Surgical Treatment for Patients with Moyamoya Syndrome and Type 1 Neurofibromatosis

Jose L. Porras, Wuyang Yang, Tomas Garzon-Muvdi, Risheng Xu, Jaishri Blakeley, Allan Belzberg, Justin M. Caplan, Syed Khalid, Geoffrey P. Colby, Alexander L. Coon, Rafael J. Tamargo, Edward S. Ahn, Judy Huang

■ INTRODUCTION: **The current study describes the impact of surgery in preventing follow-up ipsilateral transient ischemic attacks (TIAs)/strokes in an East Coast North American cohort of patients with both moyamoya syndrome (MMS) and neurofibromatosis type 1 (NF1) (MMS-NF1).**

■ METHODS: **We retrospectively reviewed records of patients with MMS and NF1 at the Johns Hopkins Medical Institutions from 1990–2014. Baseline characteristics and follow-up results including subsequent ipsilateral strokes were collected and compared between a revascularization group (group 1) and a conservatively managed group (group 2) on a per-hemisphere basis.**

■ RESULTS: **A total of 9 patients (14 hemispheres) were included in our study. The average age of all patients at NF1 diagnosis was 2.1 ± 7.7 years, with 6 being female (66.7%). The average age of all patients at MMS diagnosis was 10.4 ± 16.6 years with the median age being 7.7 years (range: 4.1–27.0 years). Race distribution was: White (n = 4, 44.4%), Black (n = 3, 33.3%), and Asian (n = 2, 22.2%). Four patients (44.5%) experienced cerebrovascular manifestations of MMS before MMS diagnosis. Group 1 was younger at MMS diagnosis (P = 0.009), likely with a more acute symptom onset (P = 0.077). Management strategies were: pial synangiosis (n = 3, 21.4%) and conservative (n = 11, 78.6%). During an average follow-up period of 6.28 ± 2.0 years, no ipsilateral TIAs/strokes were observed for group 1; conversely, 2 ipsilateral TIAs (18.2%) and 2 ipsilateral strokes (18.2%) occurred in group 2.**

■ CONCLUSIONS: **In our study of non-Asian patients with MMS-NF1, revascularization reduced stroke recurrence and deterioration of symptoms. However, more studies are warranted to further explore the role of revascularization procedures given the rarity of this disease combination.**

INTRODUCTION

Neurofibromatosis 1 (NF1) is a common, multisystemic, autosomal-dominant disorder involving a mutation of the NF1 gene on chromosome 17 with an incidence reported to be 1 in 3500 individuals.[1,2] Occlusion of the terminal internal carotid artery (ICA) with compensatory capillary network neovascularization is often referred to as "moyamoya syndrome" (MMS) and is a well-known manifestation in NF1 patients with a poorly understood natural disease progression.[3-7] Children with NF1 who develop MMS (MMS-NF1) often present asymptomatically, presumably due to inadvertent screening from NF1-related surveillance, but may later become symptomatic with MMS progression.[8] The rate of stroke in untreated MMS-NF1 patients relative to idiopathic MMS is uncertain. However, it is known that the most important predictor of overall clinical outcome for MMS patients is clinical status at the time of MMS diagnosis relative to surgical intervention.[8,9] Existing literature suggests that revascularization is safe for MMS-NF1 patients, and provided the established benefits of revascularization for idiopathic MMS, revascularization is recommended to ameliorate symptoms and protect against stroke in MMS-NF1.[8,10]

While mounting evidence suggests that surgical intervention in MMS-NF1 patients may be efficacious and safe, these conclusions

Key words
- Moyamoya
- Neurofibromatosis 1
- Revascularization
- Stroke

Abbreviations and Acronyms
ICA: Internal carotid artery
IRB: Institutional Review Board
MMS: Moyamoya syndrome
mRS: Modified Rankin Scale
NF1: Neurofibromatosis 1
TIA: Transient ischemic attack

Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

To whom correspondence should be addressed: Judy Huang, M.D. [E-mail: jhuang24@jhmi.edu]

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Table 1. Characteristics of All Patients with Moyamoya Syndrome (MMS) and Neurofibromatosis Type 1

Patient	Age*/Sex/Race	MMS Laterality	Baseline Stroke Laterality	Baseline TIA	Treatment Type	Follow-Up Length (years)	Stroke-Free Interval (years)	Follow-Up Stroke Laterality	Last Follow-Up Functional Status†
1	2/F/Black	Bilateral	Left	—	Conservative	10.2	1.1	Left	Improved
2	0/F/Black	Bilateral	—	—	Conservative	16.1	—	—	Worsened
3	18/F/White	Bilateral	—	—	Conservative	2.1	—	—	Unchanged
4	4/M/White	Bilateral	Left	—	Pial Synangiosis	6.3	—	—	Worsened
5	9/M/White	Right	—	—	Conservative	6.4	—	—	Improved
6	10/F/Asian	Bilateral	—	+	Conservative	0.7	—	—	Improved
7	27/F/Asian	Left	—	+	Conservative	5.8	5.7	Left	Worsened
8	8/M/White	Left	—	—	Conservative	2.9	—	—	Unchanged
9	5/F/Black	Left	—	—	Pial Synangiosis	2.0	—	—	Unchanged

TIA, transient ischemic attack; F, female; M, male.
*Defined as age at the time of diagnosis of MMS.
†Functional status as compared by last follow-up modified Rankin Scale (mRS) score with baseline mRS score.

are largely drawn from sporadic case reports without comparative evidence. In this study, we provide a retrospective description of an East Coast North American cohort of 9 patients with MMS-NF1. We also characterize the role of surgery in preventing follow-up ipsilateral strokes compared with conservative management—an undertaking that is under-reported in both the non-Asian literature and in patients with MMS-NF1.

MATERIALS AND METHODS

Study Population

We retrospectively reviewed records of patients diagnosed with moyamoya disease or MMS at the Johns Hopkins Medical Institutions from 1990–2014. After screening 115 adult and pediatric patients within our Institutional Review Board (IRB)-approved moyamoya database, a total of 9 patients (7.8%) with 14 affected hemispheres were identified as having MMS-NF1. All included patients met National Institutes of Health diagnostic criteria for NF1. Exclusion criteria included patients with incomplete clinical and angiographic data, patients without definitive documentation of MMS, nonidiopathic internal carotid artery occlusion, and patients lost to follow-up. We made no exclusions from our study as none of our MMS-NF1 patients satisfied the exclusion criteria.

Definition of Variables

Baseline demographics and clinically related variables such as vessel patency and ischemic events (transient ischemic attack (TIA)/stroke) were obtained from our institution's database of medical records. We investigated patient age, sex, clinical manifestations of cerebral vasculopathy, and surgical records. Age was defined as age at diagnosis of MMS. Functional outcomes were measured using a modified Rankin Scale (mRS) score at intervals, represented in years, between the times at diagnosis, initial follow-up, at 1 year, 2 years, and at the last follow-up available. We compared results between a revascularization group (group 1) and a conservatively managed group (group 2) on a per-hemisphere basis. Our institutional management strategy for all patients in group 1 was indirect bypass owing to concern for vessel patency after direct bypass due to smaller vessel sizes found in pediatric patients.[11] The outcome variable was defined as whether any strokes occurred during the follow-up period.

Statistical Analysis

Descriptive statistics were used in this study to compare patient demographics, baseline clinical parameters, treatment modality, and follow-up outcomes between groups 1 and 2.

Statistical significance was defined as $P < 0.05$, and all P values were reported as 2-sided. Statistical analyses were performed using R Statistical Software (Version 3.1.1, Vienna, Austria).

RESULTS

Patient Population and Baseline Characteristics

A total of 9 patients (14 hemispheres) were included in our study, and detailed characteristics of each patient were described in detail in Table 1. The review of patient records between 1990 and 2014 revealed 115 patients with confirmed MMS, and there were 9 patients with MMS-NF1 comprising 7.8% of the 115 patients. Three out of 9 patients had a confirmed family history of NF1, and none had a reported family history of MMS. The average age of all patients at NF1 diagnosis was 2.1 ± 7.7 years, with 6 being female (66.7%). The average age of all patients at MMS diagnosis was 10.4 ± 16.6 years with the median age being 7.7 years (range: 4.1–27.0 years). The average time interval between diagnosis of NF1 and MMS was 8.2 years (range: 0–27 years). The distribution of race was: White ($n = 4$, 44.4%), Black ($n = 3$, 33.3%), and Asian ($n = 2$, 22.2%). Four out of 9 patients (44.5%) experienced cerebrovascular manifestations of MMS before diagnosis of MMS, including all 3 patients in group 1. The other 5 patients (55.5%) were diagnosed with MMS incidentally through NF1-related screening. As