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Increased Thyroid Hormones and Autoantibodies Levels Associated with Quasi-Moyamoya Disease

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Abstract

Objectives: The purpose of this study was to investigate whether elevated thyroid autoantibodies associated with Quasi-Moyamoya Disease (MMD).

Methods: We retrospectively investigated angiographically defined patients with quasi-MMD patients. We compared clinical features, serum thyroid autoantibody values and T cell levels between quasi-MMD patients and control subjects.

Results: A total of 103 patients with MMD and an equal number of healthy control subjects (n=103) were included. The prevalence of elevated thyroid autoantibodies (P=0.008) was significantly higher in patients with MMD than in control subjects. The increased thyroid hormone (OR: 11.03; 95% CI, 1.22-96.13; P=0.034) and increased thyroid autoantibodies (OR, 6.38; 95% CI, 1.12 to 46.52; P=0.040) were significantly associated with increased risks of quasi-MMD, respectively. The antithyroid therapy can significantly attenuate disease progression than without special treatment in quasi-MMD patients with thyroid disease (P=0.041).

Conclusion: Increased thyroid hormone and thyroid autoantibodies levels in serum were significantly in association with quasi-MMD. Antithyroid therapy may significantly attenuate or slow disease progression in quasi-MMD with thyroid disease patients. The results suggested that both abnormal thyroid hormones and elevated thyroid autoantibodies played important roles in MMD development, which might help to better manage and further study underlying pathogenesis mechanisms of quasi-MMD.

Keywords: quasi-Moyamoya Disease; Thyroid Autoantibodies; T cell; Thyroid hormones

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Abbreviations

MMD: Moyamoya Disease; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-Stimulating Hormone; TGAb: Antithyroglobulin Antibody; TPOAb: Anti-Thyroperoxidase Antibody; TRAb: Thyrotropin Receptor Antibody

Introduction

The increased thyroid hormones and elevated thyroid autoantibodies were found frequently in Quasi-Moyamoya Disease (MMD) patients, indicating increased thyroid function and elevated thyroid autoantibodies were associated with patients with MMD [1-4]. Whether increased thyroid hormones and elevated thyroid autoantibodies were associated with quasi-MMD patients remains to be explored. Using case-control and retrospective cohort study, we explored and compared clinical features, serum thyroid hormones and autoantibodies levels, and analyzed disease progression between quasi-MMD patients and control subjects, to elucidate whether abnormal increased thyroid hormones and elevated thyroid autoantibodies associated with quasi-MMD.

Methods

We retrospectively included with quasi-MMD (confirmed by digital subtraction angiography) patients admitted to our hospital, from August 2016 to June 2023. We included MMD patients with Graves' disease, thyroid goiter, Hashimoto thyroiditis and apparent euthyroid state. Sex and age-matched healthy controls (confirmed by physical examination) were recruited in this study. All study subjects were residents of Central China.

Clinical and laboratory examinations were conducted on each subject. Clinical features, including smoking and hypertension history, hyperlipidemia, abnormal homocysteine and family history of cerebrovascular disease.

Serum Triiodothyronine (T3), free T3, Thyroxine (T4), free T4, Thyroid-Stimulating Hormone (TSH), Antithyroglobulin Antibody (TGAb), Anti-Thyroperoxidase Antibody (TPOAb), and Thyrotropin Receptor Antibody (TRAb) were examined by employing electrochemical luminescence. When serum TGAb>115 IU/L, or TPOAb>34 IU/L, or TRAb>3 IU/L was identified as elevated thyroid autoantibodies according to the manufacturer' reference values.

Data were analyzed by employing IBM SPSS 26.0 (Chicago, IL, USA). Continuous variables were analyzed by independent-samples *t* test, whereas categorical variables were analyzed by Pearson c^2 test. Forward stepwise conditional logistic regression analysis was conducted to investigate the correlation of abnormal thyroid hormones and elevated thyroid autoantibodies with quasi-MMD. Any variable from the univariate analysis at P<0.15 were considered to be included.

The effects of antithyroid therapy on disease progression of patients with MMD were assessed by using retrospective cohort design during follow-up period.

Results

Clinical and laboratory characteristics are presented in Table 1. In the study, 65 of 103 (63.1%) patients with quasi-MMD were female, and the average age was 41.1 ± 13.8 years. And 33 of 103 (32.0%) patients was association with increased thyroid hormones and thyroid autoantibodies levels, at average age of 38.1 ± 12.6 years, and 30 (90.9%) was female. Multivariate analysis indicated that the female with thyroid disease had a higher risk of association with quasi-MMD. Family history of cerebrovascular disease, smoke, hypertension, diabetes, hyperlipidemia and homocysteine were not association with MMD when compared with control subjects.

Thyroid hormones examinations displayed that average values of serum T3, free T3, T4, free T4 and TSH were significantly increased in quasi-MMD patients' comparison with control subjects (P<0.05 for all). Thyroid dysfunction was significantly higher in quasi-MMD patients than in control subjects (31.6% *vs.* 1.9%, P=0.000).

Increased thyroid autoantibodies were detected in 35 of 103 patients with MMD. The increased thyroid autoantibodies were significantly higher in quasi-MMD patients than in healthy control subjects (35.3% *vs.* 2.9%, P=0.000). TGAb, TPOAb and TRAb were significantly higher in quasi-MMD than in healthy control subjects (24.3% *vs.* 1.9%, P=0.000; 33.0% *vs.* 2.9%, P=0.000; 14.6% *vs.* 0%, P=0.006, respectively).

Forward stepwise conditional logistic regression analysis further assessed the correlation of increased thyroid hormones and autoantibodies with quasi-MMD. After adjusting the covariates, including age, sex, smoking, hypertension, diabetes, hyperlipidemia, homocysteine, family history of cerebrovascular, the increased thyroid hormone (OR: 11.03; 95% CI, 1.22-96.13; P=0.034) and increased thyroid autoantibodies (OR: 6.38; 95% CI, 1.12-46.52; P=0.040) were significantly associated with quasi-MMD, respectively.

During follow-up period (from 6 mo to 72 mo, mean 43.2 ± 14.2 months), 8 of 76 (10.5%) quasi-MMD patients who were treated with antithyroid therapy involved in disease progression. 8 of 27 (29.6%) quasi-MMD patients without antithyroid therapy involved disease progression. After adjusting the covariate of surgical treatment, the prevalence of disease progression was significantly lower in quasi-MMD patients with antithyroid therapy than in quasi-patients MMD without antithyroid treatment (10.5% *vs.* 29.6%, p=0.043, OR: 1.003, 95% CI, 0.970-12.186) (Table 2).

Table 1: Baseline clinical and laboratory features of onset in quasi-MMD patients and control subjects.

	MMD (103)	Controls (103)	P-Value
Age, years	38.5 ± 12.1	39.0 ± 10.8	
Female	63.1	62.1	
Current smoker	14.6	15.5	0.802‡
Hypertension	24.3	19.4	0.731‡
Diabetes	8.7	4.9	0.608‡
Hyperlipidemia	15.5	9.7	0.196‡
Homocysteine	15.5	6.8	0.148‡
Family history of cerebrovascular disease	17.5	14.6	0.786‡
sTHT			
TSH, mU/L [0.27-0.42]	1.58±1.46	2.12±1.36	0.077†
T3, nmol/L [1.30-3.10]	2.67±0.54	1.65±0.5	0.002†
Free T3, pmol/L [3.60-7.50]	5.89±2.36	4.46±1.28	0.003†
T4, nmol/L [62-164]	121.6±45.6	60.5±20.9	0.002†
Free T4, pmol/L [12.0-22.0]	22.31±10.58	14.25±2.69	0.035†
Thyroid function abnormalities			
Increased thyroid hormones	31.6	1.9	0.000‡
Subclinical hyperthyroidism	13.6	1.9	0.029‡
Overt hyperthyroidism	17.5	NA	0.000‡
Decreased thyroid function	2.9	1.9	1.000‡
Subclinical hypothyroidism	3.9	1.9	
Elevated thyroid autoantibodies	35.3	2.9	0.000‡
TGAb-positive	24.3	1.9	0.000‡
TPOAb-positive	33	2.9	0.000‡
TRAb-positive	14.6	NA	0.000‡

Numbers in brackets are reference ranges.
quasi-MMD: quasi-Moyamoya Disease; sTHT: serum Thyroid Hormones Tests; TGAb: antithyroglobulin Antibody; TPOAb: Antithyroperoxidase antibody; TRAb: Thyrotropin Receptor Antibody
Data presented as mean ± SD or percentage (%). NA: not available
†Independent-samples *t* test; ‡ Pearson c^2 test

Discussion

In this respective study, we analyzed the clinical features, serum thyroid hormones and thyroid autoantibodies levels and assessed disease progression in quasi-MMD patients. We can get the following results: 1) The sex and age features of onset predominately affected the female, and female patients with quasi-MMD had a higher risk than male patients in association with thyroid disease; 2) Antithyroid treatment could attenuate disease progression in quasi-MMD with thyroid disease; 3) These clinical characteristics and laboratory values also demonstrated increased thyroid hormones and thyroid autoantibodies levels associated with quasi-MMD patients [4-7].

In the study, we found that about 31.6% of quasi-MMD patients displayed overt plus subclinical thyroid dysfunction and up to 35.3% of quasi-MMD patients displayed increased thyroid autoantibodies. Especially noteworthy, both increased thyroid hormones and thyroid autoantibodies were significantly associated with quasi-MMD after adjusting the covariates. There were several possible

Table 2: The summary of disease progressions in MMD with and without elevated thyroid autoantibodies.

	Quasi-MMD after antithyroid treatment	Quasi-MMD without antithyroid treatment	P-Value
No. of persons	76	27	
Follow-up (months)	44.2 ± 17.6	42.2 ± 12.1	0.896†
Age, years	38.0 ± 8.2	36.2 ± 16.2	0.712‡
Female	85.5	51.8	0.000‡
Disease progression	10.5 (n=8)	29.6 (n=8)	0.019‡

Data presented as mean ± SD or percentage (%)
†Independent-samples *t* test; ‡ Pearson c^2 test

reasons for explanation [8-11]. First, thyrotoxicosis was known to result in changes in cerebral hemodynamics that may increase brain metabolism and oxygen consumption, which is harmful to the artery wall.

Secondly, there is an excess of thyroid hormone, which causes a long-term increase in sympathetic nervous system activity and may be involved in the formation of a narrowing or occlusion of brain arteries. Finally, increased thyroid autoantibodies may lead to autoimmune cerebrovascular inflammation and stimuli is thought to occur simultaneously with Graves' disease and Moyamoya-like vascular changes. Previous studies suggested the underlying common mechanism between these two entities is T-cell dysfunction, which involved in immunologic stimulation of thyroid gland thyroid autoimmune disease. All above might involve in cellular proliferation and vascular remodeling of intracranial artery in quasi-MMD [12,13]. Therefore, both increased thyroid hormones and thyroid autoantibodies could be associated with quasi-MMD.

The association that increased thyroid hormones and thyroid autoantibodies with quasi-MMD development was further demonstrated when compared disease progression in quasi-MMD patients after antithyroid treatment. To our knowledge, previous studies rarely explored disease progression in quasi-MMD patients by treatment reducing the levels of thyroid hormones and thyroid autoantibodies. Chronic disease progression such as cerebrovascular stroke is feature of patients with quasi-MMD [14,15]. The quasi-MMD after thyroid treatment had significantly less disease progression than quasi-MMD patients without special treatment. The results suggested that normal thyroid hormones and autoantibodies might play protective effect on disease progression in quasi-MMD patients with thyroid disease. However, abnormal increased thyroid hormones and autoantibodies may induce arterial stenosis and occlusion in quasi-MMD [15,16]. It was thought that physiological thyroid hormones and autoantibodies levels which maintained normal cerebral hemodynamics and sympathetic nervous system activity could not be harmful to intracranial arterial walls. Therefore, the disease progression does not continue [3,17]. In addition, immune stimulation and inflammatory response in quasi-MMD patients may stop under physiological levels of thyroid autoantibodies [18-20].

In conclusion, both increased thyroid hormones and thyroid autoantibodies were significantly associated with quasi-MMD. Antithyroid treatment could significantly attenuate or slow disease progression in quasi-MMD with thyroid disease. Both increased thyroid hormones and elevated thyroid autoantibodies involved immune abnormalities also play underlying roles in quasi-MMD development, which was helpful for the management and research of this disease of quasi-MMD.

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