

Adult Moyamoya Disease in an Urban Center in the United States Is Associated With a High Burden of Watershed Ischemia

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Background—Adult moyamoya disease is rare in the United States, and patients mostly present with cerebral ischemia. However, clinical and neurodiagnostic correlates of ischemia are not well known in this population. We sought to characterize the clinical and radiographic features of moyamoya disease in a large urban center in the United States, with a focus on angiographic and neuroimaging patterns of ischemia.

Methods and Results—We retrospectively reviewed charts of consecutive adult moyamoya disease patients evaluated at 2 centers in Houston, Texas from January 2002 to December 2011. We reviewed all available cerebral angiograms and neuroimaging studies to evaluate the Suzuki grades, presence of intracranial hemorrhage or ischemia, infarct patterns, and vascular territory distribution. Our analysis was mainly descriptive. We identified 31 adults with moyamoya disease who met our inclusion criteria. The female-to-male ratio was 2.4:1. The majority of patients were white, followed by Hispanic, black, and Asian. Most presented with ischemia (61%), followed by headaches, and intracranial hemorrhage. Of the 22 patients with available neuroimaging, 72.7% had ischemic findings, with the vast majority having a watershed pattern (81.3%).

Conclusions—We observed a high burden of ischemia, mostly watershed pattern on neuroimaging in our adult moyamoya disease patients. Long-term monitoring of adult moyamoya disease patients in the United States would be useful to better understand the natural history of this condition. (*J Am Heart Assoc.* 2014;00: e001123 doi: 10.1161/JAHA.114.001123)

Key Words: ischemia • moyamoya disease • outcomes • United States • watershed

Moyamoya disease (MMD) is a rare, progressive cerebrovascular occlusive condition characterized by narrowing of the proximal arteries of the circle of Willis, and development of arterial collaterals at the skull base.¹ The incidence of MMD in the United States is growing, but only about 2000 admissions nationwide in the last decade have been reported.^{2–5} Furthermore, a detailed analysis of angiographic and neuroimaging patterns is relatively sparse in the adult MMD population in the United States. The purpose of our retrospective study was to characterize and describe the clinical and radiological patterns of MMD in the ethnically diverse population of Houston, Texas.

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Material and Methods

Subjects and Setting

We obtained Institutional Review Board approval from Baylor College of Medicine prior to study initiation. All patients with a primary or secondary diagnosis of MMD or moyamoya syndrome (MMS) over the 10-year period from January 1, 2002 to December 1, 2011 seen at Saint Luke's Episcopal Hospital or Kelsey Seybold Clinic, Houston, Texas were screened for the study. Saint Luke's Episcopal Hospital is an academic affiliate of Baylor College of Medicine and a large 900-bed tertiary care hospital in the Texas Medical Center, and Kelsey Seybold Clinic is a large managed-care system in the Houston metropolitan area. We identified patients from hospital and clinic electronic databases using the International Classification of Diseases, Ninth Revision, Clinical Modification procedure code 437.5 (Moyamoya Disease). In the International Classification of Diseases, Ninth Revision coding system, there is no distinct code for MMS.

Next, we manually reviewed each chart with the selected MMD code to validate the diagnosis. The diagnosis of definite or probable MMD was determined as per the Guidelines for Diagnosis and Treatment of Moyamoya Disease.⁶ Inclusion criteria were age ≥ 18 with probable or possible MMD or MMS.

We excluded patients with no definite angiographic evidence of moyamoya vasculature based on established diagnostic criteria,⁶ or those with MMS due to neurofibromatosis type 1, Down syndrome, sickle cell disease, and cranial irradiation.^{1,6} We did not exclude patients with vascular risk factors, since these are very common in adults, generally have a distinct pattern to MMD, and an aim of our study was to explore interactions between vascular risk factors and MMD clinical manifestations. Patients with bilateral intracranial stenocclusive disease and no secondary etiology were categorized as having definite MMD, whereas those with unilateral involvement were classified as having probable MMD.⁶

Data collected included patient demographics, presenting symptoms, comorbid illnesses, medical and surgical management, and discharge disposition for hospitalized patients. Ischemic stroke was defined as radiological evidence of recent ischemic stroke on magnetic resonance imaging or computed tomography imaging, and transient ischemic attack was defined by acute focal neurological symptoms without imaging evidence for new ischemic injury. Intracerebral hemorrhage was determined by acute hematoma on neuroimaging. Diabetes mellitus was defined as HgbA1C ≥ 6.5 mg/dL,⁷ or previous diagnosis. Hypertension was defined as blood pressure $>140/90$ mm Hg,⁸ or previous diagnosis. Hyperlipidemia was defined as total cholesterol >200 mg/dL,⁹ on lipid-lowering treatment or previous diagnosis. Cerebral angiograms were initially interpreted by board-certified neuroradiologists. For the purposes of our study, we retrospectively determined Suzuki scores for all available cerebral angiograms. Two board-certified vascular neurologists independently assigned a Suzuki score for the right and left vasculature for each patient's angiogram. If there was a disagreement, consensus was reached by co-reviewing the specific angiographic study. The Suzuki score ranges from 0 to 6, with higher scores indicating more advanced vasculopathy.⁶ We also retrospectively reviewed all computed tomography and magnetic resonance imaging brain imaging done during the same admission as cerebral angiography using the same methodology. We only reviewed imaging that was done in the preoperative setting, in order to exclude ischemia or hemorrhage related to postoperative changes. We determined the vascular patterns and territory including presence of watershed, cortical or subcortical ischemia, based on the established patterns on neuroimaging by Damasio and methods described by Rovira et al.^{10,11}

Statistical Analysis

Due to the rarity of MMD, statistical analysis was mainly descriptive, as we did not want to overanalyze our relatively small sample size. We used the Wilcoxon signed-rank test for ordinal data to analyze the differences in median Suzuki

grading between the right and left side in a given patient. We used Spearman's ρ correlation coefficient for nonparametric and ordinal data to evaluate associations between clinical characteristics and angiographic Suzuki grade. Significance was defined as $P < 0.05$. Bonferroni correction was applied for multiple analyses. We used SPSS Statistics Version 22 (IBM, Armonk, NY) for data analysis.

Results

One hundred patients with the diagnosis of International Classification of Diseases, Ninth Revision code "437.5" were initially identified from hospital and clinic databases. After manual chart review, 52 were excluded for not meeting the angiographic diagnostic criteria, 9 were excluded due to the presence of sickle cell disease, and 8 were excluded with age < 18 . This left 31 patients with definite or probable MMD/MMS for analysis.¹

The 31 adult MMD/MMS patients had a mean age of 37.6 (12.1), range 18 to 68 years. Patients were predominantly female (71%), by 2.4:1 ratio. The majority of patients were white (45%), followed by Hispanic (29%), black (13%), and Asian (10%) racial category. Six of our patients had prior surgical revascularization, including direct ($n=5$) and indirect ($n=1$) bypass. Nineteen (61%) patients presented with ischemic symptoms (61%) including stroke ($n=14$) or transient ischemic attack ($n=5$). Seven (23%) presented with headache, and 3 (10%) had intracerebral hemorrhage (Table 1).

Relationship Between Patient Characteristics and Suzuki Grade

The Suzuki grade data for the 27 available cerebral angiograms is presented in Figure. We observed an inverse relationship between the number of vascular risk factors and the Suzuki grade ($P=0.04$) in a given patient; this was of borderline significance after Bonferroni correction for multiple analyses. We found no significant associations between age, racial category, individual vascular risk factors (ie, hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, and tobacco), presenting symptoms (ischemia versus hemorrhage versus other), and Suzuki grade (data not shown).

Evaluation of Ischemic Patterns

We identified 22 patients who had neuroimaging during the same admission as cerebral angiography, with either magnetic resonance imaging of the brain ($n=17$) or computed tomography of the head ($n=5$). Of these, 16 (72.7%) had signs of acute or chronic ischemia. Of the patients with ischemia, 9 (40.9%) had right hemispheric and 13 (59.1%) had left

Table 1. Patient Characteristics and Presenting Symptoms

Age, y	37.6 (SD 12.1)
Sex	
Female	71.0% (n=22)
Male	29.0% (n=9)
Race	
White	45.2% (n=14)
Hispanic	29.0% (n=9)
Black	12.9% (n=4)
Asian	9.6% (n=3)
Other	3.2% (n=1)
Presenting syndrome	
Ischemia	
Ischemic stroke	45.2% (n=14)
Transient ischemic attack	16.1% (n=5)
Intracranial hemorrhage	9.6% (n=3)*
Other	
Headache	22.5% (n=7)
Altered mental status	3.2% (n=1)
Incidental	3.2% (n=1)

*All 3 had intracerebral hemorrhage, but 1 patient had concurrent subarachnoid hemorrhage.

hemispheric injury. Of the 16 patients with ischemia, the vast majority, 13 (81.3%), had a watershed pattern. Compared to the expected frequency of watershed distribution strokes in general stroke patients, this was highly significant: 23/891 (2.6%) versus 13/16 (81.3%), $P < 0.0001$.¹² Of note, 4 patients who presented without any ischemic symptoms still had neuroimaging evidence of silent ischemic injury on neuroimaging, all in a watershed pattern. In a univariate analysis between white and nonwhite racial category, we did not see any significant difference ($P > 0.05$) for radiological evidence of ischemia or watershed ischemia (Fisher's exact test), or Suzuki grades (Pearson χ^2). Table 2 shows the ischemic pattern and vascular territories of the patients.

Discussion

The main finding in our study is that the adult MMD patients in Houston, Texas had a very high incidence of watershed ischemia (81.3%) that was both symptomatic and asymptomatic. In general, about 5% to 10% of strokes of all etiologies have a watershed pattern.¹² Even in studies of patients with carotid artery stenosis or occlusion, the rates range from 7% to 40%,^{13,14} whereas we observed an 81% rate. Furthermore, a previous study of MMD patients presenting with acute stroke found a rate of watershed

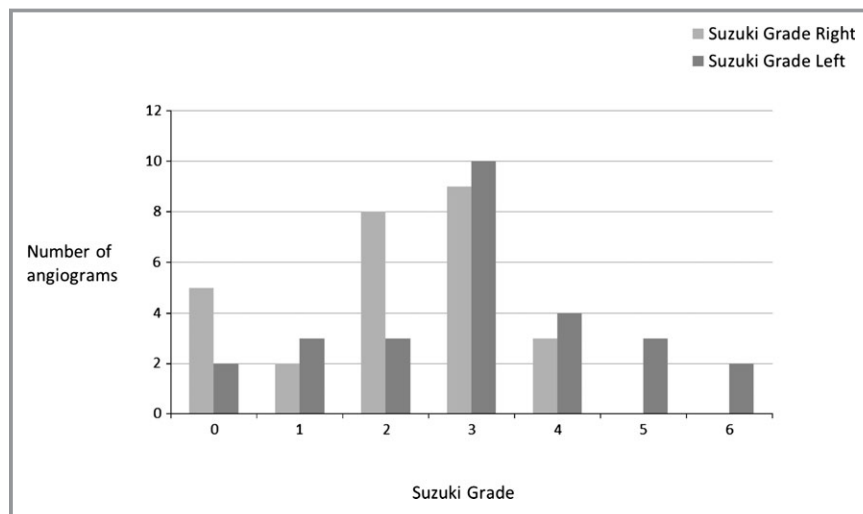


Figure. Suzuki grading for the right and left hemispheres of each patient. The distribution of Suzuki grades is shown. The left and right side for each patient were graded separately. The median Suzuki grade was significantly higher on the left compared to right side, 3 (2 to 4) and 2 (interquartile range 1 to 3), respectively, $P = 0.045$. *Suzuki grading scale: “0”=normal, “1”=narrowing of the terminal internal carotid artery bifurcation, “2”=initiation of basal moyamoya, “3”=intensification of moyamoya with steno-occlusion of middle cerebral artery (MCA) and anterior cerebral artery (ACA), “4”=minimization of moyamoya, with steno-occlusion of MCA, ACA, and posterior cerebral artery (PCA), “5”=reduction of moyamoya with steno-occlusion of all main cerebral arteries, and “6”=disappearance of moyamoya with cerebral blood flow supplied only from external carotid artery.

Table 2. Ischemic Patterns and Vascular Territories

Subject	Age, y	Gender	Suzuki Grade	Infarct Pattern	Vascular Territory	Suzuki Grade	Infarct Pattern	Vascular Territory
			Right	Left				
1	25	Female	4	None	None	3	None	None
2	31	Female	2	None	None	4	None	None
3	34	Female	0	None	None	3	None	None
4	39	Female	0	None	None	2	None	None
5	46	Male	2	None	None	1	None	None
6	49	Female	1	None	None	3	None	None
7	20	Male	2	None	None	4	Subcortical	MCA
8	21	Male	3	Subcortical	PCA	1	None	None
9	24	Male	3	None	None	3	Watershed	ACA/MCA, MCA/PCA
10	27	Female	1	None	None	1	Watershed	ACA/MCA
11	28	Female	4	None	None	5	Watershed	ACA/MCA
12	29	Female	3	Watershed	ACA/MCA	3	Watershed	ACA/MCA
13	30	Female	2	Subcortical	MCA	2	Watershed	ACA/MCA
14	38	Female	3	None	None	3	Watershed	MCA deep/M2 anterior/posterior
15	39	Female	2	Watershed	ACA/MCA	4	Watershed	ACA/MCA
16	46	Male	3	Watershed	ACA/MCA	3	None	None
17	47	Female	2	Cortical and subcortical	MCA	3	Watershed	ACA/MCA
18	49	Male	4	Watershed	MCA	0	None	None
19	50	Female	2	None	None	6	Watershed and subcortical	MCA/PCA
20	50	Female	0	None	None	5	Watershed	MCA deep/M2 anterior/posterior
21	63	Female	0	Subcortical	MCA and PCA	2	Cortical and subcortical	MCA
22	68	Female	2	Watershed	MCA/ACA	5	Watershed	ACA/MCA

ACA indicates anterior cerebral artery; MCA, middle cerebral artery; M2, second division of MCA; PCA, posterior cerebral artery.

infarction of only 3.9% (2/51) and 7.5% (3/40) in adult and pediatric patients, respectively. We cannot fully explain these discrepant results, but they may relate to the fact that in our study some of the watershed ischemia was asymptomatic, whereas in the study by Cho et al, only patients presenting with acute ischemia on diffusion-weighted imaging were included. Also, 2 board-certified vascular neurologists (E.B. and C.R.) carefully and manually reviewed all the computed tomography and magnetic resonance imaging scans to classify both the presence and pattern of ischemic injury, so we likely detected subtle ischemic changes that were not necessarily dictated by the radiologist. Finally, in contrast to the study by Cho et al where most Suzuki grades were between 4 and 5, our median grades were 2 to 3. This may indicate that in earlier stages of MMD, when the carotid fork is narrowed, watershed ischemia may be a more important mechanism; however, in later stages when the carotid artery is completely occluded, compensation with collateral flow

may alter the hemodynamic supply and favor a different infarct pattern.

The demographic data in our population closely matches that of previous US case series, with respect to female predominance, mean age of onset, and ethnic distribution.^{4,15,16} The Asian phenotype typically has a bimodal distribution with the initial presentation in the first and third/fourth decades, whereas the North American–European phenotype usually presents in the second decades. The reasons for the variation in phenotype between Asian and non-Asian MMD is not well known but may relate both to genetic and environmental factors, the latter including diet and lifestyle.¹⁵ Approximately 60% of our patients presented with ischemic symptoms, which is similar to other published case series conducted in North America.^{1,4,16} About 23% of our patients presented with headaches, which is also a common presenting symptom of MMD and is thought to be triggered by the response of dural nociceptors to vasodilation

of the dural and leptomeningeal vessels.¹ Also, the presence of comorbid risk factors for vascular disease in our cohort was consistent with previous studies. Given that there was no association between the presence of these risk factors and the angiographic Suzuki staging, it may suggest no overt interaction with the underlying MMD pathophysiology; however, we acknowledge that our small sample size may limit interpretations. The best long-term strategy for management of MMD patients with ischemia remains to be determined. Chiu et al reported comparable 5-year stroke risks in medically treated versus surgically treated patients, but more recent data from Hallemeier et al highlight the potential benefit of surgery.¹⁶ In their study of 34 patients, the 5-year risk of recurrent ipsilateral stroke from time of diagnosis in medically treated patients was 27%, and the 5-year risk of recurrent ipsilateral stroke or death in surgically treated patients was 17%.

Our study had several notable limitations worth mentioning. First, the sample size was relatively small, so this limited our power to perform statistical analyses. Specifically, detailed analyses of the various racial groups within our population would be underpowered. Second, International Classification of Diseases, Ninth Revision codes may not detect all cases of MMD or MMS; thus, we may have missed cases that were improperly coded. Third, we did not have long-term follow-up data on patients, given that many did not represent to the original hospital or may have presented late in our time period studied. Fourth, given the retrospective nature of this study, neuropsychiatric examinations and hypercoagulable testing were not performed in a standardized manner, so we did not include these factors in our analysis. Fifth, although we made our best effort to exclude patients with other etiologies for ischemic symptoms, we did not have access to all of the previous hospital records for each patient. Next, we did not have complete information about duration of antiplatelet or anticoagulation use, thus limiting our ability to analyze efficacy of medical therapy. Finally, our identification of patients presenting with MMD in the hospital or clinic setting may select those with more severe disease that require medical attention, rather than a random selection from the community; however, this an inherent limitation with any retrospective study.

Summary

We observed a high burden of watershed ischemia in our population of MMD patients. It would be useful to predict which of these patients may benefit from revascularization in

the future, but there are no randomized controlled trials to guide this decision. There may be a role for establishing a MMD registry in the United States to better understand the long-term outcomes in adult MMD with regard to disease progression, ischemic patterns, and effect of surgical intervention.

Disclosures

None.

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