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Research Paper

Characteristics of Moyamoya Syndrome in Pediatric Patients With Neurofibromatosis Type 1

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ABSTRACT

Background: Moyamoya syndrome (MMS) is a progressive cerebral arteriopathy with increased incidence in children with neurofibromatosis type 1 (NF1). Despite the potential for significant neurological morbidity including stroke, little is known about the natural history, and no guidelines exist for screening and management of NF1-associated MMS.
Methods: We identified 152 literature cases of children aged ≤18 years with NF1-associated MMS. A meta-analysis was performed evaluating clinical and neuroimaging findings and patient outcomes. Data from 19 patients with NF1-associated MMS from our center treated from January 1995 to July 2020 were abstracted via chart review and similarly analyzed for clinical and neuroimaging features.
Results: Meta-analysis of literature cases showed a median age of MMS diagnosis of 6 years (interquartile range 3 to 10.8 years). Optic pathway gliomas were more common in patients with MMS (42%) compared with historical prevalence. Stroke or transient ischemic attack (TIA) was present at diagnosis in 46%. TIA and stroke were more common in patients with bilateral versus unilateral MMS (62% vs 34%, $P = 0.001$) and in children aged <4 years versus those aged ≥4 years (61% vs 40%, $P = 0.02$). Compared with the literature cases, our cohort was more frequently asymptomatic (42% vs 25%) and less likely to present with TIA or stroke (32% vs 46%) at diagnosis.
Conclusions: These data suggest there is an aggressive form of MMS in children with NF1 <4 years of age. Therefore, early screening should be considered to facilitate early detection and treatment of cerebral arteriopathy.

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder impacting one in 3000 children. Cerebral arteriopathy is a well-known, but poorly understood manifestation of NF1 estimated to occur in 2.5% to 6% of children with the disease.[1-5] There are no prospective studies of cerebral arteriopathy in NF1, and analyses are challenging because there are no standard

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screening guidelines for asymptomatic children with NF1. The most prevalent form of NF1-associated arteriopathy is moyamoya syndrome (MMS), a progressive steno-occlusive disease of the intracranial arteries resulting in collateral vessel formation that causes a characteristic "puff of smoke" appearance on catheter angiogram.[6] Although MMS can cause significant neurological morbidity due to an increased risk of stroke, no guidelines exist for monitoring and arteriopathy management among children with NF1.

The objective of this study was to understand phenotypic diversity with respect to age at onset and clinical and imaging characteristics of NF1-associated MMS. We addressed these aims in two ways—first with a systematic review and meta-analysis of published cases and second with a single-center 25-year cohort study involving analysis of retrospectively abstracted chart data and centralized imaging review. Better understanding of age-related incidence, risk factors, natural history, and presenting clinical and imaging features is necessary to optimize early detection strategies and interventions aimed at decreasing the occurrence and severity of stroke due to MMS.

Methods

Systematic literature review and meta-analysis

A systematic literature review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Search criteria included neurofibromatosis type 1, NF1, pediatric, moyamoya, arteriopathy, and vasculopathy to maximize the number of references identified. PubMed and Google Scholar electronic databases were surveyed in June 2020 and then combined with a manual search of all reference lists for pertinent articles. The review was not registered.

Potentially eligible citations' titles and abstracts were evaluated for relevance. Studies published in languages other than English were excluded. Full-text articles of eligible citations were then reviewed. Case series and case reports were included if individualized data could be extracted for each patient. Eligible patients were those aged 29 days to less than or equal to 18 years at the time of MMS diagnosis. Variables extracted included patient sex, age at diagnosis of NF1, age at diagnosis of MMS, symptoms at time of MMS diagnosis, laterality of MMS, intracranial vessels involved, TIA or stroke at the time of MMS diagnosis, evidence of clinically silent infarct, evidence of systemic arteriopathy, presence of optic pathway glioma (OPG), MMS treatment, and evidence of clinical and/or radiographic evidence of MMS progression. Patient numbers were reported for each variable to account for missing data.

Single-center case series

Eligible patients included those with NF1 determined by NIH criteria,[7] age 29 days to less than or equal to 18 years, and cerebral arteriopathy diagnosed between January 1995 and July 2020. All patients were enrolled in the pediatric stroke registry at the Children's Hospital of Philadelphia (CHOP), and informed consent was obtained per protocol approved through the institutional review board. The cases were cross-referenced with the institutional NF1 database to ensure complete ascertainment. Retrospective chart review was performed, and data extracted were the same as described above for the meta-analysis of published cases with the addition of the following variables: evidence of systemic arteriopathy, Suzuki score, recurrent stroke or TIA, time to clinical or radiographic disease progression, and prior chemotherapy for nervous system neoplasms. Time to follow-up was measured from date of initial arteriopathy diagnosis via magnetic resonance imaging (MRI) to the date of the last appointment with a complete neurological examination documented. Patients who had received cranial radiation before MMS diagnosis were described but were excluded from statistical analysis.

Neuroimaging review

The diagnosis of arteriopathy was confirmed radiographically by a board-certified pediatric neuroradiologist (A.V.) by review of MRI and magnetic resonance angiography (MRA). Patients were classified as having focal stenotic arteriopathy or MMS, which was defined as either unilateral or bilateral stenosis of the terminal internal carotid arteries or middle cerebral arteries with associated moyamoya-type collateral formation. Neuroimaging was evaluated for the following: intracranial vessels involved; location of collaterals; circle of Willis variants; presence of an ivy sign; changes in perfusion or transit time noted on arterial spin labeling (ASL); evidence of acute, chronic, and silent infarcts; and presence of gliomas or intracranial tumors. For patients with a catheter angiogram, Suzuki scoring was performed by a board-certified pediatric neurosurgeon (S.L.). Composite cerebrovascular stenosis score (CVSS) was measured as previously described by Sultan et al.[8] Briefly, intracranial vessels or their major branches were assigned a score of 1 to 3 based on the degree of stenosis (0 = no stenosis, 1 = less than or equal to 50% stenosis, 2 = 50% to 99% stenosis, 3 = occlusion of the vessel).

Statistical analysis

Statistical analysis was performed using SAS 9.4 (Cary, North Carolina, USA). Age at MMS diagnosis, age at first neuroimaging, CVSS, duration of follow-up, and multiple time-to-event variables were not normally distributed and were reported as medians with interquartile and overall ranges. Time to event variables include time to clinical or radiographic disease progression, time to new onset or recurrent stroke, time from radiographic diagnosis to pial synangiosis, and time from earliest imaging findings to documentation of MMS diagnosis. We described categorical variables using counts and frequencies and compared intergroup differences using the χ^2 test. Denominators differed among variables due to missing data; there was heterogeneity in data reported in the articles included in the meta-analysis. We described categorical variables using counts and frequencies and compared intergroup differences using the χ^2 test. A Wilcoxon rank-sum test was used to determine whether the age distribution was different between children with and without stroke at the time of MMS diagnosis. A P value <0.05 was considered statistically significant.

Results

Literature review

A total of 276 references were identified via electronic database searches (Supplemental Figure 1), and 63 full-text articles met inclusion criteria (Supplemental Table 1). Data on 152 unique patients were extracted. Identified cases had a median age of 6 years at MMS diagnosis (interquartile range [IQR] 3 to 10.8 years, range 0.4 to 18 years, Fig 1), although a large proportion of patients (30%) presented before age four years. Presenting symptoms and clinical characteristics of patients at time of MMS diagnosis are detailed in Table 1.

MMS caused significant morbidity in these children; 50 of 140 (36%) presented with arterial ischemic stroke and 14 of 139 (10%) had TIA at the time of arteriopathy diagnosis. An additional two of 140 patients (1%) had intracranial hemorrhage. Patients with

bilateral disease had higher rates of TIA or stroke (34 of 57, 60%) compared with those with unilateral disease (26 of 81, 32%, $P = 0.001$, χ^2). A significant difference in age distribution was also evident in children diagnosed concomitantly with stroke or TIA and MMS compared with those without stroke or TIA (Fig 1, $P = 0.02$, Wilcoxon rank sum). In particular, TIA and stroke were more common in children younger than four years (25 of 42, 60%) compared with those aged four years or older (35 of 96, 36%, $P = 0.02$, χ^2). Interestingly, children aged less than four years were not more likely than older children to have bilateral MMS (21 of 46 [46%] vs 43 of 112 [38%]), $P = 0.4$, χ^2). Females and males were equally likely to present with stroke or TIA (33 of 69 [48%] vs 26 of 62 [42%], $P = 0.5$, χ^2).

Data regarding treatment and outcomes were limited. Of the 101 patients with treatment data, 17 patients received aspirin monotherapy (17%), 33 underwent surgical revascularization (33%), 23 were treated with dual aspirin and surgical revascularization (23%), and 28 were monitored clinically without treatment (28%). Of the 62 patients with longitudinal data, two who were asymptomatic at initial presentation subsequently suffered stroke or TIA (3%), and 11 had recurrent TIA or stroke during follow-up (18%). Nine of these 11 patients had treatment data available. Five received aspirin monotherapy (56%), one underwent surgical revascularization (11%), one received both aspirin and surgical revascularization (11%), and two patients were monitored clinically without treatment (22%).

CHOP cases: demographics and presenting symptoms

A total of 24 patients with cerebral arteriopathy were identified from the CHOP NF1 cohort (Table 3). Of these patients, five had focal stenotic arteriopathy based on MRA but did not meet criteria for MMS diagnosis based on findings from the MRI and MRA. The remaining 19 patients had MMS diagnosed based on findings from MRI with MRA and were subsequently confirmed with catheter angiogram in 15 of 19 cases (79%). Presenting characteristics are summarized in Table 1. In contrast to the literature data, eight of 19 (42%) of the CHOP cohort were asymptomatic at diagnosis. Of the six patients with OPGs, four (67%) had concordance in laterality of their tumor and MMS. There was evidence of systemic arteriopathy in three of the 19 patients (Table 2). For the six patients (32%) who presented with TIA (three, 16%) or stroke (three, 16%) at the time of diagnosis, the median age of MMS diagnosis was 4 years (IQR 1.5 to 7.3 years, range 1.2 to 11 years), whereas those without stroke or TIA at presentation were diagnosed at a median age of 7.3 years (IQR 2.7 to 9.3 years, range 1.5 to 16.5 years, $P = 0.18$, Wilcoxon rank-sum). In addition, two of 19 (11%) had evidence of prior clinically silent infarctions on MRI. Eight of 19 patients (42%) had intracranial neoplasms requiring chemotherapy.

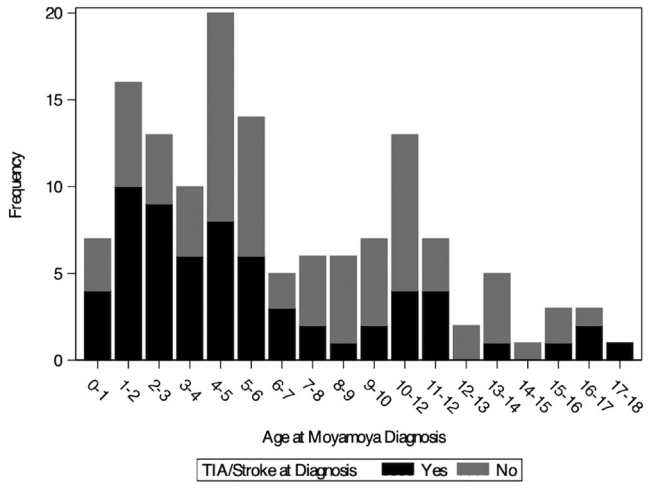

FIGURE 1. Age distribution at moyamoya syndrome diagnosis among literature cases with overlay of stroke or transient ischemic attack (TIA) at time of diagnosis.

CHOP cases: treatment

All 19 patients were treated with a combination of aspirin and surgical revascularization. The median time from radiographic diagnosis to pial synangiosis was 5 months (IQR 1.3 to 6.9 months, range 1 week to 6.25 years). The five children with focal stenotic arteriopathy who did not meet criteria for a diagnosis of MMS were also treated with aspirin but did not undergo surgical revascularization and showed no evidence of disease progression during the follow-up period. Of note, two of 19 received cranial radiation before MMS diagnosis. Given that cranial radiation is known to significantly increase the risk of MMS in children with NF1 and accelerate disease progression, these patients were excluded from further analysis.[8]

Patients were followed clinically for a median of 4.3 years (IQR 2.1 to 7.7 years, range 0.25 to 12.4 years). New onset or recurrent stroke or TIA occurred in five of 17 (29%) patients at a median time of 5 months (IQR 4 to 15 months, range 0 weeks to 5.5 years) from radiographic diagnosis of MMS (Fig 2). Following surgical revascularization, one of 17 (6%) had recurrent stroke and three of 17 (18%) had recurrent or new-onset TIA. Of note, the child with recurrent stroke following synangiosis was aged less than three years and had bilateral MMS. Children with stroke or TIA before surgery were more likely to suffer stroke or TIA following revascularization than those who did not suffer ischemic insults before surgery (three of seven, 43% vs one of 10, 10%, Fig 2). Notably, all but one of these ischemic events (a single TIA) occurred within the initial six-month window following revascularization, during which time collateral formation may not be complete.[9,10]

CHOP cases: neuroimaging characteristics

To determine the earliest neuroimaging findings associated with MMS in patients with NF1, MRI and MRA studies performed before MMS diagnosis, when available, were reviewed. Neuroimaging findings are summarized in Table 3. Sixteen of 23 children (70%) with arteriopathy underwent neuroimaging before their MMS diagnosis. The median age at first neuroimaging was 1.6 years (IQR 1 to 3.7, range 0.17 to 12.25 years). Indications for obtaining neuroimaging included screening for OPG (13 of 15, 87%), headache (one of 15, 7%), and seizures (one of 15, 7%). MMS was diagnosed on initial neuroimaging in five of 16 children (31%). All 10 remaining patients had subtle evidence of disease before formal diagnosis of MMS, with a median time from earliest imaging findings to documentation of MMS diagnosis of 11 months (IQR 5.25 to 28.9 months, range 4 to 100 months). Examples of subtle evidence of disease included the presence of the ivy sign, abnormal sulcal enhancement, and perfusion abnormalities on ASL (Fig 3). An ivy sign was observed in 15 of 17 patients (88%) at the time of MMS diagnosis and resolved in five patients following surgical revascularization. Evidence of abnormal perfusion at time of MMS diagnosis was seen in all 10 patients for whom an ASL sequence was obtained. Subtle changes in ASL were also noted in three patients before MMS diagnosis, although the sequence was only obtained in studies performed after 2008. Other benign circle of Willis variants such as fetal posterior cerebral artery or hypoplastic vessels were identified in six of 17 children (35%).

TABLE 1.
Clinical Features of Children With NF1-Associated Moyamoya Syndrome

Clinical Characteristic	Literature Cases (n = 152)	CHOP Cohort (n = 19)
Age at MMS diagnosis	Median: 6 years IQR: 3-10.8 years Range: 0.4-18 years	Median: 7 years IQR: 1-9.25 years Range: 1.2-16.5 years
Female patients	53% (79/148)	63% (12/19)
Bilateral disease	42% (64/152)	58% (11/19)
Presenting symptoms		
Hemiparesis	41% (58/142)	32% (6/19)
Headache	18% (26/142)	16% (3/19)
Seizure	19% (27/142)	11% (2/19)
Asymptomatic, detected on MRI to evaluate for OPG	25% (35/142)	42% (8/19)
OPG	41% (32/79)	32% (6/19)

Abbreviations:
CHOP = Children's Hospital of Philadelphia
IQR = Interquartile range
MMS = Moyamoya syndrome
NF1 = Neurofibromatosis type 1
OPG = Optic pathway glioma

CVSS was also calculated for each patient (Table 3). Prior research has shown that in patients with MMS, CVSS of 7 or greater was associated with a three-fold increased risk of recurrent stroke.[8] In our cohort, the median CVSS at diagnosis was 8 (IQR 4 to 12, range 3 to 17), which increased to 10 (IQR 4 to 13, range 3 to 20) at the time of most recent follow-up. Given all patients in this cohort underwent surgical vascularization, it is challenging to use CVSS as a predictor of recurrent stroke. However, five of 15 patients (33%) had an increase in CVSS following revascularization (median CVSS increase 3 points, IQR 3 to 4, range 1 to 5). Two of these children had first strokes or TIAs following diagnosis, and one had recurrent stroke despite surgical revascularization.

TABLE 2.
Clinical Characteristics of Children With NF1-Associated Cerebral Arteriopathy at Our Center

Patient No.	Age at Diagnosis (y)	Race or Ethnicity	Sex	Arteriopathy Type	Presenting Symptoms	Unilateral vs Bilateral	TIA or Stroke at Diagnosis	Systemic Vasculopathy	OPG
1	1.2	Caucasian	F	MMS	Hemiparesis	Bilateral	Stroke	Coarctation of aorta	Yes
2*	9.3	Caucasian	F	MMS	Asymptomatic	Bilateral	No	No	Yes
3	11	Caucasian	F	MMS	Hemiparesis, seizure	Bilateral	Stroke	Renal artery stenosis	Yes
4	3.8	Caucasian	F	MMS	Asymptomatic	Bilateral	No	No	No
5	3.8	Black	F	MMS	Asymptomatic	Unilateral	No	No	No
6	12.3	Hispanic	M	MMS	Asymptomatic	Bilateral	No	No	Yes
7	1.5	Caucasian	M	Hypoplastic ICA	Non-localizing	Unilateral	No	No	No
8	8.6	Caucasian	M	MMS	Seizure	Unilateral	No	No	No
9	9.2	Caucasian	M	MMS	Asymptomatic	Unilateral	No	Essential HTN	Yes
10*	6.4	Caucasian	F	MMS	Hemiparesis	Bilateral	TIA	No	Yes
11	7	Caucasian	M	Hypoplastic ICA	Non-localizing	Unilateral	No	No	No
12	2.3	Black	F	Stenosis of R petrous ICA and aneurysm of R cavernous ICA	Non-localizing	Unilateral	No	No	Yes
13	7.3	Black	F	MMS	Hemiparesis	Unilateral	TIA	Essential HTN	Yes
14	9.2	Mixed race	F	Hypoplastic ICA, dysplastic vessels	Asymptomatic	Unilateral	No	No	Yes
15	7.6	Caucasian	F	Focal ICA stenosis	Asymptomatic	Unilateral	No	No	Yes
16	4.3	Asian	F	MMS	Headache	Unilateral	No	No	No
17	1.5	Caucasian	M	MMS	Hemiparesis	Unilateral	Stroke	No	No
18	16.5	Hispanic	F	MMS	Headache	Bilateral	No	No	No
19	1.7	Caucasian	M	MMS	Hemiparesis	Bilateral	TIA	No	No
20	14.7	Caucasian	M	MMS	Asymptomatic	Bilateral	No	No	Yes
21	1.7	Asian	F	MMS	Asymptomatic	Unilateral	No	No	No
22	14.9	Caucasian	F	MMS	Headache	Bilateral	No	No	No
23	2.6	Caucasian	F	MMS	Asymptomatic	Bilateral	No	No	Yes
24	2.7	Asian	F	MMS	Non-localizing	Unilateral	No	Essential HTN	Yes

Abbreviations:
F = Female
HTN = Hypertension
ICA = Internal carotid artery
M = Male
MMS = Moyamoya syndrome
NF1 = Neurofibromatosis type 1
OPG = Optic pathway glioma
R = Right
TIA = Transient ischemic attack
* Patient treated with cranial radiation.

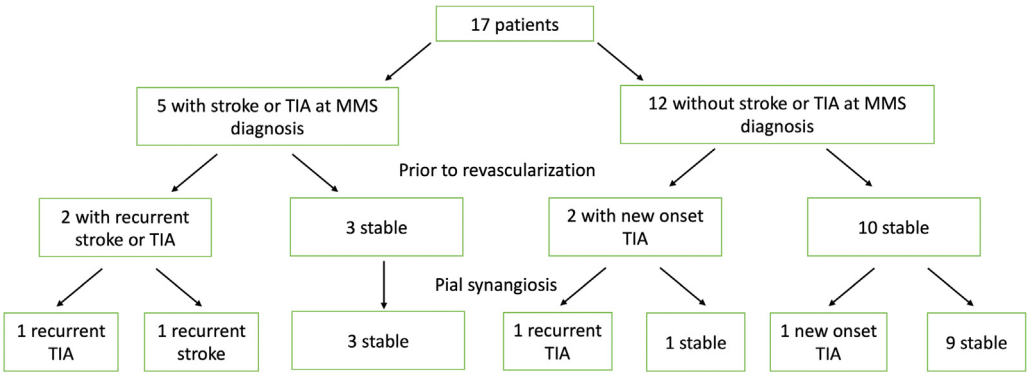

FIGURE 2. Flowchart of longitudinal outcomes for our cohort of patients with NF1-associated MMS. MMS, moyamoya syndrome; NF1, neurofibromatosis type 1; TIA, transient ischemic attack. The color version of this figure is available in the online edition.

Discussion

This report represents the largest systematic review and meta-analysis of children with NF1-associated MMS. Most systematic, previously published literature reviews on this topic to date omitted case reports, which comprise the vast majority of published cases.[11,12] Furthermore, systematic reviews based solely on case series are underpowered for meta-analysis due to the rarity of NF1-associated MMS. Inclusion of case reports enabled us to identify 152 unique cases of NF1-related MMS and draw broader conclusions regarding the natural history of the disease. Furthermore, we pair the data with one of the largest single-center case series reported and identified early imaging findings of MMS in children with NF1.

Radiographically, NF1-associated MMS is indistinguishable from moyamoya disease. Although the median age at MMS diagnosis was 6 years in our meta-analysis, one-third of children presented with MMS by four years of age. This is important because previous research has reported that young age of moyamoya disease onset has been associated with a higher risk of arterial ischemic stroke.[13] We confirmed this previously reported finding in our meta-analysis as children younger than four years at the time of MMS diagnosis were significantly more likely to present with TIA or stroke compared with those older than four years. Consistent with a recent series of patients with MMS of various etiologies,[14] patients with bilateral disease also had higher risk of stroke or TIA at initial diagnosis; however, younger children (less than four years) did not have a higher rate of bilateral MMS than older children. This finding indicates that the higher rate of stroke or TIA at presentation among younger children was not related to a higher incidence of bilateral disease. Although not statistically significant, in our single-institution cohort the median age of MMS diagnosis in children with TIA or stroke was four years compared with 7.3 years in those without TIA or stroke at MMS diagnosis. This lack of statistical significance may be related to the small sample size of our cohort. It is possible that clinicians may not order neuroimaging unless symptoms are severe in very young children due to the need for sedation, resulting in missed diagnoses of early MMS. Although the ability of young children to communicate early symptoms such as headache may limit diagnosis before onset of stroke, the data from this meta-analysis suggest that patients with NF1-associated MMS who present at a very young age may have more aggressive arteriopathy.

In both our meta-analysis and our patient cohort, stroke was a significant source of morbidity in children with NF1 and MMS. Although two other recent publications have reported lower risk of stroke (11% [15] and 4.4%[14]) compared with 17.6% observed in our cohort, patients in each of these studies were more likely to be asymptomatic than in our cohort (64%[15] and 56.5%[14] vs 42% in our group). In addition, our patients tended to be diagnosed at a younger age (median 7 years, IQR 1 to 9.25 years vs 8.9 years, IQR 5.7 to 11.8 years[14]). This is notable given the propensity for very young children to present with stroke at diagnosis per our meta-analysis.

We identified several differences between NF1-associated MMS and idiopathic moyamoya disease. Idiopathic moyamoya disease typically has a 2:1 female to male distribution[16]; however, sex distribution was equal in our meta-analysis of children with NF1-associated MMS. Unilateral moyamoya disease is rare, accounting for approximately 15% of incident MMS cases.[16-18] However, nearly 60% of the meta-analysis cases and 47% of our cohort with NF1-associated MMS had unilateral disease. Although it has been suggested that unilateral MMS in NF1 may be due to identification of children at an earlier disease stage,[19] none of the patients in our cohort with unilateral disease progressed to bilateral disease during follow-up of 4.6 years. We also followed several patients with isolated internal carotid artery disease who were maintained on aspirin monotherapy and who did not have disease progression. These findings imply that not all arteriopathy in NF1 is rapidly progressive and that unilateral MMS in patients with NF1 may be a disease variant rather than an early detection bias.

Previous case series have suggested a correlation between a diagnosis of OPG and MMS in children with NF1, which was also observed in our data. The systematic review and our case series demonstrated a higher prevalence of OPGs (42% and 32%, respectively) than the historically reported 15% to 20% prevalence of OPGs in all children with NF1.[20] It is unclear if this finding is due to a detection bias due to increased frequency of imaging of children with OPGs or whether the tumor itself secretes a growth factor stimulating proliferation within the vessel wall that triggers development of MMS. In the latter scenario, one might expect a high degree of concordance between the laterality of MMS and OPGs, although we only observed concordance in four of six (66%) patients.

MMS can present with a wide array of symptoms including hemiparesis, headache, and seizures, but it is important to note that a substantial portion of both our cohort and the literature cases were asymptomatic at the time of diagnosis. Importantly, asymptomatic MMS in children with NF1 is not benign. We observed clinical disease progression in three of eight children (37.5%) with asymptomatic MMS in our cohort at a median of 15 months from initial diagnosis (range 4 to 66.6 months). This observation is consistent with prior research that demonstrated that 32% of

TABLE 3.
Outcomes and Neuroimaging Data for Children With NF1-Associated Cerebral Arteriopathy at Our Center

Patient No.	New or Recurrent Stroke/TIA Before Revascularization	Time to Surgery (m)	New or Recurrent Stroke/TIA Post-revascularization	Duration Follow-up (y)	Ivy Sign	ASL	Other COW Abnormalities	Suzuki Score (R, L)	CVSS	Follow-up CVSS
1	No	1	No	7.7	No	N/A	Fetal PCA	N/A	10	14
2*	Yes, new-onset strokes at 15 months and 21 months post-diagnosis	29	Peri-operative stroke, no recurrence post-procedure	11.9	R	N/A	No MRA	N/A	N/A	20
3	Peri-procedural TIA	1.25	Yes recurrent TIAs 3.8 months and 5.8 months post-revascularization	12	N/A	N/A	No	(4, 4)	17	20
4	No	14.5	Yes, new-onset TIAs 2.5 weeks and 9 months after revascularization	13.5	L	N/A	Hypoplastic L Pcomm	(2, 6)	7	12
5	New-onset TIAs 5.5, 5.6, and 5.7 years post-diagnosis	75	Yes, recurrent TIA 6 months post-synangiosis	6.3	L	Delayed L MCA transit	No	(0, 2)	3	3
6	New-onset TIA 4 months post-diagnosis	17.5	No	8.5	R	Delayed R MCA transit	No	(3, 2)	N/A	6
7	No	N/A	N/A	5.9	N/A	N/A	No	N/A	N/A	N/A
8	No	3	No	4.8	R	Delayed R MCA transit	No	(2, 0)	4	4
9	No	6.75	No	6.7	R	Delayed R MCA transit	No	N/A	8	6
10*	Yes, recurrent TIAs 3 days and 3 weeks post-diagnosis	4	Yes, recurrent TIAs with staged revascularization. First TIA occurred 6.5 months post-revascularization, but in opposite hemisphere. Second TIA occurred 50 months after complete revascularization	9.2	No	N/A	Hypoplastic L Pcomm	(2, 2)	10	16
11	N/A	N/A	N/A	3.8	N/A	N/A	No	N/A	N/A	N/A
12	No	N/A	N/A	5.3	N/A	N/A	N/A	N/A	N/A	N/A
13	No	0.25	No	14	L	N/A	No	(1, 6)	11	10
14	No	N/A	N/A	3.4	N/A	N/A	No	N/A	N/A	N/A
15	No	N/A	N/A	2.7	N/A	N/A	No	N/A	N/A	N/A
16	No	1	No	2.3	L	Delayed L MCA transit	No	N/A	11	11
17	No	7	No	12.4	L	N/A	Hypoplastic L Pcomm	(N/A, 3)	3	3
18	No	1.75	No	1.5	L	N/A	No	(1, 3)	13	13
19	Yes, stroke 4 days after diagnosis	0.75	Yes, stroke 2 weeks after synangiosis and second stroke 4 months after synangiosis	0.6	B	Delayed B MCA, R ACA transit	No	(2, 3)	12	15
20	No	6.75	No	0.6	B	Delayed B ACA, L PCA transit	R Fetal PCA	(2, 2)	14	N/A
21	No	5	No	2.1	R	Delayed R MCA transit	No MRA	(3, 0)	N/A	3
22	No	1.25	No	2.4	L	Delayed L MCA transit	No	(3, 2)	4	4
23	No	5	No	0.4	No	N/A	Hypoplastic Pcomms	(0, 3)	7	8
24	No	6.5	No	0.5	R	Delayed R MCA transit	No	N/A	4	4

Abbreviations:
ASL = Arterial spin labeling
B = Bilateral
COW = Circle of Willis
CVSS = Composite cerebrovascular stenosis score
F = Female
HTN = Hypertension
ICA = Internal carotid artery
L = Left
M = Male
m = Months
MCA = Middle cerebral artery
MMS = Moyamoya syndrome
MRA = Magnetic resonance angiography
N/A = Not applicable
NF1 = Neurofibromatosis type 1

OPG = Optic pathway glioma
PCA = Posterior cerebral artery
Pcomm = Posterior communicating artery
R = Right
TIA = Transient ischemic attack
y = Years
* Patient treated with cranial radiation.

children who were initially asymptomatic progressed to having a TIA and 12% ultimately had a stroke.[21] Although stroke related to MMS caused significant neurological morbidity in this patient population, there are no standard treatment protocols for NF1-associated arteriopathy and MMS. Surgical revascularization for children with NF1-associated MMS has been shown to improve outcomes, with a 27-fold risk reduction of stroke.[19,22] At our institution, all children are treated with aspirin and indirect surgical revascularization with pial synangiosis, thereby precluding an analysis comparing patients managed medically versus surgically. In our cohort, patients who underwent surgical revascularization before onset of stroke or TIA were more likely to remain stroke-free and TIA-free than those whose revascularization took place after ischemic insult. Some of these differences between groups may be attributed to identifying and treating asymptomatic patients who have less severe disease and may never have progressed to have an ischemic event. Unfortunately, there are currently no clinical or radiographic methods of distinguishing asymptomatic patients who will remain clinically stable without intervention and those who are at high risk of developing stroke. This is an area that warrants further investigation. Given these considerations, the development of screening protocols for MMS in children with NF1 may lead to initiation of treatment before stroke onset, but additional studies are required to determine whether surgery before the onset of ischemia impacts outcomes.

Challenges for screening include the relatively large number of patients with NF1 (1:3000), the need for sedation or anesthesia to obtain imaging in a substantial portion of the at-risk population, and the broad age range over which MMS is diagnosed. The ivy sign is often one of the early imaging indicators of inadequate cerebrovascular reserve. In our cohort 79% had an ivy sign at the time of diagnosis, which was frequently the first neuroimaging evidence of evolving MMS. The advent of advanced imaging techniques such as ASL offers the opportunity to gather additional information regarding cerebral perfusion without radiation exposure. Addition of ASL sequences may enhance the sensitivity of neuroimaging for MMS in children, especially in young patients undergoing screening for OPGs who are at higher risk of severe disease and

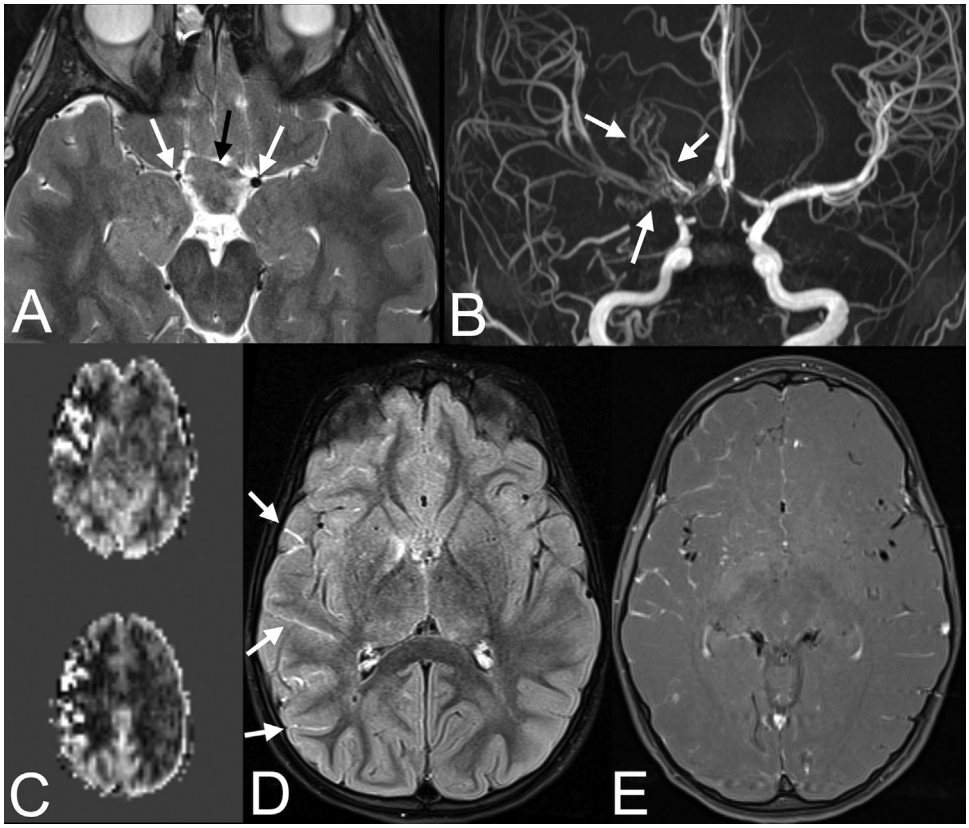

FIGURE 3. Various MRI manifestations of moyamoya syndrome in neurofibromatosis type 1. (A) Axial T2-weighted image shows asymmetric narrowing of the flow void of the right distal intracranial internal carotid artery compared with the left (white arrows). The patient's chiasmatic glioma is also seen (black arrow). (B) Time-of-flight magnetic resonance angiography more clearly shows the marked narrowing of the distal right internal carotid artery and parts of the right middle cerebral artery (MCA) and the anterior cerebral arteries. There is development of extensive collateral vessels in the MCA cistern and basal ganglia lenticulostriate vasculature (white arrows). (C) Arterial spin labeling (ASL) perfusion imaging shows delayed arterial transit in the right MCA branches. (D) Axial fluid-attenuated inversion recovery (FLAIR) image shows high signal in the sulcal vessels due to slower flow (FLAIR ivy sign, white arrows). (E) Axial postcontrast T1-weighted image shows asymmetric contrast enhancement of the right-sided sulcal vessels, also due to slower flow.

stroke. In the follow-up period, resolution of the ivy sign may indicate successful revascularization, although more study is required to determine whether resolution of the ivy sign is associated with disease and symptom stabilization.

Limitations

There are a number of limitations to this study including the retrospective design, small sample size, and missing data from many of the literature cases. There may also be bias in the previously published case reports toward patients with more clinically significant findings and therefore more severe disease. Furthermore, some of the cases reported as MMS may actually represent focal cerebral arteriopathy as not all cases included imaging for review. Some of the largest case series evaluating long-term outcomes[19,21] were also omitted from this study because no individualized data were included. In addition, these data are not generalizable to patients who have received cranial radiation, although its use is discouraged in children with NF1 due to the risk of developing cerebral arteriopathy[23] and secondary neoplasms.[24]

Our case series, although large for a rare disease, remains small in scope. Therefore, nearly all statistics reported are descriptive. Unfortunately, we cannot estimate the prevalence of MMS among all children with NF1, as our institution does not perform routine screening MRI on patients with NF1. Rather, neuroimaging is obtained when a patient presents with a concerning neurological symptom, an ophthalmologic concern is identified, or an adequate ophthalmologic evaluation cannot be obtained in a young patient being screened for OPG. The screening of young patients with inadequate ophthalmologic evaluations may contribute to the discovery of more asymptomatic MMS in our cohort compared with centers included in the meta-analysis. Thus, direct comparisons with the meta-analysis are difficult. However, the findings of our study complement those of the meta-analysis given the similar age distribution of patients presenting with MMS. Although there was concordance in laterality between the OPGs and MMS in four of our six patients, statistical analysis was not possible due to the small sample size. Further study is required to determine if universal neuroimaging screening is warranted in children with NF1.

Conclusions

Young children with NF1 and MMS are at high risk for presenting with stroke or TIA. Future directions include prospective imaging studies to evaluate the prevalence of MMS among children with NF1, to identify early biomarkers of disease and predictors of MMS progression, to determine the optimal age at which to begin screening with neuroimaging, and to evaluate the impact of screening on outcomes. Additional research efforts should also investigate the use of MRI sequences like perfusion imaging to predict disease stabilization.

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Supplementary data

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