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Authors
Shi, Zhenghao
Zhang, Xuting
Chen, Zhicai
et al.

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Elevated thyroid autoantibodies and intracranial stenosis in stroke at an early age

Zhenghao Shi[1], **Xuting Zhang**[1], **Zhicai Chen**[1], **David S. Liebeskind**[2], and **Min Lou**[1,*]

[1]Department of Neurology, The 2nd Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, China

[2]Department of Neurology, UCLA Stroke Center, Los Angeles, CA, USA

Abstract

Background—Previous studies have shown that hyperthyroidism was related to Moyamoya disease and intracranial artery stenosis. However, it is not clear whether thyroid hormone or thyroid autoantibodies was associated with them.

Aims and/or hypothesis—Thyroid autoimmunity was previously shown to be associated with Moyamoya disease. Our study aimed to investigate the association between thyroid autoantibodies and intracranial large artery stenosis in young ischemic stroke patients with apparent euthyroid states.

Methods—We retrospectively reviewed first-onset ischemic stroke patients (age ≤55 years old) consecutively admitted to a single academic center. Intracranial large artery stenosis was defined as ≥50% luminal diameter narrowing. We compared demographic profiles, risk factors (age, hypertension, diabetes, current smoker, atrial fibrillation, hyperlipidemia), thyroid function test, and thyroid autoantibodies including antithyroperoxidase antibody and antithyroglobulin antibody between patients with and without intracranial large artery stenosis. We also performed multivariate logistic regression analysis to evaluate the association between thyroid autoantibodies and intracranial large artery stenosis.

Results—A total of 351 patients were analyzed. The mean age of the patients was 47.0 ± 7.7 (range, 10–55 years), and 252 (71.8%) patients were male. We identified intracranial large artery stenosis in 121 (34.5%) patients. Patients with intracranial large artery stenosis showed a higher frequency of elevated antithyroperpxidase antibody levels in comparison with nonintracranial large artery stenosis group (16.5% vs. 3.9%, $P < 0.001$). After adjusting for covariates, the presence of elevated antithyroperpxidase antibody levels (odds ratio: 5.318; 95% confidence interval: 2.157–13.110, $P < 0.001$), age (odds ratio: 1.037; 95% confidence interval: 1.002–1.073, $P = 0.039$), and atrial fibrillation (odds ratio: 0.091; 95% confidence interval: 0.011–0.756, $P = 0.027$) was independently associated with intracranial large artery stenosis.

*Correspondence: Min Lou, Department of Neurology, The 2nd Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou 310009, China. loumingxc@vip.sina.com.

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Conclusions—Thyroid autoantibodies may be associated with the presence of intracranial large artery stenosis in young stroke patients, potentially providing insight on immune pathogenesis of intracranial large artery stenosis.

Keywords

age; antithyroperoxidase antibody; stenosis; stroke; thyroid

Introduction

Moyamoya syndrome (MMS) was categorized as a characteristic Moyamoya vasculopathy with well-recognized associated conditions, whereas patients with no known associated risk factors were categorized as having Moyamoya disease (MMD). MMS was an infrequent complication of Graves' disease, typically affecting young women (1). Recently, a high prevalence of thyroid autoantibodies was observed in a large population of Chinese pediatric patients with MMD (2) and patients with adult-type MMD (3). Our recent study also demonstrated that elevated thyroid antibody, especially antithyroperpxidase antibody (TPO-Ab), was associated with the development of intracranial stenosis in hyperthyroid patients in adult stroke patients (4). These findings suggest that thyroid autoimmunity may be associated with MMD or intracranial artery stenosis. However, in some studies, thyroid function studies were also significantly higher in patients with MMD than those non-MMD patients, raising questions about pathogenesis and whether thyroid hormone as well as thyroid autoantibodies was also associated with MMD. Excessive thyroid hormones are considered harmful to the arterial wall due to alteration of cerebral hemodynamics and increased sympathetic nervous system sensitivity. We sought to clarify the relationship between thyroid autoantibodies and intracranial large artery stenosis (ILAS), focusing attention on those young stroke patients with an apparent euthyroid state.

Material and Methods

Patient selection and grouping

Our study is a retrospective analysis of prospectively collected stroke registry. We analyzed a consecutive series of patients with acute ischemic stroke admitted to our center from April 2010 to June 2012, excluding cases in our prior report. These patients were identified as (1) having first-onset acute infarct with focal symptoms that lasted for >24 h, (2) observed within seven-days of the onset of symptoms, (3) age ≤55 years old, and (4) with comprehensive evaluation regarding stroke etiology including intracranial magnetic resonance angiography (MRA) or computed tomography angiography (CTA) or digital subtraction angiography (DSA). Exclusion criteria included (1) patients with an overt history of hyperthyroidism or hyperthyroidism diagnosed during admission; (2) patients with explicit secondary causes of ILAS, such as immunological, infectious, toxic, and other causes; (3) patients with 50–99% stenosis of the extracranial carotid artery tandem to an intracranial carotid or middle cerebral artery (MCA) stenosis; and (4) incomplete workups. Our study was approved by the hospital ethics committee.

Based on angiographic results, we divided the patients into two groups, including (1) patients with ILAS defined as ≥50% stenosis of a major intracranial large artery and (2) those without ILAS. Intracranial large arteries were assessed by at least one of the following examinations: MRA, CTA, or DSA. Two neurologists (Z. S. and M. L.) blinded to the clinical information and results of other diagnostic evaluations independently assessed intracranial arterial status, with disagreements decided by consensus readings. The kappa value for intraobserver agreements was 0.786. Intracranial large artery segments included intracranial internal carotid artery (ICA), anterior cerebral artery (ACA, A1, and A2 segment), the stem or a major division of the MCA (M1, proximal M2 segment), posterior cerebral artery (PCA), and basilar artery (BA) (5). ILAS was defined if there was a reduction of ≥50% in luminal diameter of any of these arterial segments (5). The exact degree of stenosis was measured by comparing the diameter of the vessel at the site of stenosis (D stenosis) with the normal diameter of the vessel just distal to the stenosis (D distal) using the following formula: % stenosis = [1 − (D stenosis/D distal)] × 100% (5). For our research purposes, we identified ILAS patients according to the angiographic findings regardless of its attribution to stroke. For example, a patient with ≥50% stenosis in the left MCA who developed a lacunar infarction in the right corona radiata was also defined as ILAS patient. MMD was diagnosed according to the guidelines of the Research Committee on Spontaneous Occlusion of the Circle of Willis (6). ILAS included both MMD and isolated stenosis of intracranial large artery in our study.

Assessment of clinical courses

We collected baseline demographic data; risk factors for ischemic stroke including hypertension, diabetes mellitus, atrial fibrillation (AF), hyperlipidemia, and current smoking status (a person who smoked at least one cigarette per day for the preceding three-months or more) (7); admission blood pressure; and National Institutes of Health Stroke Scale (NIHSS) score. Stroke subtypes were determined according to the Chinese ischemic stroke subclassification (CISS) (8) which includes five categories: (1) large artery atherosclerosis (LAA), including atherosclerosis of aortic arch and intra/extracranial large arteries; (2) cardioembolic stroke; (3) penetrating artery disease; (4) other etiology; and (5) undetermined etiology.

Laboratory tests included blood lipid profile, homocysteine (Hcy), and thyroid function studies. At our center, we systematically evaluate thyroid function tests in acute ischemic stroke patients for assessment of stroke pathogenesis. Thyroid hormones were measured using commercialized radioimmunoassy kits. Elevated thyroid autoantibodies were determined as either TPO-Ab > 34 U/ml or antithyroglobulin antibody (TG-Ab) > 115 U/ml in accordance with the manufacturer's reference.

Statistical analysis

A sample size calculation was performed based on the assumption that the study was only concerned with an increase in ILAS caused by TPO-Ab (i.e. one sided). It was determined that more than 150 patients in each arm (a total of 300 patients) would be enough to provide 80% statistical power for odds ratio (OR) = 4. Fisher's exact test was used to compare dichotomous variables, whereas independent samples two-tailed *t*-test or the Wilcoxon test

was used for continuous variables. Variables with a $P < 0.1$ in univariate analyses were included in the multivariate logistic regression models. All analyses were performed blinded to participant identifying information. Statistical significance was set at a probability value of <0.05. All statistical analysis was performed with spss package [14.0 (SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Corporation, Redmond, WA, USA)].

Results

In total, 2304 patients with acute ischemic stroke were admitted to our center between April 2010 and June 2012. Among these, 396 patients were identified based on our inclusion criteria. Forty-five patients were subsequently excluded as five patients had a history of hyperthyroidism or had hyperthyroidism diagnosed during admission; 34 patients had incomplete workups, and six patients had explicit secondary causes of ILAS including intracranial metastases, neurosyphilis, radiation encephalopathy, and antiphospholipid antibody syndrome. As a result, a total of 351 patients were included in this study. The age of the study population ranged from 10 to 55 (47.0 ± 7.7) years old, and 252 (71.8%) patients were men. NIHSS of the patients was 4.7 ± 4.7. Based on CISS criteria, 178 (50.7%) patients were classified as LAA, 26 (7.4%) cardioembolic stroke, 96 (27.4%) penetrating artery disease, 19 (5.4%) other etiology, and 32 (9.1%) undetermined etiology.

Twenty-nine (8.3%) patients were noted to have elevated TPO-Ab and 14 (4.0%) patients with elevated TG-Ab. Intracranial large arteries were assessed by MRA in 315 (90%) patients, CTA in 24 (7%) patients, and DSA in 12 (3%) patients. There were no significant differences in these modalities between ILAS and non-ILAS patients ($P = 0.182$) and between elevated TPO-Ab and normal TPO-Ab patients ($P = 0.383$). ILAS was noted in 121 (34.5%) patients. Of these, 11 (9.1%) patients were diagnosed as MMD; 10 (8.3%), 40 (33.1%), 2 (1.7%), 13 (10.7%), 4 (3.3%) patients had stenosis of ICA, MCA, ACA, PCA, and BA; and 41 (33.9%) patients had stenosis of multiple arteries (≥2 arteries), respectively. Concerning the grade of stenotic arteries, 26 (21.4%) patients had 50–69% stenosis, 57 (47.1%) patients with 70–99% stenosis, and 38 (31.4%, including 11 MMD) patients with complete occlusion.

Demographic characteristics of our study population are shown in Table 1.

ILAS patients had lower prevalence of AF ($P = 0.04$) and were older ($P = 0.058$) compared with non-ILAS patients. Elevated thyroid autoantibodies (TPO-Ab) were observed more frequently in the ILAS cohort than in non-ILAS subjects (16.5% vs. 3.9%, $P < 0.001$). The level of free T3 was lower in ILAS patients than in non-ILAS patients ($P = 0.050$); however, the mean value of h-TSH, T3, T4, free T3, and T4 was all within the normal or euthyroid reference range.

Multiple logistic regression analyses were performed to further evaluate the independent contributing factors to ILAS. The presence of elevated TPO-Ab levels (OR: 5.318; 95% CI: 2.157–13.110, $P < 0.001$), age (OR: 1.037; 95% CI: 1.002–1.073, $P = 0.039$), and AF (OR: 0.091; 95% CI: 0.011–0.756, $P = 0.027$) was independently associated with ILAS (Table 2). There was a significant relationship between the presence of elevated TG-Ab and TPO-Ab

($r = 0.468$, $P = 0.000$). The presence of elevated TPO-Ab level was not independently associated with ILAS (OR: 2.804, 95% CI 0.931–8.443, $P = 0.067$) when excluding the presence of elevated TPO-Ab levels. Three of 11 MMD patients had elevated TPO-Ab. After excluding those MMD patients, the presence of elevated TPO-Ab (OR: 5.395, $P < 0.001$), age (OR: 1.037, $P = 0.039$), and AF (OR: 0.102, $P = 0.035$) was still independently associated with ILAS.

Table 3 shows that more female patients had elevated TPO-Ab (48.3% vs. 26.4%, $P = 0.017$), in comparison with the normal TPO-Ab group. Elevated TG-Ab level existed more frequently in patients with elevated TPO-Ab (34.5% vs. 1.2%, $P < 0.001$). FT4 levels were lower in patients with elevated TPO-Ab but within the reference range. Patients with elevated TPO-Ab demonstrate higher frequency of ILAS (69.0% vs. 31.4%, $P < 0.001$) and mainly had stenosis of MCA and PCA. The grade of stenosis in patients with elevated TPO-Ab was severer than those with normal TPO-Ab. However, after excluding the non-ILAS subjects, there is no significant difference with the grade of stenosis between patients with elevated TPO-Ab ($n = 20$) and normal TPO-Ab ($n = 101$) ($P = 0.154$).

Discussion

In the general population, the prevalence of elevated TPO-Ab level ranges 3.4–13.4% (9–12). In this study, we found 16.5% of the young ILAS stroke patients exhibited elevated TPO-Ab level, with 3.9% in non-ILAS patients. Our study also demonstrated an independent association of elevated TPO-Ab level with ILAS in young stroke patients with normal thyroid function. These findings suggest that thyroid autoimmunity, especially TPO-Ab, may be related to the presence of ILAS in stroke patients with apparent euthyroid state.

Intracranial LAA research has recently been enriched by new pathogenetic concepts targeting inflammatory and infectious risk factors, and the potential role of the immune system in atherogenesis has also been explored. Recent studies have elucidated the association between intracranial atherosclerosis and C. pneumoniae IgG (13), immunoreactivity against heat-shock proteins (14), CD40/CD154 system (15), and proinflammatory cytokines. Our finding of an independent relationship between elevated TPO-Ab and ILAS draws attention to the potential immune pathogenesis of intracranial atherosclerosis. Our results suggest a new risk for stenosis focusing on immunity in young age group and indicate a need for evaluation of the intracranial vasculature in young, euthyroid individuals when their thyroid autoantibodies, particularly TPO-Ab, are elevated. Interestingly, in a previous case report, intracranial stenoses have been noted in autoimmune Graves' disease, with reversibility after high-dose methylprednisolone therapy and plasmapheresis (16). Plasmapheresis has also been suggested for the stabilization of MMD with hyperthyroidism (17). This consideration suggests a novel potential treatment for ILAS in euthyroid patients yet requires future prospective analyses for confirmation.

The actual mechanisms of TPO-Ab immune pathogenesis in intracranial atherosclerosis have not been elucidated. TPO-Ab level was found negatively correlated with endothelium-mediated arterial dilation in autoimmune thyroiditis with euthyroidism (18), which plays an important role in atherogenesis. In our study, we did not find the independent effect of

elevated TG-Ab on ILAS. These two autoantibodies arise independently in response to TG and TPO. Unlike TG-Ab, TPO-Ab was able to damage thyrocytes by an antibody-dependent cytotoxic mechanism and has long been known to be associated with lymphocytic infiltration of the thyroid gland (19). Our finding that lower FT4 levels were observed in patients with elevated TPO-Ab, though within the reference, potentially reflects the presence of thyroid cell damage. Moreover, in autoimmune thyroiditis, T cells from patients with a high TPO-Ab titer had significantly higher percentages of cells producing interferon (IFN)-γ compared with healthy donors, which suggests that high TPO-Ab titer correlates with increased frequencies of T cells producing Th/Tc1 cytokines (20,21). Previous studies have shown that there were abundant T cells in lesions of atherosclerosis, whereas inappropriate secretion of IFN-γ from Th1 cells is an important event in the development of atherosclerosis and plaque rupture (22). Therefore, further study may be needed to clarify the possible effect of T cells on the relationship between TPO-Ab and the pathogenesis of atherosclerosis in euthyroidism patients.

Age-related linear increases in systolic blood pressure, pulse pressure, as well as the early rise and late fall from age 50 to 60 years in diastolic blood pressure, are consistent with increased large artery stiffness (23). Increased arterial stiffness among hypertensive Chinese was independently associated with intracranial large artery disease, including stenosis and calcification (24). Moreover, diabetes mellitus was also found more frequently in older individuals (age ≥55 years) (25). Therefore, in our study, in order to reduce the influence of age-related risk factors on ILAS, we focused on young ischemic stroke patients aged ≤55 years old. Previous studies have reported that low high-density lipoprotein cholesterol, male gender, smoking, hypertension, and hyperhomocystinemia were the main risk factors of intracranial stenosis in young patients (26,27); however, we only found age and the presence of elevated TPO-Ab as predictors of ILAS.

In this study, we found more women in patients with elevated TPO-Ab, which is consistent with a prior study that revealed a clear female preponderance with high prevalence of TPO-Ab in the general population (9–12). The female : male ratio ranged from 1.8 to 4.4:1 in those studies, whereas it was 2.4:1 in our analyses. Monoclonal antibodies specific to estrogen receptors and progesterone receptors were found present in the human thyroid gland (28). Thus, there may be relevance between thyroid autoimmunity and sex hormone receptors. We also found that ILAS patients had low rate of AF in our study. Increases in cerebral atherosclerosis were found according to CHADS2 scores in patients with stroke with nonvalvular AF recently (29). However, we only recruited young patients aged ≤55 years old, and most of the AF patients had history of rhematic valvular disease, with lower prevalence of hypertension and diabetes. Thus, the decreased frequency of AF in ILAS patients may be explained by the absence of concomitant risk factors of artery atherosclerosis.

Our study limitations include the retrospective nature of our analyses, limited to a single academic institution. Multicenter studies are needed to validate our findings. Thyroid autoantibodies were not serially measured, and the imaging was performed in the setting of recent ischemia, whereas ILAS may have progressed over time. Prospective studies are needed to follow up the changes of intracranial large artery in patients with elevated thyroid

autoantibodies. Furthermore, patients with mild intracranial artery stenosis (<50%) were excluded, because patients with ILAS were defined as ≥50% stenosis of a major intracranial large artery according to previous criteria. This might underestimate the incidence of intracranial stenosis. Future study is needed to compare the relationship between serial imaging of those mild stenosis and thyroid autoantibodies.

In conclusion, our results indicate an independent association of elevated TPO-Ab level and ILAS in young stroke patients with euthyroid status. Our findings warrant further studies investigating the role of immune aberrancies in the pathogenesis of ILAS.

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Table 1

Baseline characteristics, thyroid function test, and prevalence of thyroid autoantibodies in stroke patients with and without ILAS

	ILAS (*n* = 121)	Non-ILAS (*n* = 230)	*P* value
Age, years	48.1 ± 7.1	46.5 ± 8.0	0.058
Female, *n* (%)	37 (30.6)	62 (27.0)	0.474
History			
Hypertension, *n* (%)	70 (57.9)	123 (53.5)	0.434
Diabetes, *n* (%)	27 (22.3)	48 (20.9)	0.754
Hyperlipidemia, *n* (%)	36 (29.8)	72 (31.3)	0.765
Current smoker, *n* (%)	43 (35.5)	103 (44.8)	0.095
Atrial fibrillation, *n* (%)	1 (0.8)	13 (5.7)	0.040*
Chinese ischemic stroke subclassification			0.000†
LAA, *n* (%)	104 (86.0)	74 (32.2)	
Cardiogenic stroke, *n* (%)	1 (0.8)	25 (10.9)	
Penetrating artery disease, *n* (%)	4 (3.3)	92 (40)	
Other etiology, *n* (%)	11 (9.1)	8 (3.5)	
Undetermined etiology, *n* (%)	1 (0.8)	31 (13.5)	
NIHSS	5.2 ± 5.6	4.4 ± 4.2	0.151
Blood pressure at admission			
Systolic blood pressure, mmHg	143.9 ± 25.1	149.1 ± 25.6	0.070
Diastolic blood pressure, mmHg	89.6 ± 15.2	88.5 ± 14.6	0.536
Blood lipid profile			
Triglycerides, mMol/l	1.71 ± 0.91	1.95 ± 1.32	0.489
Total Cholesterol, mMol/l	4.56 ± 1.04	4.41 ± 0.93	0.071
Low.density lipoprotein cholesterol, mMol/l	2.89 ± 0.78	2.80 ± 0.80	0.359
Homocysteine, umoI/I	15.67 ± 9.95	14.51 ± 8.72	0.271
Thyroid function test			
TT3, pM0l/l	1.52 ± 0.37	1.6 ± 0.38	0.072
FT3, pMol/l	4.30 ± 0.69	4.45 ± 0.72	0.050
TT4, nMol/l	108.76 ± 21.2	108.49 ± 19.28	0.905
FT4, pMol/l	15.26 ± 2.37	15.30 ± 2.05	0.895
h.TSH, mlU/ml	1.87 ± 1.57	2.15 ± 1.46	0.095
Thyroid autoantibodies			
Persons with elevated TG-Ab, *n* (%)	8 (6.6)	6 (2.6)	0.086
Persons with elevated TPO-Ab, *n* (%)	20 (16.5)	9 (3.9)	0.000†

Data presented as mean ± SD or percentage. ILAS, intracranial large artery stenosis; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; TG-Ab, antithyroglobulin antibody; TPO-Ab, antithyroperoxidase antibody; SD, standard deviation.

*$P < 0.05$;

†$P < 0.01$.

Table 2

Independent influencing factors for ILAS

Factors	OR	EXP(B) 95% CI	P value
Presence of elevated TPO-Ab	5.318	2.157–13.110	<0.001
Age	1.037	1.002–1.073	0.039
Atrial fibrillation	0.091	0.011–0.756	0.027

Adjusting for age, gender, history of diabetes mellitus, hypertension, atrial fibrillation, total glycerin, total cholesterol, low-density lipoprotein cholesterol, homocysteine and thyroid function test. ILAS, intracranial large artery stenosis; TPO-Ab, antithyroperoxidase antibody; OR, odds ratio; EXP (B), exponentiation of the B coefficient, which is an odds ratio; CI, confidence interval.

Table 3

Comparison of patients with and without elevated TPO-Ab levels

	TPO-Ab (+) (*n* = 29)	TPO-Ab (−) (*n* = 322)	*P*
Age, years	46.5 ± 7.8	47.1 ± 7.7	0.686
Female, *n* (%)	14 (48.3)	85 (26.4)	0.017*
Risk factors			
Hypertension, *n* (%)	13 (44.8)	180 (55.9)	0.251
Diabetes, *n* (%)	5 (17.2)	70 (21.7)	0.571
Hyperlipidemia, *n* (%)	5 (17.2)	103 (32.0)	0.099
Current smoker, *n* (%)	11 (37.9)	135 (41.9)	0.676
Atrial Fibrillation, *n* (%)	1 (3.4)	14 (4.0)	1.000
Blood lipid			
Total Glycerin, mMol/l	1.73 ± 1.24	1.88 ± 1.19	0.835
Total Cholesterol, mMol/l	4.57 ± 0.96	4.45 ± 0.97	0.337
LDL cholesterol, mMol/l	2.88 ± 0.74	2.83 ± 0.80	0.239
Homocysteine, umoI/I	15.51 ± 9.54	14.87 ± 9.16	0.602
ILAS, *n* (%)	20 (69.0)	101 (31.4)	0.000†
Stenotic artery of ILAS, *n* (%)			0.000†
ICA	0	10 (3.1)	
ACA	0	2 (0.6)	
MCA	6 (20.7)	34 (10.6)	
PCA	4 (13.8)	9 (2.8)	
BA	0	4 (1.2)	
MMD	3 (10.3)	8 (2.5)	
Multiple arteries (≥2 arteries)	7 (24.1)	34 (10.6)	
Percentage stenosis of affected artery			0.000†
<50%	9 (31.0)	221 (68.6)	
50–69%.	7 (24.1)	19 (5.9)	
70–99%.	6 (20.7)	51 (15.8)	
100% (include MMD)	7 (24.1)	31 (9.6)	
Thyroid Function Test			
TT3, pMol/l	1.65 ± 0.33	1.58 ± 0.38	0.316
FT3, pMol/l	4.39 ± 0.68	4.40 ± 0.72	0.940
TT4, nMol/l	108.0 ± 15.4	108.6 ± 20.3	0.859
FT4, pMol/l	14.41 ± 2.33	15.34 ± 2.13	0.022*
h.TSh, mlU/ml	2.45 ± 1.85	2.02 ± 1.46	0.139
Thyroid autoantibodies			
Persons with elevated TG-Ab, *n* (%)	10 (34.5)	4 (1.2)	0.000†

Data presented as mean ± SD or percentage. TPO-Ab (+) and (−) indicate patients with and without elevated TPO-Ab levels, respectively. TPO-Ab, antithyroperoxidase antibody; LDL, low-density lipoprotein; ILAS, intracranial large artery stenosis; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; MMD, Moyamoya disease; SD, standard deviation.

*$P < 0.05$;

†$P < 0.01$.