Moyamoya Disease in a Primarily White, Midwestern US Population
Increased Prevalence of Autoimmune Disease

Regina S. Bower, MD; Grant W. Mallory, MD; Macaulay Nwojo, BS; Yogish C. Kudva, MD; Kelly D. Flemming, MD; Fredric B. Meyer, MD

Background and Purpose—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. (Stroke. 2013;44:1997-1999.)

Key Words: immunology ■ moyamoya ■ pathogenesis ■ risk factor

Moyamoya disease is an uncommon cerebrovascular condition characterized by stenosis or occlusion of the anterior circulation vasculature of the brain, with development of a network of collateral vessels resembling a puff of smoke on angiography.1 The epidemiology of moyamoya is well described in the literature among East Asian populations.2 Incidence of moyamoya disease in Japan has been reported as 0.35 per 100,000.3 Moyamoya has been described in all races and ethnicities worldwide,4 with a reported incidence in the Western United States of 0.086 per 100,000.5 Less is known about moyamoya among North Americans, in particular, whites. Recent North American studies have described the epidemiological characteristics of moyamoya in the Western United States, Missouri, and across the United States.5-7 However, these cohorts were diverse in their racial and ethnic make-up.

The pathogenesis of moyamoya is not well understood. A genetic role has been postulated, supported by the much higher incidence of moyamoya and familial moyamoya among Asians and Asian-Americans.5,4 However, the pathogenesis underlying moyamoya among other ethnicities, and within North American populations, is less clear. An immunologic basis has also been suggested, and recent reports have noted an association between moyamoya and autoimmune diseases, including Graves disease and systemic lupus erythematosus.9,10 Analysis of comorbidities may be helpful in determining the pathogenesis of moyamoya. However, this has been lacking in many studies. Among the US studies, stroke risk factors were assessed in 2, but no other comorbidities were assessed, other than well-known associated syndromes.5-7 We, therefore, sought to determine the epidemiological characteristics and comorbidities of the unique, primarily white, Midwestern US population of moyamoya patients at our institution.

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. Prevalence of comorbidities, cerebrovascular risk factors, and autoimmune diseases were compared with the general population.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.000307/-/DC1.

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.000307
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 \( \chi^2 \) 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 (\( P=0.003; \chi^2 \) 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%; \( P<0.001, \chi^2 \) 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, \( \chi^2 \) 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 (\( P<0.001, \chi^2 \) 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


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Stroke. 2013;44:1997-1999; originally published online May 7, 2013; doi: 10.1161/STROKEAHA.111.000307

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/44/7/1997

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/06/21/STROKEAHA.111.000307.DC1

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SUPPLEMENTAL MATERIAL

Moyamoya disease in a primarily Caucasian Midwestern U.S. population: Increased prevalence of autoimmune disease
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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. 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</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</td>
<td>National U.S.</td>
<td>2002-2008</td>
<td>2280</td>
<td>49%</td>
</tr>
<tr>
<td>Lee and Liebeskind, 2011</td>
<td>National U.S.</td>
<td>1988-2004</td>
<td>2247</td>
<td>35.4%</td>
</tr>
<tr>
<td>Uchino et. al, 2005</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</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


