacks, EDAS was performed later.

Case 3

A 36-year-old Japanese woman had been treated for Graves' disease with anti-thyroid drugs for two years. She took the anti-thyroid medication irregularly; she suddenly developed aphasia, and was admitted to a hospital when she had no good control for thyroid function. Brain MRI showed high-density lesions on T2WI in the deep white

Table 1. Summary of 23 Cases of Moyamoya Diseases or Probable Moyamoya, Coexisting with Graves' Disease.

Series (Ref. No.)	Sex /Age,y	Symptoms	Angiographic features	Onset of GD	Improvement by anti-thyroid drugs
¹⁴ Matsubayashi et al, 1983	F / 30s	CS	n.d.	n.d.	n.d.
	F / 30s	CS	n.d.	n.d.	n.d.
	F / 30s	CS	n.d.	n.d.	n.d.
¹⁵ Aono et al, 1985	F / 15	TIA	BTICS, MV	13	yes
¹⁶ Gotoh et al, 1990	F / 13	TIA	n.d.	n.d.	yes
¹⁷ Yukitake, et al. 1991	F / 40	Hemichorea	n.d.	40	n.d.*
⁸ Kushima, et al. 1991	F / 21	TIA, then CS	BTICS, NV	21	yes
	F / 22	CS	BTICS, NV	17	yes
¹² Matsumoto, et al. 1992	F / 35	CS, aphasia	BTICS, MV	35	yes
⁹ Liu, et al. 1994	F / 28	TIA, then CS	BTICO, NV	28	n.d.
¹⁰ Tendler, et al. 1997	F / 37	TIA	RC3ICS, MV	37	yes
	F / 47	CS	BTICS, NV	38	n.d.**
¹³ Ishikawa, et al. 1998	F / 28	TIA, then CS	BTICS, MV	15	n.d.
	F / 33	TIA, then CS	BTICS, MV	31	n.d.
	F / 5	TIA	BTICS, MV	5	n.d.
	F / 38	SAH	BC3ICO/S	28	n.d.
¹⁸ Sumigoe, et al. 1998	M / n.d.	Chorea	n.d.	n.d.	yes
¹⁹ Wakamoto, et al. 2000	F / 19	IVH	BTICS	17	yes
¹¹ Nakamura, et al. 2003	F / 23	TIA, then CS	LTIC	23	yes
	F / 54	TIA	LTIC	42	n.d.
Present Case 1	F / 27	TIA, then CS	BTICS, MV	27	yes
Present Case 2	F / 16	TIA, then CS	BTICS, MV	16	n.p.
Present Case 3	F / 36	TIA, then CS	LTICS	34	n.p.

GD: Graves' disease; TIA: transient ischemic attack; CS: complete stroke; B/L: TICS/O: bilateral/left terminal internal carotid artery stenosis/occlusion; R/BC3ICS/O: right/bilateral C3 portion internal carotid artery stenosis/occlusion; NV: net-like vessels; MV: moyamoya vessels; SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage; IV: involuntary movement; n.d.: not described; n.p.: not prescribed; * Cured by Haloperidole, **by radioactive iodine

matter of the left cerebral hemisphere (Fig. 5A, B). One month later, she was referred to our hospital. On physical examination, left carotid bruit and symmetric enlargement of thyroid gland were detected. On neurological examination, she had exaggerated deep tendon reflexes in the right extremities with a dorsiflexed plantar response on the right side. Laboratory data demonstrated hyperthyroidism (TSH < 0.1 μ U/ml; fT₃ 4.0 ng/dl; fT₄ 1.5 ng/dl; TRAb 2.9%, anti-thyroglobulin antibody, TGAb <0.3 U/ml, anti-thyroid peroxidase antibody, TPO Ab 65.0 U/ml). Immunologically, she was positive for antinuclear antibody (speckled pattern), but negative for other autoantibodies. Her EEG was within normal limits. SPECT using ^{99m}Tc-HM-PAO showed decreased regional cerebral blood flow in the left ICA region (Fig. 5C). Four-vessel cerebral angiography showed long narrowed segments at the cervical portions of the left ICA and perfusion by superficial temporal artery via a trans-dural anastomosis (Fig. 5D). She was then maintained on regular antithyroid medication and the findings of MR angiography did not change and she had no ischemic attacks.

Discussion

We present two cases of definite moyamoya disease and one patient with unilateral occlusion of the ICA complicated with Graves' disease. Following the diagnostic guidelines, any history of causative systemic diseases should be ruled out as having moyamoya disease (6). As major cerebral artery occlusions were not fully improved by antithyroid ther-

apy alone, we are convinced that the present cases were not types of Graves' disease having transient moyamoya-like vasculature. Although many disorders are reported to be associated with moyamoya disease, Graves' disease has not been described in any major review article (7). To our knowledge only 5 moyamoya disease and 2 probable Moyamoya cases with thyrotoxicosis or a high serum level of thyroid hormone have been reported in the English journals (8-11). In Japanese reports, 2 such cases have been reported in journals (12, 13), 7 cases at annual or regional meetings of the Japanese Society (14-18), and 4 cases in the annual report of the research committee of the Japanese Ministry of Health and Welfare in 1998 (19) (Table 1). The coexistence of moyamoya disease and Graves' disease is not coincidence. Although the incidence of Graves' disease is about 0.4-0.8/1,000 in Japan and 3,900 moyamoya disease cases were identified in Japan up to 1994; the prevalence rate of moyamoya disease is 3.16/100,000 (20); at least 11 cases of definite moyamoya disease have been reported to be complicated with Graves' disease (Table 1). The association of these disorders is important because the pathogenesis common to the two diseases may eventually help us to clarify the etiology of moyamoya disease.

Hereditary and immunogenic inflammatory factors have been implicated as the etiology of moyamoya disease. A family history of Moyamoya disease is found in 10% of the patients in Japan. The cellular proliferation and vascular dysregulation in moyamoya and immunologic stimulation of the thyroid in Graves' disease were suggested to have a common pathogenic link involving T-cell dysregulation (10). Lymphocytotoxic antibodies present in autoimmune thyroid disease were reported to be responsible for defective antigen-associated suppressor T cell function (21). Utku et al reported that moyamoya-like vasculitic changes improved gradually after treatment with the combination of steroid and plasmapheresis in Graves disease (22). Inflammation of the arterial wall due to an altered immune status may be a key link to the double disorders occurring in these patients.

Another possible link between these disorders is atherosclerosis. Colleran et al demonstrated the positive correlation between free thyroxine levels and both homocysteine and methylmalonic acid, suggesting the possibility of thyrotoxicosis to induce hyperhomocysteinemia (23). As homocysteinemia has been implicated in atherosclerotic and embolic disorders (24, 25), it would be another key to the patho-

physiology of moyamoya disease.

Hemodynamic factors have also been implicated in the underlying mechanism of moyamoya disease. Graves' disease is an autoimmune disorder and the associated thyrotoxicosis is thought to enhance the effects of sympathetic nervous activity (26). The carotid fork and arteries around cerebral base, main foci of moyamoya disease, are distributed with sympathetic nerves derived from superior cervical ganglion. Sato et al reported that cerebral blood flow increased 18.8% after dissection of superior cervical ganglion in moyamoya disease patients (27). Regional sympathetic nervous stimulation may contribute to pathological changes involving the carotid arteries (28). The superior cervical ganglion is adjacent to not only the cervical lymph nodes but also the thyroid. Inaba et al reported that arterial stiffness in the common carotid artery was increased in hyperthyroidism (29). Therefore, Graves' disease could be associated with the causal mechanism of moyamoya disease in terms of hemodynamics as well as hereditary and immunogenic factors.

From the clinical point of view, to cure the ischemic attack of patients suffering from both moyamoya and Graves' disease is important. Altered cerebral hemodynamics as well as hypercoagulability in thyrotoxicosis may have triggered vascular attacks in patients with moyamoya disease. In case 1 and in other reported cases, cerebrovascular accidents occurred when patients were in thyrotoxicosis. In those patients anti-thyroid drug medication was effective (Table 1). As thyroid hormones are thought to increase sensitivity to sympathetic stimulation in the various organs (8), it is probable that thyrotoxicosis accelerated superior cervical ganglion and decreased regional cerebral blood flow, leading to TIA or stroke (12). In addition, hypercoagulability can influence these ischemic events because it is known to occur in thyrotoxicosis (30, 31). Anti-thyroid medication should be selected for TIA occurring in moyamoya patients in thyrotoxicosis with Graves' disease to prevent further attacks.

In summary, we reported and reviewed the cases providing the possible association between Graves' disease and the etiology of moyamoya disease.

We appreciate the advice and expertise of Dr. Mamoru Shibata and Dr. Manabu Ohtomo, Department of Neurology at Keio University School of Medicine. We also wish to thank Ms. Rie Umehara for excellent secretarial assistance.

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