

Elevated Thyroid Autoantibodies and Intracranial Stenosis in Early-Onset Stroke

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**Abstract:**

**Background:** The correlation between thyroid autoimmunity and cerebrovascular diseases, particularly intracranial stenosis, is increasingly recognized. Early-onset stroke, occurring in individuals under 50 years, often involves non-traditional risk factors, including autoimmune disorders. Elevated thyroid autoantibodies, such as thyroid peroxidase (TPO) and thyroglobulin (TG) antibodies, have been implicated in vascular abnormalities. In patients with early-onset stroke, the study aims to investigate into the relationship between increased thyroid autoantibodies and intracranial stenosis.

**Methods:** A retrospective cohort study included 180 patients diagnosed with early-onset stroke. Data were collected from medical records, focusing on thyroid function tests, thyroid autoantibody levels, and imaging results for intracranial stenosis. Multivariate logistic regression, t-tests, and chi-square tests were used in the statistical analysis to determine whether higher thyroid autoantibodies independently caused intracranial stenosis.

**Results:** Intracranial stenosis was present in 40% of the patients. Elevated TPO antibodies were found in 62.5% of patients with intracranial stenosis compared to 25.0% without ( $p < 0.001$ ). Elevated TG antibodies were present in 54.2% of patients with intracranial stenosis compared to 25.0% without ( $p < 0.001$ ). Univariate analysis showed that elevated TPO antibodies (OR=4.75) and elevated TG antibodies (OR=3.44) were significantly associated with intracranial stenosis. Multivariate logistic regression confirmed these associations, with adjusted odds ratios of 4.23 for TPO and 3.16 for TG antibodies.

**Conclusion:** Elevated thyroid autoantibodies are significantly related with an elevated risk of intracranial stenosis in early-onset stroke patients. This suggests that thyroid autoimmunity plays a critical role in the pathogenesis of intracranial vascular abnormalities.

**Recommendations:** Routine screening for thyroid autoantibodies in young stroke patients is recommended to identify those at higher risk for intracranial stenosis. Further research is needed to explore the mechanisms linking thyroid autoimmunity to vascular abnormalities and to develop targeted therapeutic strategies.

**Keywords:** Thyroid Autoantibodies, Intracranial Stenosis, Early-Onset Stroke, Thyroid Peroxidase Antibodies, Thyroglobulin Antibodies.

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## Introduction

The relationship between thyroid autoimmunity and cerebrovascular diseases has gained considerable attention in recent years, particularly concerning the role of thyroid autoantibodies in stroke and intracranial stenosis (IS). Early-onset stroke, defined as stroke occurring in individuals under 50 years, poses unique clinical challenges and is often associated with non-traditional risk factors, including autoimmune disorders. Elevated thyroid autoantibodies, such as thyroid peroxidase (TPO) and thyroglobulin (TG) antibodies, have been implicated in the pathogenesis of various vascular abnormalities, including intracranial stenosis, a significant cause of stroke recurrence and morbidity.

Recent studies have highlighted the potential link between elevated thyroid autoantibodies and the development of IS. For instance, research has demonstrated that patients with hyperthyroidism and elevated TPO antibodies are at an increased risk of intracranial arterial stenosis. This association is particularly pronounced in patients with Graves' disease, an autoimmune disorder characterized by hyperthyroidism and high levels of thyroid autoantibodies [1]. The pathophysiological mechanisms underlying this association are not fully understood but are thought to involve immune-mediated vascular injury and inflammation.

In a study examining the incidence and clinical correlates of IS in stroke patients, it was found that the presence of elevated thyroid autoantibodies significantly raised the risk of IS. This was particularly evident in younger populations, suggesting a specific vulnerability in early-onset stroke patients [2]. The study emphasized the importance of considering thyroid autoimmunity as a potential contributing factor in the evaluation and management of stroke patients.

Moreover, autoimmune conditions like moyamoya disease, characterized by

progressive stenosis of the intracranial arteries, have also been associated with elevated thyroid autoantibodies. Patients with moyamoya disease often present with high levels of TPO and TG antibodies, indicating a possible autoimmune component to the disease's progression [3]. This further supports the hypothesis that thyroid autoimmunity may play a critical role in the development of intracranial vascular abnormalities.

The clinical implications of these findings are significant. Routine screening for thyroid autoantibodies in young stroke patients could help identify those at higher risk for IS, enabling earlier and more targeted interventions. Additionally, understanding the underlying mechanisms may lead to the development of novel therapeutic strategies aimed at reducing the burden of cerebrovascular diseases in patients with thyroid autoimmunity.

The study aims to investigate the association between elevated thyroid autoantibodies and intracranial stenosis in patients who experienced an early-onset stroke.

## Methodology

### *Study Design*

A retrospective cohort study.

### *Study Setting*

The study was done at a SCB Medical College specializing in neurological disorders, over a period of April 2022 to June 2023.

### *Participants*

A total of 180 participants were comprised in the study.

### *Inclusion Criteria*

1. Patients diagnosed with an early-onset stroke,

2. with available medical records including thyroid function tests and autoantibody profiles,
3. who underwent imaging studies for intracranial stenosis.

### **Exclusion Criteria**

1. Patients with a record of thyroid disease prior to the stroke,
2. with incomplete medical records,
3. with other significant comorbidities that could influence stroke outcomes (e.g., severe cardiovascular diseases, malignancies).

### **Bias**

To minimize selection bias, we ensured that all eligible patients meeting the inclusion criteria during the study period were included. Data extraction was performed by two independent reviewers to reduce information bias.

### **Variables**

Variables included presence of elevated thyroid autoantibodies, demographic factors (age, sex), risk factors for stroke (hypertension, diabetes, smoking status), presence of intracranial stenosis, confirmed through imaging studies (MRI, MRA).

### **Sample size:**

To calculate the sample size for this study, the following formula was used for estimating a proportion in a population:

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Where:

- n = sample size
- Z = Z-score corresponding to the desired level of confidence
- p = estimated proportion in the population
- E = margin of error

### **Data Collection**

Data were gathered from the electronic medical records. Information on thyroid function tests, thyroid autoantibody levels,

and imaging results for intracranial stenosis were extracted. Additional data on demographic factors and stroke risk factors were also gathered.

### **Procedure**

Patient records were reviewed, and relevant data were extracted systematically. Thyroid autoantibody levels were categorized as elevated or normal based on reference ranges. Imaging results were reviewed to confirm the presence of intracranial stenosis. The collected data were entered into a standardized database for analysis.

### **Statistical Analysis**

The study population's baseline characteristics were compiled using descriptive statistics. The variables were displayed as means, standard deviations, frequencies, and percentages. Chi-square tests were used to assess the relationship between high thyroid autoantibodies and intracranial stenosis, while t-tests were utilised to assess the relationship between continuous variables. To account for various confounders and ascertain the independent impact of high thyroid autoantibodies on the existence of intracranial stenosis, multivariate logistic regression analysis was conducted. Statistical significance was attained when the p-value was less than 0.05. The statistical software SPSS (version 25.0) was used for the analyses.

### **Ethical considerations:**

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

### **Result**

The study involved 180 patients in all, 102 (56.7%) of whom were male and 78 (43.3%) of whom were female. The participants' average age was 44.3 years ( $\pm$  5.2). Table 1 provides a summary of the research population's baseline characteristics.

**Table 1: Baseline Characteristics of the Study Population**

Variable	Total (N=180)	With Intracranial Stenosis (N=72)	Without Intracranial Stenosis (N=108)	p-value
Mean Age (years)	44.3 ± 5.2	45.1 ± 4.9	43.7 ± 5.4	0.054
Gender, n (%)				
Male	102 (56.7%)	42 (58.3%)	60 (55.6%)	0.742
Female	78 (43.3%)	30 (41.7%)	48 (44.4%)	
Hypertension, n (%)	96 (53.3%)	45 (62.5%)	51 (47.2%)	0.041*
Diabetes, n (%)	48 (26.7%)	24 (33.3%)	24 (22.2%)	0.105
Smoking Status, n (%)				
- Current smoker	54 (30.0%)	21 (29.2%)	33 (30.6%)	0.838
- Former smoker	36 (20.0%)	18 (25.0%)	18 (16.7%)	0.155
- Never smoker	90 (50.0%)	33 (45.8%)	57 (52.8%)	0.348
Elevated TPO antibodies, n (%)	72 (40.0%)	45 (62.5%)	27 (25.0%)	<0.001*
Elevated TG antibodies, n (%)	66 (36.7%)	39 (54.2%)	27 (25.0%)	<0.001*

\*Statistically significant at p<0.05

Out of the 180 patients, 72 (40.0%) had intracranial stenosis confirmed through imaging studies. The prevalence of intracranial stenosis was considerably higher in individuals with elevated TPO antibodies (62.5%) and elevated TG antibodies (54.2%) compared to those without elevated antibodies (25.0% for TPO and TG antibodies, both p<0.001).

The univariate analysis demonstrated a noteworthy correlation between elevated

thyroid autoantibodies and the presence of intracranial stenosis (Table 2). Individuals with elevated TPO antibodies had a significantly higher likelihood of intracranial stenosis (OR=4.75, 95% CI: 2.49-9.08, p<0.001). Similarly, elevated TG antibodies were also correlated with an elevated risk of intracranial stenosis (OR=3.44, 95% CI: 1.80-6.60, p<0.001).

**Table 2: Univariate Analysis of Factors Associated with Intracranial Stenosis**

Variable	OR (95% CI)	p-value
Age	1.05 (0.99-1.10)	0.096
Male	1.12 (0.61-2.05)	0.742
Hypertension	1.84 (1.02-3.33)	0.041*
Diabetes	1.75 (0.88-3.47)	0.112
Current smoker	0.94 (0.48-1.84)	0.857
Former smoker	1.63 (0.75-3.56)	0.214
Elevated TPO antibodies, n (%)	4.75 (2.49-9.08)	<0.001*
Elevated TG antibodies, n (%)	3.44 (1.80-6.60)	<0.001*

\*Statistically significant at p<0.05

To control for potential confounders, a multivariate logistic regression analysis was performed. After adjusting for age, sex, hypertension, diabetes, and smoking status,

elevated TPO and TG antibodies remained significant independent predictors of intracranial stenosis. The adjusted odds ratios (aOR) are presented in Table 3.

**Table 3: Multivariate Logistic Regression Analysis**

Variable	OR (95% CI)	p-value
Age	1.04 (0.98-1.11)	0.163
Male	1.05 (0.53-2.06)	0.898
Hypertension	1.58 (0.83-3.00)	0.167
Diabetes	1.41 (0.67-2.97)	0.363
Current smoker	0.88 (0.42-1.84)	0.736
Former smoker	1.41 (0.60-3.29)	0.428
Elevated TPO antibodies, n (%)	4.23 (2.12-8.46)	<0.001*
Elevated TG antibodies, n (%)	3.16 (1.61-6.21)	<0.001*

\*Statistically significant at  $p < 0.05$

## Discussion

Among the 180 participants, intracranial stenosis was found in 40% of the patients. A significant association was observed between elevated thyroid peroxidase (TPO) antibodies and intracranial stenosis, with 62.5% of those with elevated TPO antibodies presenting with the condition. Similarly, 54.2% of patients with elevated thyroglobulin (TG) antibodies had intracranial stenosis. In contrast, only 25.0% of patients without elevated antibodies showed intracranial stenosis, highlighting the statistical significance of these associations.

Univariate analysis revealed that patients with elevated TPO antibodies had an odds ratio (OR) of 4.75 for developing intracranial stenosis, while those with elevated TG antibodies had an OR of 3.44, both indicating a strong correlation. These relations remained considerable even after adjusting for potential confounders such as age, sex, hypertension, diabetes, and smoking status in a multivariate logistic regression analysis. The adjusted odds ratios were 4.23 for elevated TPO antibodies and 3.16 for elevated TG antibodies, further underscoring the independent predictive value of these biomarkers for intracranial stenosis.

The results suggest that thyroid autoimmunity may play a crucial role in the pathogenesis of intracranial stenosis in young stroke patients, independent of other traditional stroke risk factors. This finding

is clinically significant as it points to the potential benefit of incorporating thyroid autoantibody screening in the routine assessment of young patients with stroke. Identifying elevated thyroid autoantibodies could help in recognizing patients at higher risk for intracranial stenosis, thereby enabling more comprehensive and tailored management strategies. This may include additional endocrine evaluations and potentially earlier or more aggressive interventions to mitigate the risk of further cerebrovascular complications.

Particularly in individuals with early-onset stroke, recent research has demonstrated a strong correlation between increased thyroid autoantibodies and IS. Elevated antithyroperoxidase antibody (TPO-Ab) levels were shown to be substantially linked with intracranial stenosis in stroke patients with hyperthyroidism, with a 100% frequency in those with stenosis compared to 33.3% in those without [4]. Similarly, elevated TPO-Ab levels were more common (16.5% vs. 3.9%) in a group of 351 young ischemic stroke patients with cerebral major artery stenosis, and these levels were independently linked to the stenosis [5].

Even after accounting for vascular and demographic factors, additional studies revealed that increased TPO-Ab levels are associated with unfavourable arterial remodelling in individuals with intracranial stenosis [6]. Furthermore, higher NIHSS scores upon admission and discharge have been linked to poorer outcomes for patients

with acute ischemic stroke who had thyroid autoantibodies [7].

Furthermore, studies on patients with Moyamoya disease, which is defined by the gradual blockage of the cerebral carotid artery, revealed a greater frequency of increased thyroid autoantibodies in afflicted individuals, lending credence to the theory of an immune-mediated aetiology [8].

### Conclusion

The study emphasizes the significant relation between elevated thyroid autoantibodies and IS in early-onset stroke patients, suggesting that thyroid autoimmunity should be considered in the risk assessment and management of this patient population.

**Limitations:** The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

**Recommendation:** Routine screening for thyroid autoantibodies in young stroke patients is recommended to identify those at higher risk for intracranial stenosis. Further research is needed to explore the mechanisms linking thyroid autoimmunity to vascular abnormalities and to develop targeted therapeutic strategies.

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### List of abbreviations:

IS: Intracranial Stenosis

TPO: Thyroid Peroxidase

TG: Thyroglobulin

OR: Odds Ratio

CI: Confidence Interval

MRI: Magnetic Resonance Imaging

MRA: Magnetic Resonance Angiography

aOR: Adjusted Odds Ratio

TPO-Ab: Antithyroperoxidase Antibody

NIHSS: National Institutes of Health Stroke Scale

### References

1. Zhou H, Jing J, Pu Y, Li W, Meng X, Wang A, Zuo Y, Xu Z, Xu Q, Suo Y, Li H. Detailed phenotype of RNF213 p. R4810K variant identified by the Chinese patients with acute ischaemic stroke or transient ischaemic attack. *Stroke and Vascular Neurology*. 2023 Dec 1;8(6).
2. Christine C. Thyrotoxicosis. *MedLink Neurology*. 2006 Mar 13.
3. Kim SK, Lee JY, Wang KC. Pathophysiology of Moyamoya Disease. *Stroke Revisited: Hemorrhagic Stroke*. 2018:79-87.
4. Zhang X, Chen Z, Shi Z, Lou M. Correlation between thyroid autoantibodies and intracranial arterial stenosis in stroke patients with hyperthyroidism. *J Neurol Sci*. 2012;318(1-2):82-4.
5. Shi Z, Zhang X, Chen Z, Liebeskind D, Lou M. Elevated thyroid autoantibodies and intracranial stenosis in stroke at an early age. *Int J Stroke*. 2014;9(6):735-40.
6. Zhang X, Zhou Y, Ding W, Zhang R, Yan S, Deng Y, et al. TPO-Ab plays a role in arterial remodeling in patients with intracranial stenosis. *Atherosclerosis*. 2019;280:140-6.
7. Li J, Hu S, Liu F, Wu D, Song W, Hui M. Elevated thyroid autoantibodies aggravate stroke severity in euthyroidism with acute ischemic stroke. *Dis Markers*. 2022;2022.
8. Kim SJ, Heo K, Shin H, Bang O, Kim GM, Chung C, et al. Association of thyroid autoantibodies with moyamoya-type cerebrovascular disease: a prospective study. *Stroke*. 2010;41(1):173-6.