Clinical features of moyamoya disease with Graves’ disease: a retrospective study of 394,422 patients with thyroid disease

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Abstract. Graves’ disease has been reported to affect the clinical features of moyamoya disease (MMD), an occlusion of the circle of Willis. This study aimed to clarify the characteristics of MMD in patients with Graves’ disease. This was a single-center, retrospective study. The prevalence and clinical features of MMD patients among all patients with thyroid disease who visited Ito hospital from January 2005 to December 2019 were evaluated. The relationship between MMD and hyperthyroidism was analyzed in new-onset Graves’ disease patients during the same period. Of all 394,422 patients with thyroid disease, 88,180 had Graves’ disease, and 40 had MMD with Graves’ disease, i.e., the prevalence was 45.36 per 100,000 patients with Graves’ disease (0.0454%). The median age at onset of MMD was 39 years (interquartile range, 31–54 years), with a male to female ratio of 1:12. The most common time that MMD was diagnosed was within 1 year after the onset of Graves’ disease, in 9 of 40 patients (22.5%), and 19 of 40 patients (47.5%) underwent bypass surgery for MMD. In MMD with Graves’ disease, headache was the most frequent symptom, and ischemic types of stroke and bilateral lesions were common. Of 23,347 patients with new-onset Graves’ disease, 7 were diagnosed with MMD and the incidence of MMD was 5.94 patients per 100,000 person-years. Most patients developed MMD symptoms during hyperthyroidism. Although MMD is a rare condition, it should be noted that it can occur with Graves’ disease.

Key words: Graves’ disease, Hyperthyroidism, Thyroid diseases, Moyamoya disease, Moyamoya syndrome

MOYAMOYA DISEASE (MMD), an occlusion of the circle of Willis, was first reported from Japan in 1957 as the appearance of peculiar cerebral arteries on cerebral angiography bilaterally [1]. The concept of the disease was established in the 1960s [2-5]. MMD causes chronic progressive stenosis at the ends of bilateral internal carotid arteries, and an abnormal vascular network is formed at the base of the brain as collateral circulation. MMD is a rare disease, with a reported prevalence of 5.22 per 100,000 persons (0.0052%) and incidence of 1.13 patients per 100,000 person-years in the general population [6]. Concomitant MMD and Graves’ disease was first reported in 1991 [7]. Since then, many studies of the relationship between thyroid disease and MMD have been conducted [8-14]. MMD has a high frequency of hyperthyroidism [8], and MMD with Graves’ disease is more progressive [9]. Thus, Graves’ disease can adversely affect the clinical course of MMD, and it is important to know in detail the clinical characteristics of MMD in patients with Graves’ disease.

Our facility, Ito Hospital, is a hospital specialized in thyroid diseases. This study aimed to clarify the clinical characteristics of MMD in patients with Graves’ disease in a large number of patients.

Materials and Methods

Study design and participants

This was a retrospective study based on the electronic medical records of Ito hospital in Tokyo, Japan. From January 2005 to December 2019, 394,422 patients with thyroid disease visited our hospital, and 23,347 patients were newly diagnosed with Graves’ disease during the
same period. The numbers of patients with Graves’ disease, Hashimoto’s disease, and nodules were determined from the medical record database search. After a screening search using the word “moyamoya”, MMD was identified by reviewing the medical records. MMD was diagnosed at another hospital.

This study was divided into two parts. First, the prevalence and clinical features of MMD patients from among all 394,422 patients with thyroid disease were examined. Second, the incidence of MMD and the thyroid function and characteristics of MMD patients from among the 23,347 patients with newly diagnosed Graves’ disease were investigated. Medical records were analyzed up to March 2021.

This study was approved by the Ethics Committee of Ito hospital (approval number 340) and was conducted according to the Declaration of Helsinki and current legal regulations in Japan. The opt-out gave patients the opportunity to refuse to participate in the study.

**Assay**

Serum free T₃ (FT₃), free T₄ (FT₄), TSH, and TSH receptor antibody (TRAb) were measured using the Roche ECLusys kit (Roche Diagnostics GmbH, Basel, Switzerland). The reference values used in Ito hospital were as follows: FT₃ 2.2–4.3 pg/mL, FT₄ 0.8–1.6 ng/dL, TSH 0.2–4.5 μIU/mL, and TRAb <2.0 IU/L.

**Statistical analysis**

Data are expressed as medians and interquartile ranges for continuous non-parametrically distributed variables, and numbers with frequencies are shown for dichotomous variables. Statistical analyses were performed using Fisher’s exact test. The Kruskal-Wallis test was performed to assess relationships among 3 variables, followed by Dunn’s test. A p-value <0.05 was considered significant. JMP software, version 14.0.0 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

**Results**

**Prevalence and background of MMD with each thyroid disease**

Of the 394,422 patients with thyroid disease, 88,180 had Graves’ disease, 83,810 had Hashimoto’s disease, 145,544 had thyroid nodules including benign and malignant, and 76,888 had other diseases. Sixty-two patients had MMD, and the accompanying thyroid diseases were Graves’ disease (n = 40), Hashimoto’s disease (n = 12), thyroid nodules (n = 8), and other diseases (n = 2, multiple endocrine neoplasia type 2B and silent thyroiditis). The prevalence of MMD per 100,000 patients with Graves’ disease, Hashimoto’s disease, and thyroid nodules was 45.36 (0.0454%), 14.32 (0.0143%) and 5.50 (0.0055%), respectively.

Of the 40 MMD patients with Graves’ disease, 3 were male, 37 were female, and the male to female ratio was 1:12 (Table 1). The age at the time of diagnosis of MMD was 39 years (interquartile range, 31–54 years) (Table 1). The median ages of onset of MMD were the late 30s for all three thyroid disease patients, and MMD was more common in women, with no significant difference in MMD by each thyroid disease. However, for the time from the diagnosis of thyroid disease to the diagnosis of MMD, there was a significant difference between MMD with Graves’ disease and MMD with nodules (median +4 years, interquartile range 0–+11 years vs. 0 years, −12.5–+2, p = 0.036). The median diagnostic interval between thyroid nodules and MMD was 0 years, but the range was wide, as shown in Fig. 1. MMD was most commonly diagnosed within 1 year after the onset of Graves’ disease, in 9 of 40 patients (22.5%) (Fig. 1).

The comorbidities of thyroid disease patients with MMD were hypertension in 5 cases, type 2 diabetes mellitus in 3 cases, Sjogren’s syndrome in 2 cases, ovarian cyst in 2 cases, autoimmune hepatitis in 1 case, chronic kidney disease in 1 case, angina pectoris in 1 case, Crouzon syndrome in 1 case, and atrial fibrillation in 1 case.

**Symptoms and conditions of MMD in MMD patients with Graves’ disease**

The clinical manifestations of the 40 MMD patients with Graves’ disease were headache in 9 cases, numbness in 7 cases, dysarthria in 4 cases, weakness in 4 cases, dizziness in 3 cases, tremor in 2 cases, consciousness disorder in 2 cases, epilepsy in 1 case, visual field disorder in 1 case, and asymptomatic in 14 cases (Table 1). The most common symptoms of MMD with Graves’ disease were headache and numbness. There was no significant difference in the symptoms of MMD in patients with other thyroid diseases.

Symptomatic MMD patients with Graves’ disease were diagnosed with transient ischemic attack in 2 cases, cerebral infarction in 4 cases, and cerebral hemorrhage in 3 cases (Table 1). Ischemic lesions were more common than hemorrhagic lesions. Of the 23 MMD patients with Graves’ disease whose laterality of the lesion was known, 19 cases were bilateral, and 4 were unilateral (Table 1). Fig. 2 shows typical magnetic resonance angiography findings of an MMD patient with bilateral lesions.

Treatment of MMD with Graves’ disease included surgery in 19 cases (47.5%), medication in 9 cases (22.5%), observation in 7 cases (17.5%), and unknown in 5 cases (12.5%). Of the 10 cases in which thyroid function
during surgery for MMD was known, surgery for MMD was performed after hyperthyroidism was almost improved by medication (n = 5) or radioactive iodine (RAI) therapy (n = 5) for Graves’ disease.

Regarding the treatment of Graves’ disease, as of March 2021, 11 patients (27.5%) were on medication, and 12 patients (30%) were in remission. The remaining 17 patients underwent definitive treatment, 12 (30%) with RAI therapy and 5 (12.5%) with thyroidectomy. One patient developed dysarthria on the day of RAI therapy and was then diagnosed as having MMD.

Incidence, thyroid function, and characteristics of patients with newly diagnosed Graves’ disease who developed MMD

Many patients were diagnosed with MMD within one year of the onset of Graves’ disease (Fig. 1). Therefore, to clarify the symptoms and thyroid function leading up to the diagnosis of MMD, patients with new-onset Graves’ disease who developed MMD were investigated.

Of the 23,347 newly diagnosed Graves’ disease patients from January 2005 to December 2019, 7 were newly diagnosed with MMD by March 2021 (Table 2). The incidence of MMD in the 23,347 patients with Graves’ disease was 5.94 patients per 100,000 person-years.

Thyroid function test results at the onset of MMD were available in 6 of 7 patients, and 5 patients showed overt hyperthyroidism. In case 5 (Table 2), the intervals between visits were somewhat irregular, but the patient was not in a hyperthyroid state when the symptoms of MMD appeared. Thereafter, she was asymptomatic for

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of MMD patients with thyroid diseases</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Graves’ disease</td>
</tr>
<tr>
<td>Total patients with MMD, n</td>
<td>40</td>
</tr>
<tr>
<td>Age, median [IQR], years</td>
<td>30.5 [25.3–42]</td>
</tr>
<tr>
<td>At the diagnosis of thyroid disease</td>
<td>39 [31–54]</td>
</tr>
<tr>
<td>Time from diagnosis of thyroid disease to that of MMD, median [IQR], years</td>
<td>+4 [0 – +11]</td>
</tr>
<tr>
<td>Sex (male/female), n (%)</td>
<td>3/37 (7.5/92.5)</td>
</tr>
<tr>
<td>Clinical manifestation of MMD, n (%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Numbness</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Weakness</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Tremor</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Consciousness disorder</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Visual field disorder</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Subtype of stroke, n (%)</td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>TIA</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>31 (77.5)</td>
</tr>
<tr>
<td>Lesion side for MMD, n (%)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>19 (47)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (43)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

MMD, moyamoya disease; IQR, interquartile range; TIA, transient ischemic attack.

* Even if there were multiple symptoms, they were included in each symptom.

† p < 0.05 in comparison with MMD with Graves’ disease.
several years. However, after self-interruption of treatment for Graves’ disease, hyperthyroidism appeared and the symptoms of MMD flared up, and close examination showed that MMD had progressed. Stenosis of the bilateral internal carotid arteries and loss of the right anterior cerebral artery A1 was observed, and it was considered to be stage 3 of Suzuki’s classification [5]. She underwent bypass surgery for advanced MMD.

For Graves’ disease, all 7 patients were treated with anti-thyroid drugs, and one patient underwent thyroidec-
tomy after medication. Four of the seven patients (57.1%) self-interrupted their visits for treatment of Graves’ disease during their clinical courses.

**Discussion**

MMD was first described in Japan in 1969 by Suzuki and Takaku [5]. The diagnostic criteria were first formulated by a Japanese research group in 1978 and have been revised five times since then [15]. MMD is an occlusion of the circle of Willis of unknown cause and had been distinguished from quasi-MMD (moyamoya syndrome) when there are other comorbidities that cause it. Hyperthyroidism, mainly Graves’ disease, had been included in the causative diseases of quasi-MMD, but the frequency of hyperthyroidism is high when subclinical hyperthyroidism is included, and it seems impossible to determine a clear causal relationship [15]. For this reason, the revised version of 2021 excluded hyperthyroidism from the causative diseases of quasi-MMD and described it as a combination of MMD and Graves’ disease [15]. However, MMD is often associated with hyperthyroidism [8], and disease progression and the incidence of stroke are high in MMD patients with Graves’ disease [9]. Therefore, the revised 2021 guidelines caution that continued attention should be paid to the impact of Graves’ disease on the clinical features of MMD.

In the present study, the prevalence and incidence of MMD in patients with Graves’ disease were 45.36 per 100,000 patients (0.0454%) and 5.94 patients per 100,000 person-years, respectively. In previous reports, the prevalence and incidence of MMD in the general population were 5.22 per 100,000 persons (0.0052%) and 1.13 patients per 100,000 person-years, respectively [6]. Though it is difficult to directly compare the previous
reported frequency of MMD in the general population and the frequency in patients with Graves’ disease in the current study, the prevalence and incidence of MMD with Graves’ disease appear to have been higher than of MMD in the general population.

In the previous survey, the male-female ratio of MMD was 1:1.8 [16], but in the present study, the male-female ratio of MMD with Graves’ disease was 1:12, which was overwhelmingly female. This may be thought to be due to the large number of women with Graves’ disease. However, the male to female ratio of Graves’ disease was 1:4.5 [17], and more than sex differences in Graves’ disease, the prevalence of MMD in patients with Graves’ disease appeared to be significantly higher in females.

MMD is common between the 20s and 40s after adulthood [16], and Graves’ disease is common in the 20s to 40s [17]. In the present study, the median age of onset of Graves’ disease was 30.5 years. The median time between the diagnosis of Graves’ disease and the diagnosis of MMD was 4 years, often less than one year. The time of onset may affect the manifestation of the symptoms of MMD. It should be noted that the age of disease onset in non-elderly generations makes it difficult to assume the onset of cerebrovascular disease and may lead to a delay in diagnosis.

A past nationwide survey of MMD showed that both cerebral infarction and cerebral hemorrhage can occur in adulthood [18]. In MMD patients with Graves’ disease, transient ischemic attack (TIA) and cerebral infarction, which mainly consisted of ischemic lesions, were more common (Table 1).

The range of symptoms of MMD can vary, from asymptomatic to motor weakness, headache, and seizure [18]. In recent years, with the widespread use of MRI, more and more MMD patients are being found with non-specific symptoms such as headache or asymptomatic MMD [18]. As with MMD in general, MMD associated with Graves’ disease also causes a wide variety of symptoms, with no significant differences in presentation. In the present study of MMD with Graves’ disease, headache and numbness were particularly common in symptomatic cases, but any symptom could be present, depending on the type (ischemic or hemorrhagic). It is necessary to pay attention to the possibility of MMD when these symptoms are recognized in cases of Graves’ disease.

MMD has more bilateral lesions than unilateral lesions [6]. In the present study, MMD with Graves’ disease had a higher percentage of bilateral lesions (Table 1). Since unilateral lesions may progress to bilateral lesions [19], this may reflect the progression of MMD with Graves’ disease.

MMD with Graves’ disease was often diagnosed within one year after the onset of Graves’ disease (Fig. 1) and symptoms of MMD were likely to appear with hyperthyroidism (Table 2). This would suggest that thyroid dysfunction may affect the onset of MMD and the manifestation of the symptoms of MMD. Past studies have reported that hyperthyroidism leads to MMD because of increased cerebral oxygen consumption and cerebral blood flow, resulting in damage to blood vessel walls [20], sympathetic regulation causing cerebral vascular stenosis [20, 21], and immune stimulation of the thyroid gland being involved in T cell function, resulting in vascular abnormalities [22, 23]. Though MMD symptoms may have appeared by such mechanisms in the present cases, further studies are needed to confirm them.

In MMD with Graves’ disease, it has been reported that normalization of thyroid function eliminated the symptoms of MMD [7] and improved the findings of internal carotid artery stenosis [24]. On the other hand, there are also reports that, even if thyroid function is normalized, MMD progresses [9], and surgical revascularization is required [25-27]. Extensive research with frequent imaging examinations will be needed to prove that MMD progresses in cases with hyperthyroidism.

In addition, asymptomatic MMD was often not followed-up in the present patients. However, asymptomatic MMD...
is not a stable disorder. It can potentially progress and cause ischemic or hemorrhagic stroke [26]. Case number 5 (Table 2) had been asymptomatic for a long time after the initial symptom appeared and the diagnosis of MMD was made and interrupted visits to the hospital for MMD. However, the symptoms recurred, and when the patient was referred to neurosurgery, the MMD worsened, and she underwent surgery.

Surprisingly, more than half of Graves’ disease patients with MMD (4 of 7 patients) often had their treatment for Graves’ disease discontinued transiently (Table 2). In one of the cases, the symptoms of MMD worsened after discontinuation of oral therapy for Graves’ disease, and surgery was performed for MMD. MMD may be exacerbated in patients who tend to forget the condition and treatment of MMD, maintaining close contact and treatment of Graves’ disease and the progression of MMD.

From the standpoint of an endocrinologist, in Graves’ disease patients with MMD, it is necessary to pay attention to not only the control of Graves’ disease, but also the condition and treatment of MMD, maintaining close contact with a neurosurgeon.

There are some limitations to consider. This study was conducted at a thyroid specialty hospital in Japan and might have patient selection bias. In addition, it was a retrospective study, and the patient information obtained from the medical record was limited. The details of the MMD imaging findings are desirable, and a future study is needed. Furthermore, arteriosclerosis is also said to be a cause of MMD [15, 28], and it is necessary to evaluate the comorbid conditions.

### Conclusion

MMD was found in 0.0454% of Graves’ disease patients. Although it is a rare condition, we should consider the possibility of MMD when Graves’ disease patients develop chronic headaches or neurological symptoms, and the symptoms of MMD often appear during hyperthyroidism.
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Conflict of Interest Statement

The authors have nothing to disclose.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship

Study planning and coordination: M.H., N.W., and T.M. Investigation: M.H., N.W., T.M. N.S., M.F., M.M., A.Y., and J.Y. Noh. Data curation and statistical analysis: M.H., N.W., and J.Y. Noh. Writing original draft: M.H. Supervision: K.S. and K.I. All authors contributed to the discussion and approved this article.

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