Association of Thyroid Autoantibodies With Moyamoya-Type Cerebrovascular Disease
A Prospective Study

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Background and Purpose—To investigate the association between thyroid autoantibodies and moyamoya disease (MMD) in patients with an apparent euthyroid state.

Methods—We prospectively studied angiographically diagnosed patients with MMD. We compared demographic profiles, thyroid function test, and thyroid autoantibody status between MMD and control groups.

Results—A total of 63 patients with MMD, 71 patients with non-MMD stroke, and 200 healthy control subjects were included. The prevalence of elevated thyroid autoantibodies was higher in the MMD group than in other groups (P<0.01 for MMD versus non-MMD; P<0.001 for MMD versus control subjects). After adjusting for covariates, the elevated thyroid autoantibodies (OR, 4.871; 95% CI, 1.588 to 15.277) and smoking habits (OR, 0.206 for current smoker; 95% CI, 0.054 to 0.786) were independently associated with MMD versus non-MMD stroke.

Conclusions—Elevated thyroid autoantibodies were frequently observed in patients with MMD. The results of the present study suggest that immune aberrancies associated with or underlying thyroid autoimmunity are also playing a role in developing MMD. (Stroke. 2010;41:173-176.)

Key Words: autoantibodies  moyamoya disease  thyroid gland

Moyamoya disease (MMD) has been reported in association with various disease entities. There have been a few reported cases of the coexistence of Graves disease and MMD suggesting a possible pathogenic relationship between these 2 rare diseases.

Until now, there has been no prospective study with respect to the relationship between thyroid autoantibodies and MMD. Thus, we studied the prevalence of thyroid autoantibodies in patients with MMD with an apparent euthyroid state and compared these patients with those in aged-matched non-MMD patients with stroke and healthy control subjects.

Materials and Methods
We prospectively included patients admitted to a university medical center with MMD (confirmed by digital subtraction angiography) from March 2006 to March 2009. We excluded patients with goiter or self-reported thyroid disease (N=3) or who were currently taking thyroid hormones (N=2). As the control groups, age-matched consecutive patients with non-MMD stroke and healthy control subjects were recruited.

Serum triiodothyronine (T3), thyroxine (T4), free T4, thyroid stimulating hormone (TSH), antimicrosomal antibody (AMA), and antithyroglobulin antibody (ATA) levels were measured using commercialized radioimmunoassay kits. Activity of thyrotrophin-binding inhibitory immunoglobulin (TBII) was measured with the second-generation TSH-receptor antibodies kit.

The receiver operating characteristic curve was used to assess the maximum likelihood estimation of ATA, AMA, and TBII for the detection of MMD. The differences from the MMD group in sex- and age-adjusted mean values and proportions for cardiovascular risk factors, thyroid function test, and elevated thyroid antibodies were examined by analysis of covariance and Mantel-Haenszel χ² tests. In addition, a multivariate logistic regression analysis was performed to predict the independent contribution of factors in the MMD group as compared with the non-MMD stroke group. Variables from the univariate analyses at P<0.1 were considered to represent explanatory variables.

Results
A total of 63 patients with MMD (definite, 44; probable, 19), 71 patients with non-MMD stroke (atherosclerotic, 22; cardioembolic, 14; small arterial, 17; undetermined, 11; and other causes, 7), and 200 healthy control subjects were included in the study. Clinical and laboratory characteristics of patients are presented in Table 1. Male sex and current...
smoker were observed more frequently in patients with non-MMD stroke than those with MMD. Hypertension and diabetes were more frequent in the MMD group than in healthy control subjects.

Thyroid function test revealed that mean serum T4 and free T4 levels were significantly higher in patients with MMD than in those with non-MMD stroke (P<0.05 in both cases). Similarly, mean serum free T4 levels were significantly higher in the MMD group than in the healthy control group (P<0.001). The mean value of TSH, T3, and T4 were all within the reference range.

Thyroid autoantibodies were measured in 45 of 63 patients with MMD (71.4%), 55 of 71 non-MMD patients with stroke (77.5%), and in all 200 healthy control subjects. Use of receiver operating characteristic curves (not shown) revealed that an AMA level of 430 U/mL, ATA level of 80 U/mL, and a TBII value of 15% forecast a high probability of MMD versus non-MMD stroke. Values above these levels in one or more thyroid autoantibodies were found in 22 (48.9%) patients with MMD and 11 (20.0%) non-MMD patients with stroke (P<0.01 for MMD versus non-MMD stroke with respect to elevated AMA, ATA, and TBII; Table 1). Elevated levels of AMA were observed only in 11 (5.5%) healthy subjects (P<0.001 for MMD versus healthy subjects). The levels of thyroid autoantibodies were higher in the MMD group than in the other groups (data not shown).

Multiple logistic regression analysis was performed to further evaluate the independent predictor for MMD (versus non-MMD stroke). After adjusting for covariates, including sex, age, diabetes, and the serum levels of T3 and T4, the presence of elevated thyroid autoantibodies (OR, 4.871; 95% CI, 1.588 to 15.277) and current smoker (OR, 0.206; 95% CI, 0.054 to 0.786) were independently associated with MMD.
In the subset analysis of MMD, comparing 22 patients with and 23 patients without elevated thyroid autoantibodies, the former had higher mean serum T3 levels \((P<0.05)\) and was less likely to have normal thyroid function test \((P<0.01)\) than the latter (Table 2). Eleven of 22 patients with MMD with elevated thyroid autoantibodies had \(\geq 2\) thyroid autoantibodies (Figure A). All patients with MMD with elevated TBII had low TSH and high/normal T4 levels (Graves-like), whereas those without it had normal thyroid function test. No patients showed Hashimoto-like condition (elevated non-TBII autoantibodies with high TSH and low/normal T4 levels; Figure B).

**Discussion**

Most previous studies of thyroid disease and MMD have been small scale series of one to 4 patients focusing on the concurrence of Graves disease and MMD.\(^1\)\(^-\)\(^3\) Whether these 2 entities share common pathophysiological mechanisms or represent epiphenomena has not been settled. It is thought that alteration of cerebral hemodynamics in thyrotoxicosis may have been the trigger of the vascular attack in these patients. Moreover, thyrotoxicosis, which increases sympathetic nervous system sensitivity, may involve the formation of abnormal cerebral vessels.\(^4\) Another possible link between these disorders is T-cell dysregulation, which is related to cellular proliferation and vascular dysregulation in MMD and immunologic stimulation of the thyroid in Graves disease.\(^2\)

Lastly, thyrotoxicosis may result in hyperhomocysteinemia, which is associated with premature atherosclerosis and MMD.\(^5\)\(^-\)\(^6\)

To clarify the relation between MMD and thyroid autoantibodies, we focused our attention only on those patients with an apparent euthyroid state. One of the key findings of our study was that nearly half of the patients with MMD exhibited elevated thyroid autoantibodies despite the absence of evidence of thyroid dysfunction. Furthermore, elevated thyroid autoantibodies were independently associated with MMD after being adjusted for other confounding factors, including levels of thyroid hormone. These findings suggest that thyroid autoimmunity may be associated with development of MMD.

The negative association of smoking habits with MMD may be explained by the differential contribution of smoking in development of stroke between MMD and non-MMD stroke. In young adult patients with stroke, current smoking is an important risk factor for stroke.\(^7\) On the other hand, in patients with MMD, other factors (ie, thyroid autoimmunity) other than conventional risk factors may be more important for stroke than smoking habits themselves.

Our study also illustrated the characteristics of patients with MMD with respect to thyroid autoantibodies. Our data suggest that non-Graves-like and non-Hashimoto-like condition (normal TBII and normal TSH and T4 levels) as well as Graves-like condition (elevated TBII, low TSH, and high/normal T4 levels) may be important in development of MMD. However, in this study, we concentrated on the role of thyroid autoantibodies for MMD in patients with apparent euthyroid state and excluded patients who had clinical thyroid disease (ie, clinical Graves disease or Hashimoto thyroiditis). In this narrow spectrum, it is difficult to identify the potential relationship between MMD and a specific thyroid condition. Further studies with larger cohorts with a full spectrum of thyroid disease (from Hashimoto thyroiditis to Graves disease) are warranted.

There are limitations to this study. First, our results are specific to a cohort including only Asian patients with adult-type MMD (all except 3 were adult-onset) and therefore cannot be generalized to a childhood-type or other racial group, which may be different from Asian and adult-type MMD.\(^8\)\(^-\)\(^12\) Further studies involving childhood-type and other racial groups were needed. Second, a causal relationship cannot be determined from the present study. Treatments targeted on reducing the levels of thyroid autoantibodies with long-term follow-up are required to delineate the causality.
In conclusion, our results indicate an independent association of elevated thyroid autoantibodies with MMD and suggest that immune aberrancies associated with or underlying thyroid autoimmunity are also playing a role in developing MMD.

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Disclosures
None.

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