

Comparison of Stroke Risk Factors between Symptomatic and Asymptomatic Patients in a North American Moyamoya Disease Cohort

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Keywords

Moyamoya · Angiopathy · Stroke · Risk factors

Abstract

Background: Risk factors for stroke in symptomatic and asymptomatic moyamoya disease (MMD) patients have recently been reported in a Japanese cohort. Such information in a North American population is lacking. **Objective:** We sought to elucidate the prevalence of stroke risk factors among North American patients with ischemic, hemorrhagic, and asymptomatic MMD. **Methods:** We retrospectively reviewed our institution's database between 1990 and 2021. We excluded cases of moyamoya syndrome. We divided 119 patients into 3 groups based on the onset pattern; ischemic, hemorrhagic, and asymptomatic. We compared the prevalence of well-known stroke risk factors (diabetes, hypertension, etc.) between these three groups of patients. In the asymptomatic group, we analyzed the prevalence of cerebrovascular events on follow-up from the time of diagnosis. **Results:** Overall, 119 patients with MMD were available with predominately White ethnicity (80.7%). The mean age was 39 years, and 73.9% were female. Patients presented with ischemic stroke (82%) and hemorrhagic stroke (11%); 7% of

patients were asymptomatic. The prevalence of stroke risk factors did not differ among ischemic, hemorrhagic, or asymptomatic MMD patients. In 8 asymptomatic patients, there was 81.8 months (SD ±51.0) of follow-up, and none of them developed any cerebrovascular events. **Conclusions:** No significant differences in the prevalence of stroke risk factors between MMD cohorts were found, corroborating evidence provided in a recent Japanese-based study. There were no apparent associations between stroke risk factors and interval cerebrovascular events in an asymptomatic group of MMD patients.

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Introduction

Moyamoya disease (MMD) is a rare cerebrovascular condition characterized by progressive narrowing of distal internal carotid arteries and development of a prominent network of cerebral collateral vessels [1, 2]. The most common presentation of MMD is stroke or TIA [3, 4]. In a Japanese population, Hirano et al. [5] recently reported that there was no significant difference in baseline stroke risk factors between patients with MMD with either is-

Table 1. Baseline characteristics

Patient characteristics	
Female, <i>n</i> (%)	88 (73.94)
Age at diagnosis (mean ± SD)	39.0±11.5
Race/ethnicity, <i>n</i> (%)	
White	96 (80.67)
Asian	10 (8.40)
Black	3 (2.52)
Other	10 (8.40)
DM, type 1, <i>n</i> (%)	4 (3)
DM, type 2, <i>n</i> (%)	18 (15)
HTN, <i>n</i> (%)	52 (43)
HLD, <i>n</i> (%)	49 (41)
Current smoker, <i>n</i> (%)	31 (26)
Former smoker, <i>n</i> (%)	58 (48)
Heavy alcohol use, <i>n</i> (%)	11 (10)

DM, diabetes mellitus.

chemic, hemorrhagic, or asymptomatic presentations. However, hypertension (HTN) and dyslipidemia were risk factors for development of cerebrovascular events in patients that were initially asymptomatic at presentation. The purpose of our study was to provide a similar comparison of stroke risk factors between symptomatic and asymptomatic patients, but in a North American MMD cohort. We also analyzed the prevalence of follow-up cerebrovascular events in a small group of asymptomatic MMD patients.

Methods

Study Population

Subjects provided their written informed consent for inclusion in this study. The study protocol was approved by the Mayo Clinic Institutional Review Board (IRB). This study was completed in accordance with the World Medical Association Declaration of Helsinki. We searched MMD adult patients (≥18 years) from our institution's clinical database from 1990 to 2021. The requirement of patient informed consent was waived. All patients with definitive diagnosis of MMD based on the criteria of clinically accepted guidelines were included [6]. Included patients were grouped by their initial presentation: asymptomatic, ischemic, and hemorrhagic. Patients meeting criteria for moyamoya syndrome were excluded. The presence of stroke-related risk factors at the initial MMD-related clinical presentation (i.e., diabetes, hyperlipidemia [HLD], etc.) was noted, and their prevalence was compared between groups. Asymptomatic patients were also compared to a broader "symptomatic" patient group which included both hemorrhagic and ischemic presentations.

Diagnostic Criteria

The following diagnostic criteria were utilized: diabetes mellitus was defined as patients who had a fasting blood glucose >126 mg/dL or 7.0 mmol/L, hemoglobin A1c ≥6.5%, or used oral anti-diabetic medication/insulin, HTN in patients who had measured systolic blood pressure ≥140 mm Hg, or used antihypertensive medication, HLD in patients with low-density lipoprotein ≥140 mg/dL, triglyceride >150 mg/dL, or used a lipid-lowering medication, and heavy alcohol use as >40 g/day or 200 g/week.

Statistical Analysis

Statistical analysis was done using SciPy (version 1.6.2), a scientific computing library using Python programming language (version 3.9.2). Univariate statistical comparison between the asymptomatic, ischemic, and hemorrhagic groups was performed. The χ^2 test was used to compare categorical data, while Kruskal-Wallis test was used to compare age between the three different groups given its nonnormal distribution. *p* values for each variable comparison were stated. A *p* value threshold of 0.05 was considered statistically significant.

Results

Out of 119 MMD subjects, there were 98 (82%) ischemic, 13 (11%) hemorrhagic, and 8 (7%) asymptomatic presentations. Baseline characteristics and risk factors are summarized in Table 1. The mean age was 39 years (SD ±11.5), and 88 (73.94%) were female. We did not find any significant differences in the frequency of risk factors for stroke between the three groups or between patients when divided into symptomatic and asymptomatic groups (Table 2). In addition, we followed 8 asymptomatic MMD patients for an average of 81.8 months (SD ±51.0) from the time of diagnosis, and none of them developed any ischemic or hemorrhagic cerebrovascular events, precluding analysis of risk factors associated with symptomatic transformation.

Discussion

This study focuses on stroke risk factors in MMD and the risk of stroke in a small asymptomatic adult MMD cohort. The role of stroke risk factors in East Asian populations has been described multiple times in the literature, where moyamoya is more common [7, 8]. However, less is known about the risk factors of stroke in a North American MMD population.

Our study supports the findings of Hirano et al. in which the authors report that the frequency of stroke risk factors such as HTN, HLD, diabetes, smoking, and alcohol in ischemic, hemorrhagic, and asymptomatic

Table 2. Stroke risk factor comparison among ischemic, hemorrhagic, and symptomatic groups, as well as between symptomatic and asymptomatic patients

Factors	Ischemic (n = 98)		Hemorrhagic (n = 13)		Asymptomatic (n = 8)		p value	Symptomatic (n = 111)		Asymptomatic (n = 8)		p value
Mean age at diagnosis (mean ± SD)	38.9±11.4		45.6±10.6		29.2±5.8		0.01*	39.7±11.5		29.2±5.8		<0.01*
Female sex, n (%)	74	75	10	76	4	50	0.27	84	75	4	50	0.23
DM, type 1, n (%)	4	4	0	0	0	0	0.64	4	3	0	0	0.63
DM, type 2, n (%)	18	18	0	0	0	0	0.10	18	16	0	0	0.46
HTN, n (%)	42	42	7	53	3	37	0.70	49	44	3	37	0.99
HLD, n (%)	41	41	5	38	3	37	0.95	46	41	3	37	0.87
Current smoker, n (%)	26	26	3	23	2	25	0.96	29	26	2	25	0.72
Former smoker, n (%)	47	47	5	38	6	75	0.24	52	46	6	75	0.24
Alcohol, n (%)	2	25	8	12	1	25	0.55	10	14	1	25	0.89

Ischemic and hemorrhagic patients were combined to form the symptomatic group. DM, diabetes mellitus. * Statistically significant p value (<0.05).

moyamoya groups was not significantly different. Although in our study the stroke risk in asymptomatic moyamoya patients was zero, earlier studies have reported ≥2.4% annual stroke risk in asymptomatic patients [3, 6, 9, 10].

An important difference between our study and Hirano et al. [5] is that our study cohort consisted of a predominantly White population. As suggested by a population-wide study from Japan, hemorrhagic MMD appears to be more prevalent in Eastern Asian populations relative to North American populations [11]. In this regard, risk factors for hemorrhagic or ischemic stroke may differ between ethnic, racial, and/or geographical populations when compared.

There are no clear guidelines on how asymptomatic MMD patients should be managed. Managing stroke risk factors, particularly HTN and HLD, could be beneficial and may prevent some MMD patients from becoming symptomatic. The role of revascularization among asymptomatic patients is controversial, but it is important to note that asymptomatic patients are at risk for disease progression, thereby warranting close follow-up [2, 12, 13]. In fact, recent angiographic studies of MMD in each onset-type (hemorrhagic vs. ischemic) revealed that angiographic findings of asymptomatic MMD patients are more similar to those of hemorrhagic-onset patients as characterized by the development of choroidal anastomoses [14, 15]. Since the development of choroidal anastomoses is closely related to posterior hemorrhage with high rebleeding risk in hemorrhagic MMD patients, close follow-up is recommended in asymptomatic MMD patients especially in those with the dangerous collateral networks (i.e., choroidal anastomoses).

We observed that no patients developed cerebrovascular events in the asymptomatic group at follow-up. However, this is likely secondary to our small sample size within this group. A higher incidence of cerebrovascular events is likely to be evident with a larger sample size and longer follow-up intervals. Additionally, our study is limited by its single center retrospective design.

Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All patients involved in this study provided written informed consent for involvement in research at our institution. Study approval was obtained from the IRB. This study protocol was reviewed and approved by the Mayo Clinic IRB approval number 19-001663. Subjects provided their written informed consent for inclusion in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mukaish Kumar: conception, data gathering, data analysis, draft writing, and draft editing. Anthony Larson: data gathering, data analysis, draft editing, and submission. Mahomed Jabal: data

analysis and draft editing. Lorenzo Rinaldo, Luis Savastano, Giuseppe Lanzino, Fredric Meyer, and Vance Lehman: data gathering, data analysis, and draft editing. James Klaas: conception, study oversight, data analysis, and draft editing.

Data Availability Statement

Data are available upon reasonable request to the corresponding author.

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