Increased Thyroid Function and Elevated Thyroid Autoantibodies in Pediatric Patients With Moyamoya Disease

A Case–Control Study

Hao Li, MS; Zheng-Shan Zhang, MM; Zhen-Nan Dong, MD; Mai-Juan Ma, MS; Wei-Zhong Yang, BS; Cong Han, MM; Ming-Mei Du, MD; Yun-Xi Liu, MD; Hong Yang, MS; Wei Liu, MD; Lian Duan, MD; Wu-Chun Cao, MD, PhD

Background and Purpose—The purpose of this study was to investigate whether thyroid function and thyroid autoantibodies were associated with the risk of moyamoya disease in pediatric subjects.

Methods—Thyroid function and thyroid autoantibodies were evaluated in patients with moyamoya disease and control subjects, and their associations with moyamoya disease were estimated using multivariate analysis.

Results—We included 114 pediatric patients and 114 healthy control subjects. The patients displayed higher prevalence of increased thyroid function and elevated thyroid autoantibodies in comparison with control subjects. These remained significant after multivariate adjustment; the ORs (95% CI) for increased thyroid function and evaluated thyroid autoantibodies were evaluated as 12.47 (1.55 to 100.51) and 4.33 (1.29 to 14.59), respectively.

Conclusions—Increased thyroid function and elevated thyroid autoantibodies are associated with moyamoya disease and therefore monitoring of thyroid function and thyroid autoantibodies in patients with moyamoya disease is suggested, which might help to guide subsequent clinical management. (Stroke. 2011;42:00-00.)

Key Words: moyamoya disease ■ thyroid autoantibodies ■ thyroid function

Moyamoya disease (MMD) as well as several other cerebrovascular diseases has been demonstrated for their associations with thyroid disease.1–3 Recently a high prevalence of thyroid autoantibodies was observed in patients with adult-type MMD,4 indicating the potential role of thyroid autoantibodies in adult-type MMD, which role, however, remains largely unknown in pediatric MMD. Using a case–control design, we investigated the contribution of abnormal thyroid function and thyroid autoantibodies to the risk of MMD in Chinese pediatric subjects.

Materials and Methods

We prospectively recruited pediatric patients (<16 years) with MMD at the Department of Neurosurgery, 307 Hospital, from May 2007 to June 2010. Age-matched healthy individuals confirmed by physical examination were selected as control subjects. Patients’ inclusion and exclusion criteria are provided in the online supplement (http://stroke.ahajournals.org).

Routine clinical and laboratory tests were performed in all subjects with additional details in the online supplement. Briefly, free-triiodothyronine, free-thyroxine, thyroid-stimulating hormone, antithyroperoxidase, and antithyroglobulin were measured by ADVIA Centaur (Siemens Healthcare Diagnostics).

All subjects were grouped into 3 grades: increased thyroid function (overt and subclinical hypothyroidism), decreased thyroid function (overt and subclinical hyperthyroidism), and euthyroidism according to the criteria in the online supplement. Elevated thyroid autoantibodies were determined as either antithyroperoxidase or antithyroglobulin >60 U/mL in accordance with the manufacturer’s reference.

Data were analyzed using SPSS 15.0. Continuous data were compared by paired t test or Wilcoxon test where appropriate, whereas categorical data were compared by McNemar test. The effects of increased thyroid function and elevated thyroid autoantibodies on MMD risk were estimated by forward stepwise conditional logistic regression analysis in Model A and Model B, respectively. Any variable with a probability value <0.15 in univariate analysis was considered for inclusion in the multivariate model.

Results

We included 114 patients with MMD and 114 healthy control subjects. Clinical and laboratory characteristics are presented in the Table and Supplemental Table 1. In comparison with control subjects, patients with MMD demonstrated with higher levels of total cholesterol, homocysteine, and family history of cerebrovascular disease (P<0.5 for all). Increased thyroid function and elevated thyroid autoantibodies were observed more frequently in patients than in control subjects (10.5% versus 0.9%, P=0.003; 13.2% versus 3.5%, P=0.019, respectively).

Received November 11, 2010; accepted November 23, 2010.
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The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.608471/DC1.

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DOI: 10.1161/STROKEAHA.110.608471
Table. Clinical and Laboratory Characteristics in Patients With MMD and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (N=114)</th>
<th>Controls (N=114)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>9.9±3.3</td>
<td>9.7±3.5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>53.5</td>
<td>47.4</td>
<td>0.435‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>83±17</td>
<td>82±14</td>
<td>0.714†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>111±15</td>
<td>109±11</td>
<td>0.264†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>68±11</td>
<td>69±9</td>
<td>0.671†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.00±0.71</td>
<td>3.80±0.72</td>
<td>0.040‡</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.20±0.62</td>
<td>1.07±0.37</td>
<td>0.050†</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>3.35±0.30</td>
<td>3.14±0.26</td>
<td>0.790‡</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.12±0.45</td>
<td>2.15±0.54</td>
<td>0.675†</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>11.08±5.29</td>
<td>9.79±4.28</td>
<td>0.047*</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.89±0.36</td>
<td>4.78±0.45</td>
<td>0.389†</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>43.3±3.6</td>
<td>43.3±3.3</td>
<td>0.907†</td>
</tr>
<tr>
<td>WBC count, 10³/μL</td>
<td>6.21±1.67</td>
<td>6.50±1.64</td>
<td>0.142†</td>
</tr>
<tr>
<td>Lymphocyte count, 10³/μL</td>
<td>2.49±0.79</td>
<td>2.53±0.84</td>
<td>0.682†</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>43±10</td>
<td>41±10</td>
<td>0.089*</td>
</tr>
<tr>
<td>Uric acid, μmol/L</td>
<td>287±64</td>
<td>283±69</td>
<td>0.680‡</td>
</tr>
<tr>
<td>Heart disease</td>
<td>0.9</td>
<td>0</td>
<td>1.000†</td>
</tr>
<tr>
<td>Family history of cerebrovascular disease</td>
<td>14.0</td>
<td>5.3</td>
<td>0.041‡</td>
</tr>
</tbody>
</table>

Thyroid function abnormalities

- Increased thyroid function: 10.5 (9) 0.003‡
- Subclinical hyperthyroidism: 6.1 (9)
- Hyperthyroidism: 4.4 (0)
- Decreased thyroid function: 3.5 (1.8) 0.687‡
- Subclinical hypothyroidism: 3.5 (1.8)
- Elevated thyroid autoantibodies: 13.2 (3.5) 0.019†
- TPOAb-positive: 11.4 (1.8)
- TGAb-positive: 12.3 (3.5)

MMD indicates moyamoya disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell; TPOAb, antithyroperoxidase; TGAb, antithyroglobulin.

Data presented as mean±SD or percentage.

*Wilcoxon test.
†Paired t test.
‡McNemar test.

In Model A in which thyroid function was evaluated, we observed a significant association between increased thyroid function and higher risk of MMD (OR, 12.47; 95% CI, 1.55 to 100.51; P=0.018) after adjustment for covariables, including total cholesterol, triglyceride, homocysteine, glucose, creatinine, white blood cell count, and family history of cerebrovascular disease, although in Model B in which thyroid autoantibodies were included, elevated thyroid autoantibodies were significantly correlated with an increased risk of MMD (OR, 4.33; 95% CI, 1.29 to 14.59; P=0.018). All variables finally included in the models are given in Supplemental Table II.

Discussion

In the present study, we demonstrated that the risk of MMD was substantially augmented for increased thyroid function and elevated thyroid autoantibodies with statistical significance. To our knowledge, this is the first study to describe the prevalence of thyroid function abnormalities and thyroid autoantibodies in a large population of pediatric patients with MMD. It is worth noting that the significantly higher prevalence of overt plus subclinical hyperthyroidism in the patients with MMD than in control subjects provided strong evidence that thyroid function abnormalities might play roles in MMD development.

The study design does not allow elucidation of the mechanism whereby thyroid function and thyroid autoantibodies are associated with MMD. Previous studies used to suggest several arguments for the association between thyroid disease and MMD. First, excessive thyroid hormones are thought to augment cerebral metabolism and oxygen consumption and be harmful to arterial walls. Second, sympathetic nervous activity could be enhanced in thyrotoxicosis and thereby may contribute to the stenosis of cerebral arteries. Finally, T-cell dysfunction related to immunologic stimulation of the thyroid in thyroid disease may be involved in cellular proliferation and vascular dysregulation.

Several limitations should be addressed. First, selection bias cannot be completely excluded when our patients came from all over the country, whereas the majority of control subjects resided locally. However, the prevalence of overt plus subclinical hyperthyroidism in our control subjects is comparable with that reported by Teng et al, which provided partial evidence that our control subjects might be well representative of the general population. Second, due to the incapability of following up these patients, the clinical significance of increased thyroid function and elevated thyroid autoantibodies remains unknown in the current stage.

Based on the results from the present study, monitoring of thyroid function and thyroid autoantibodies in patients with MMD is suggested, which might help to guide subsequent clinical management.

Sources of Funding

This study was supported by grants from the National Science Fund for Distinguished Young Scholars (30725032) and the Capital Medical Science Development (ZD1999008).

Disclosures

None.

References

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Stroke. published online February 24, 2011;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/early/2011/02/24/STROKEAHA.110.608471

Data Supplement (unedited) at:
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Increased thyroid function and elevated thyroid autoantibodies in pediatric patients with moyamoya disease: a case-control study

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Cover title: Thyroid function and thyroid autoantibodies in MMD
Number of Tables: 1
Key Words: moyamoya disease □ thyroid function □ thyroid autoantibodies
Word count: 1498
Supplemental Materials and Methods
The diagnosis for MMD was made by use of digital subtraction angiography and/or magnetic resonance angiography or magnetic resonance imaging, based on the guidelines published in 1997. From May 2007 to June 2010, totally 670 patients (including 195 pediatric patients) with MMD-type cerebrovascular disease from all over the country were treated in the hospital. Among the pediatric patients, 28 with unilateral lesions (probable MMD), 8 with atherosclerosis, Down syndrome, meningitis, neurofibromatosis, or prior skull-base radiation therapy (moyamoya syndrome), 5 with goiter and 3 with clinical symptoms of thyroid disease were excluded. Finally 114 (75.5%) of the remaining 151 pediatric patients agreed to participate in the study.

Blood pressure was measured with a standard mercury manometer after a 15 minutes rest in a sitting position. Heart rate obtained from electrocardiography was also recorded. Peripheral blood samples were taken in the morning after the subjects had fasted for at least 12 hours. Fasting blood was used to determine total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, homocysteine, glucose, uric acid, creatinine, albumin, white blood cell (WBC) count and lymphocyte count. Briefly, thyroid function was assessed by competitive immunoanalysis for free-triiodothyronine (FT3) and free-thyroxine (FT4), as well as sandwich immunoanalysis for thyroid-stimulating hormone (TSH). Serum thyroid autoantibodies were assessed by direct chemiluminometric technology for anti-thyroperoxidase (TPOAb) and anti-thyroglobulin (TGAb).

Overt and subclinical hyperthyroidism were biochemically defined as TSH below the lower limit of the manufacturer’s reference range (0.350–5.500 μIU/mL) combined with FT4 (10.45–24.30 pmol/L) and FT3 (2.8–6.3 pmol/L) concentrations above or within the manufacturer’s reference range, respectively. Overt and subclinical hypothyroidism were biochemically defined as elevated TSH combined with FT4 and FT3 concentrations below or within the reference range, respectively. Overt and subclinical hyperthyroidism were categorized into increased thyroid function, while overt and subclinical hypothyroidism as with decreased thyroid function.
### Supplemental Tables

#### Table S1. Clinical Manifestations of Pediatric Patients with MMD

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Patients (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia¹</td>
<td>93 (81.6)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>10 (8.8)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Choreiform movement</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Cognitive psychiatric change</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

¹ included infarction and transient ischemic attacks.
Table S2. Effects of Increased Thyroid Function (Model A) and Elevated Thyroid Autoantibodies (Model B) on the Risk of MMD Separately: Forward Stepwise Conditional Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model A†</th>
<th></th>
<th>Model B†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>1.08 (1.00-1.16)</td>
<td>0.033</td>
<td>2.12 (1.10-4.08)</td>
<td>0.025</td>
</tr>
<tr>
<td>Family history of cerebrovascular disease</td>
<td>3.31 (1.18-9.29)</td>
<td>0.023</td>
<td>Homocysteine</td>
<td>1.09 (1.01-1.17)</td>
</tr>
<tr>
<td>Increased thyroid function</td>
<td>12.47 (1.55-100.51)</td>
<td>0.018</td>
<td>Family history of cerebrovascular disease</td>
<td>5.09 (1.66-15.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Elevated thyroid autoantibodies</td>
<td>4.33 (1.29-14.59)</td>
</tr>
</tbody>
</table>

In forward stepwise conditional logistic regression models, variables were entered into the model with a P value of 0.05 being the probability for stepwise inclusion and a P value of 0.10 being the probability for stepwise exclusion.

†Model A with regard to thyroid function. Variables not finally entered into the model: total cholesterol (P=0.096), triglyceride (P=0.070), glucose (P=0.227), creatinine (P=0.098) and WBC count (P=0.429).

†Model B with regard to thyroid autoantibodies. Variables not finally entered into the model: total cholesterol (P=0.136), glucose (P=0.208), creatinine (P=0.068) and WBC count (P=0.186).
Supplemental References


2. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. Jama. 2004;291:228-238
