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...
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 μIU/ml, reference range: 0.1–4.5) and elevation of free T4 (FT4, 3.41 ng/dl; freeT3 (FT3), 10.08 pg/ml, reference range: 5.1–2.6) and suppression of TSH (less than 0.1 μIU/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. 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.
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 μIU/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. 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  | RBC  | Hb   | Ht   | Plt  | TSH  | FT3  | FT4  | TGAB | TPOAB | TRAB | TSAB | Thyroglobulin |
|----|------|------|------|------|------|------|------|------|------|-------|-------|------|--------------|
|    | 10200/μl | 456×10⁴/μl | 12.3 g/dl | 36.70% | 30.8×10⁴/μl | <0.01 μIU/ml | 10.08 pg/ml | 4.31 ng/dl | 33.16 IU/ml | 33.16 IU/ml | 13.30% | 135% | 134 ng/ml (0–30) |
|    |      |      |      |      |      |      |      |      |       |        |       |      |              |
|    |      |      |      |      |      |      |      |      |       |        |       |      |              |
| AST | 18 IU/l | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| IgG | 1500 mg/dl | IgA  | 217 mg/dl | IgM  | 76 mg/dl | ANA  | 40×   | Anti CL 82GPIAB | <1.2 IU/ml | Anti CL IgG | <8.0 IU/ml | MPO-ANCA | <10 EU |
| RBC | 456×10⁴/μl | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| Hb  | 12.3 g/dl | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| Ht  | 36.70% | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| Plt | 30.8×10⁴/μl | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| TSH | <0.01 μIU/ml | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| FT3 | 10.08 pg/ml | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| FT4 | 4.31 ng/dl | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| TGAB| 33.16 IU/ml | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| TPOAB| 33.16 IU/ml | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| TRAB| 13.30% | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| TSAB| 135%  | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |      |              |
| Thyroglobulin| 134 ng/ml (0–30) | AST  | 18 IU/l | ALT  | 24 IU/l | LDH  | 164 IU/l | CPK  | 106 IU/l | BUN  | 5.0 mg/dl |      |      |              |
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
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 in the development of Moyamoya disease.

### Table 2

| 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         |
| Im (5)           | 8, F     | Faint                           | +                | Unknown | Antithyroid drug/brain vessel     |
| Sasaki (6)       | 16, F    | Faint, hemiparesis              | +                | Unknown | Antithyroid drugs/brain vessel    |
| Lee (1)          | 19, F    | Diarrhea, goiter                | +                | +    | PTU*/brain vessel reconstruction   |
| Tokimura (7)     | 19, F    | Palpitation, dysesthesia         | +                | +    | Thyroidectomy/brain vessel         |
| Our case         | 14, M    | Fatigue, sweats, weakness of the right arm | +          | – to + | MMI/brain vessel reconstruction |

* Prophylthiouracil.
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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