Moyamoya disease is an uncommon cerebrovascular occlusive disease of unknown pathogenesis. Previously described Moyamoya cohorts include predominantly Asian populations or ethnically diverse North American cohorts. To gain further insight into the pathogenesis of moyamoya, we examined clinical characteristics of a primarily white, Midwestern US population.

**Methods**—Retrospective analysis of patients with angiographically confirmed moyamoya disease evaluated at our institution was performed. Prevalence of comorbidities, cerebrovascular risk factors, and autoimmune diseases were compared with the general population.

**Results**—Ninety-four patients with moyamoya were evaluated; 72.3% were female. Ethnic composition was primarily white (85%). A significantly higher prevalence of autoimmune disease was seen, particularly type 1 diabetes mellitus (8.5% versus 0.4% in the general population) and thyroid disease (17.0% versus 8.0% in the institutional general patient population). Hyperlipidemia was also increased (27.7% versus 16.3% in the general population).

**Conclusions**—This study of a unique, primarily white, Midwestern population of moyamoya patients demonstrates a significantly higher prevalence of autoimmune disease than in the general population. This supports a possible autoimmune component to the pathogenesis of moyamoya disease.

**Key Words:** immunology ■ moyamoya ■ pathogenesis ■ risk factor
among the general population, taken from national statistics, except for thyroid disease prevalence, which was obtained from our institutional database (see the online-only Data Supplement).

**Statistical Analysis**
Statistical analyses were performed using JMP statistical software (version 9.0.1, Cary, NC). Frequencies were calculated with means, medians, and SD. Comparisons between groups were made using χ² test, and differences were considered significant with a P value <0.05.

**Results**

**Demographics**
Ninety-four patients met inclusion criteria. Female patients constituted 72.3%. The mean age at presentation was 34.5 years. Patient races included the following: white (85.1%), Asian (8.5%), black (5.3%), and Native American (1.1%). One patient had a family history of moyamoya (sibling). Patient demographics are shown in Table 1.

**Anatomic Extent of Moyamoya**
The majority (86.2%) of patients had bilateral disease; 13.8% of patients had unilateral disease (Table 1). Multiple anterior circulation arteries were involved in 67.0% of patients, with 15.9% of patients having isolated internal carotid artery disease. Isolated M1 stenosis at the origin, with moyamoya collaterals, was seen in 7.4% of patients. Stenosis extending to the posterior circulation was present in 10.6% of patients. Clinical moyamoya presentations are shown in Table 1.

**Comorbidities**
Among conditions with a well-known moyamoya association, neurofibromatosis type 1 was found in 2 patients and Down syndrome was found in 1 patient.

**Cerebrovascular Risk Factors**
We found the presence of hyperlipidemia in 26.6% of patients, hypertension in 20.2%, current or previous tobacco use in 12.8%, type 2 diabetes mellitus in 5.3%, history of radiation to the head in 5.3%, history of head trauma in 4.3%, and fibromuscular dysplasia in 3.2% of patients. Among these, cerebrovascular risk factors were compared with US population prevalence (Table 2). Prevalence of hyperlipidemia was significantly higher in our cohort compared with the general population (P=0.003; χ² test). However, our cohort did not display a significant difference among other factors.

**Autoimmune Disease**
We found a high prevalence of type 1 diabetes mellitus and thyroid disease among our moyamoya cohort (Table 2). Type 1 diabetes mellitus was noted in 8 patients (8.5%), significantly higher than in the general US population (0.4%; P<0.001, χ² test). Thyroid diseases, specifically Graves disease (2.1%) and thyroiditis (14.9%), were significantly higher than in the institutional general population (0.43% and 7.6%; P=0.01 and 0.007, respectively, χ² test).

Other autoimmune diseases included the following: autoimmune gastritis, Takayasu arteritis, primary biliary cirrhosis, juvenile rheumatoid arthritis, and thrombotic thrombocytopenic purpura (1 patient each). Twenty-one patients (22.3%) had autoimmune disease of any kind, significantly higher than the 3.2% estimated prevalence of autoimmune disease in the general population (P<0.001, χ² test). There was a higher preponderance of females among those with autoimmune disease (F:M ratio 2.5:1), and 90.5% were white.

**Discussion**
We present here characteristics of a Midwestern moyamoya patient population, composed of a higher percentage of white patients than other US moyamoya studies (Table I in the online-only Data Supplement). The pathogenesis of moyamoya remains unclear. A genetic role has been theorized within East Asian countries where moyamoya is more common. However, less is known about the pathogenesis of moyamoya within white, North American patients.

An unusually high prevalence of autoimmune disease, particularly type 1 diabetes mellitus and thyroid disease, was present in our cohort, which may suggest an underlying autoimmune component to moyamoya. Elevated thyroid autoantibodies and endothelial cell autoantibodies have
been found among moyamoya patients as well, lending further support to this theory. A significantly higher rate of hyperlipidemia was seen in our moyamoya cohort than in the general population. The reason for this is unclear, although it is a known association with other occlusive vascular diseases, as well as untreated hypothyroidism.

Moyamoya presenting concurrently with another specific autoimmune disease has been described in multiple case reports in the literature. This is the first series to our knowledge in which autoimmune disease in general has been investigated among moyamoya patients and a higher overall prevalence observed. The study may be limited by referral bias of our tertiary care institution; ascertainment bias in determination of thyroid disease prevalence; and absence of age-, sex- and race-matching of data. Future studies directed toward assessment of the immune system may shed further light on the elusive pathogenesis of moyamoya and, perhaps, help clinicians better anticipate the possibility of one after the other is diagnosed.

**Disclosures**

None.

**References**


**Table 2. Comorbidities**

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Number of Patients (%)</th>
<th>Prevalence in general US population, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>26 (27.7)</td>
<td>16.3&lt;sup&gt;12&lt;/sup&gt;</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (20.2)</td>
<td>24.7&lt;sup&gt;13&lt;/sup&gt;</td>
<td>0.38</td>
</tr>
<tr>
<td>Current or previous tobacco use</td>
<td>12 (12.8)</td>
<td>19.3&lt;sup&gt;13&lt;/sup&gt;</td>
<td>0.13</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>6 (6.4)</td>
<td>7.9&lt;sup&gt;11&lt;/sup&gt;</td>
<td>0.74</td>
</tr>
<tr>
<td>Autoimmune disease of any kind</td>
<td>21 (22.3)</td>
<td>3.2&lt;sup&gt;14&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>8 (8.5)</td>
<td>0.4&lt;sup&gt;11&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves disease (hyperthyroid)</td>
<td>2 (2.1)</td>
<td>0.43*</td>
<td>0.01</td>
</tr>
<tr>
<td>Hashimoto thyroiditis (hypothyroid)</td>
<td>14 (14.9)</td>
<td>7.6*</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Data from Mayo Clinic Database, as described in Methods.*
Moyamoya Disease in a Primarily White, Midwestern US Population: Increased Prevalence of Autoimmune Disease
Regina S. Bower, Grant W. Mallory, Macaulay Nwojo, Yogish C. Kudva, Kelly D. Flemming and Fredric B. Meyer

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SUPPLEMENTAL MATERIAL

Moyamoya disease in a primarily Caucasian Midwestern U.S. population: Increased prevalence of autoimmune disease
Regina S. Bower, MD1; Grant W. Mallory, MD1; Macaulay Nwojo, BS1; Yogish C. Kudva, MD2; Kelly D. Flemming, MD3; Fredric B. Meyer, MD1
Departments of Neurosurgery1, Endocrinology2, and Neurology3, Mayo Clinic College of Medicine

Corresponding Author:
Dr. Fredric B. Meyer
200 First Street SW
Rochester, MN 55905
Phone: 507-284-5317
Fax: 507-284-5206
Email: meyer.fredric@mayo.edu

Supplemental Methods

After obtaining approval through our Institutional Review Board, a search of the clinical database was conducted for adult patients seen at our institution between 1979 and 2011 with a diagnosis of moyamoya disease. Retrospective chart review was conducted on all patients that had approved use of their records for research (two patients were eliminated due to non-consent). Patients with angiographically-confirmed moyamoya disease diagnosis were included; patients with intracranial atherosclerosis, intracranial dissection, vasculitis, and undefined inflammatory processes were excluded. Data collected included race (based on patient self-report), age at presentation, clinical presentation events, angiographic findings (laterality and involved arteries), relevant family history, and other comorbidities; specifically, syndromes with a known association with moyamoya, accepted risk factors for stroke, and autoimmune diseases. In addition, all patients were sent a brief, one and a half-page questionnaire to update and supplement the data found within the medical record. Specifically, the questionnaire asked for or confirmed race, details of their moyamoya presentation and diagnosis, relevant family history and any other comorbidities diagnosed since they were last seen. Follow up phone calls were made after four weeks for patients who had not responded. Questionnaires were returned or done by phone for 24 patients (25.5%).

Prevalence of comorbidities were analyzed and compared with prevalence among the general population. Cerebrovascular risk factors included hyperlipidemia, hypertension, history of tobacco use, type 2 diabetes mellitus, and fibromuscular dysplasia. In addition, history of radiation to the head and head trauma were investigated. Autoimmune disease was assessed, and thyroid disease was confirmed as autoimmune in nature by confirming that there was no other clear cause. All comorbidities were defined by clinical diagnosis in the patient’s medical record. Medical records were reviewed on those with a diagnosis of type 1 diabetes mellitus to confirm type 1 rather than insulin-dependent type 2. All patients had classic clinical characteristics of type 1 diabetes. Specifically, all except two were diagnosed with type 1 diabetes as children (age range 5-13). One patient was
diagnosed at age 20, and the age and details of diagnosis in the remaining patient are unknown as he was diagnosed elsewhere and was not evaluated by Endocrinology during his evaluation at our institution. He carried a diagnosis of “very longstanding type 1 diabetes mellitus” according to his chart. Among those diagnosed in childhood, all had typical clinical characteristics of type 1 diabetes at diagnosis. The 20 year old patient presented in diabetic ketoacidosis and with recent weight loss. Two patients were found to have diabetes autoantibodies (GAD65 Ab in one, insulin Ab in one), although laboratory immunology studies were unavailable on most patients. With regard to hyperlipidemia, patients were included who were on statin therapy, or who displayed elevation of one or more lipid measurements by the following current definitions: cholesterol >200mg/dL, triglycerides >150mg/dL, LDL >100mg/dL.

Data on prevalence of risk factors, autoimmune disease, and type 1 diabetes among the general population were taken from national statistics\(^1\)\(^3\). Prevalence of thyroid disease in the general population varies significantly from region to region. Therefore, we determined prevalence of thyroid disease among the adult (age >17 years) patient population at our institution for more accurate comparison. The clinical patient database between 2008 and 2011 from our institution identified 8,947 patients from Olmsted County with diagnoses of hypothyroidism or hyperthyroidism (using ICD-9 codes 244.9 and 242.9, respectively). There were 145,411 unique Olmsted County patient medical record numbers seen during that time period. We calculated the prevalence of thyroid disease as patients with these diagnoses divided by the total number of unique patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Year(s)</th>
<th>No. of moyamoya patients</th>
<th>% Caucasian patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>Rochester, MN</td>
<td>1979-2011</td>
<td>94</td>
<td>85.1%</td>
</tr>
<tr>
<td>Starke et. al, 2012(^4)</td>
<td>National U.S.</td>
<td>2002-2008</td>
<td>2280</td>
<td>49%</td>
</tr>
<tr>
<td>Lee and Liebeskind, 2011(^5)</td>
<td>National U.S.</td>
<td>1988-2004</td>
<td>2247</td>
<td>35.4%</td>
</tr>
<tr>
<td>Uchino et. al, 2005(^6)</td>
<td>Western U.S. (Washington and California)</td>
<td>1987-1998</td>
<td>298</td>
<td>Not reported, but racial analysis revealed a multi-racial mix representative of the state of California</td>
</tr>
<tr>
<td>Numaguchi et. al, 1997(^7)</td>
<td>8 institutions (across U.S.)</td>
<td>1997</td>
<td>54*</td>
<td>65%</td>
</tr>
</tbody>
</table>

Table S1. Comparison between race representation in our study and prior U.S. population studies. *54 patients out of a total of 98 identified their race in this study.
References