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Outcomes in Patients with Moyamoya Syndrome and Sickle Cell Disease: A Systematic Review

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Key words
- Chronic transfusion therapy
- Moyamoya syndrome
- Revascularization
- Sickle cell disease
- Stroke

Abbreviations and Acronyms
CTT: Chronic transfusion therapy
CVA: Cerebrovascular accident
EDAS: Encephalo-duro-arterio-synangiosis
EMAS: Encephalo-myo-arterio-synangiosis
MMS: Moyamoya syndrome
PS: Pial synangiosis
SCA: Sickle cell anemia
SCD: Sickle cell disease

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BACKGROUND: **Moyamoya syndrome, a progressive, idiopathic stenosis of the internal carotid arteries, results in increased risk for both ischemic and hemorrhagic strokes. Revascularization procedures have been shown in small studies to be both safe and efficacious for these patients; however, randomized controlled trials are lacking. The goal of this systematic review is to organize the literature evaluating surgical intervention versus conservative medical management.**

METHODS: **A systematic review was performed including studies with 3 or more participants with moyamoya syndrome in the setting of sickle cell disease and a measured outcome after either medical or surgical intervention. Relevant studies were identified using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria and a set of predetermined key words.**

RESULTS: **Sixty-one articles were identified with 6 articles ultimately included in this review (N = 122). Of the patients, 73 (59.8%) were revascularized surgically (all indirect procedures), whereas 49 (40.2%) remained on chronic transfusion therapy. Of the patients that underwent indirect revascularization surgery, a total of 1 perioperative (1.4%) and 4 postoperative strokes (5.5%) were reported over 44 months (1 stroke per 53.3 patient-years). In comparison, an average of 46.5% of patients who were receiving chronic transfusions had major events (stroke or transient ischemic attack) while undergoing therapy (1 stroke per 13.65 patient-years, $P = 0.00215$).**

CONCLUSIONS: **We present a large systematic review of the literature regarding outcomes of surgical and medical management for patients with moyamoya syndrome and sickle cell disease. The findings redemonstrate the efficacy and safety of surgical revascularization, and advocate for earlier discussion around surgical intervention.**

INTRODUCTION

Moyamoya disease describes an idiopathic stenosis of the internal carotid arteries.[1,2] When this stenosis occurs in the setting of a disease such as sickle cell anemia (SCA), which is known to predispose to internal carotid artery stenosis, it is termed moyamoya syndrome (MMS).[3] Indeed, the radiographic finding of the moyamoya pattern in the setting of SCA is an independent risk factor for a recurrent cerebrovascular accident (CVA) with worsening vasculopathy having a risk ratio of 12.7 for future infarctions.[4,5]

Although SCA-induced MMS can be debilitating for those affected, it remains a rare condition.[6-8] Because of this rarity and the inherent bias of neurosurgical providers toward action rather than observation, the literature to date consists of predominantly small, retrospective series describing the results of surgical intervention rather than trials comparing medical therapy such as chronic transfusion therapy (CTT) with surgical revascularization. Here, we present the results of a systematic literature review performed to consolidate and better understand the current state of the literature regarding the management of patients with SCA-induced MMS.

METHODS

Electronic Search Method

Electronic searches of PubMed, Scopus, and Cochrane Library databases were performed in September 2019. Relevant studies were identified according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria using the following key words and their derivatives in various combinations: moyamoya, sickle cell, stroke, cerebrovascular accident, treatment, outcomes, and revascularization. Ultimately, all results from the search term "sickle cell disease

moyamoya syndrome" were reviewed to help ensure no eligible studies were missed.

Inclusion and Exclusion Criteria

Studies eligible for review were those that included 3 or more patients with MMS and underlying SCA. Studies that included patients with other pathologies were included if the outcomes of patients with SCA-induced MMS were able to be analyzed in isolation. Additionally, studies were required to provide an outcome measure such as stroke frequency or functional status at last follow-up. Studies which only partially separated patients with SCA-induced MMS from patients with MMS preventing full data abstraction were excluded if the primary data could not be obtained from the corresponding author. Studies were identified and screened by 3 authors (S. N., J. H. B., and J. G. M.), with the lead author performing the ultimate study selection. Finally, studies published in a non-English language or that were performed on animal models were excluded (Figure 1).

Study Assessment of Bias

The Newcastle-Ottawa Scale as adapted for cohort studies was used to evaluate the quality of the included studies with only those studies scoring a 6 or higher being included.

RESULTS

Sixty-one articles were identified with only 6 articles meeting inclusion criteria (N = 122).[9-14] The reasons for exclusion included lack of measurable outcomes, extremely small sample size, and studies that did not separate out the patients with SCA-induced MMS. All included studies were retrospective reviews. One of the studies elaborated on outcomes at a single institution for patients who underwent pial synangiosis (PS) without comparison with conservative management.[14] In the study, Kennedy et al.[14] also included similar cases identified in the literature. The original research was considered for the outcomes of this study, and the other reported cases were vetted for inclusion in their original versions. Three studies compared outcomes for the same cohort of patients preoperatively while receiving CTT and postoperatively.[9-11] Fryer et al.[9] evaluated patients who transitioned from medical to surgical therapy, specifically encephalo-duro-arterio-synangiosis (EDAS) and the clinical and radiographic outcomes for these patients. They reported a single CVA perioperatively, but otherwise no postoperative neurologic events, with an average follow-up of 33 months (n = 6). Additionally, within that follow-up window, 50% of patients had radiographic evidence of collateral anastomoses between external and internal carotid arteries. Similarly, Hankinson et al.[10] performed a retrospective review of patients with sickle cell disease (SCD) who developed radiographic evidence of MMS and underwent EDAS. Two patients suffered postoperative CVAs (n = 12) with an average follow-up of 46.8 months. Seven of the patients in this study underwent postoperative angiography or magnetic resonance angiogram, which were all notable for lack of progression of disease. Smith et al.[11] evaluated a consecutive surgical series of patients with MMS and SCD pre- and postoperatively in a retrospective fashion who underwent PS for revascularization. All 12 patients included in the study presented with ischemic symptoms. With an average follow-up of 49 months, no clinical or radiographic evidence of new infarcts was observed in this cohort; however, disease progression was noted in 68% of patients. The remaining 2 studies compared outcomes for 2 separate patient groups: surgical and conservative.[12,13] Griessenauer et al.[12] evaluated patients on CTT and those within the same cohort who underwent EDAS or encephalo-myo-arterio-synangiosis (EMAS). They found a 5-fold reduction in the stroke rate for patients who had surgery as opposed to those who did not. Hall et al.[13] found a significant decrease in post-revascularization infarct recurrence rate as opposed to the overall infarct recurrence rate. Universally, studies found improved stroke rates postoperatively. All studies concluded that revascularization procedures (PS, EDAS, or EMAS) were safe and effective treatment strategies for SCD and MMS. Half of the studies suggested that screening of patients with SCD should be performed for MMS with magnetic resonance imaging or magnetic resonance angiogram. The included studies were evaluated by the Newcastle-Ottawa Scale for quality assessment. All studies were found to have a score of greater than 6 (Table 1).

The percent of male patients across all studies was 38.5%, with an average age of presentation of 9 years (Table 2). Taken together, the number of patients who underwent surgery was 73 (59.8%), and the number of patients who remained on

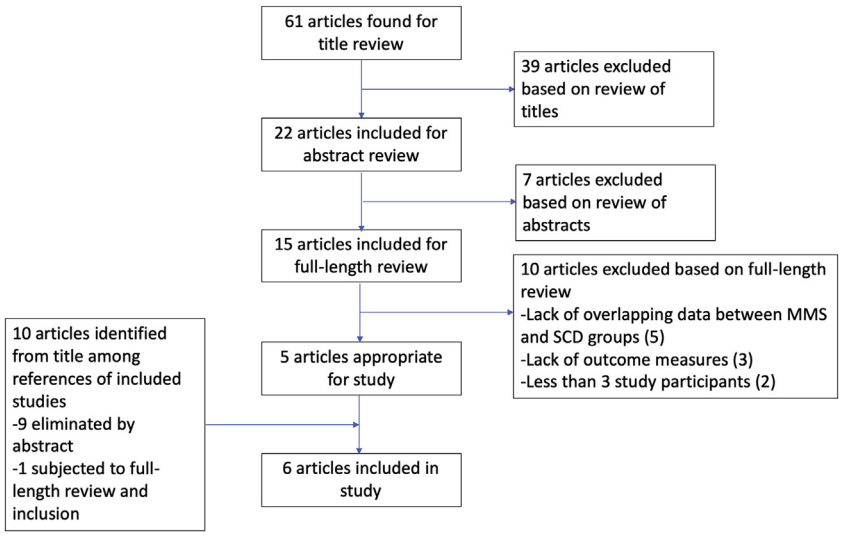

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included and excluded studies. MMS, Moyamoya syndrome; SCD, sickle cell disease.

Table 1. Newcastle-Ottawa Scores for Included Studies

Study	Study Design	Newcastle-Ottawa Scale Score				
		Selection	Comparability	Outcome	Total	Overall Quality
Fryer et al., 2003[9]	Retrospective review	2/4	2/2	3/3	7/9	Fair
Hankinson et al., 2008[10]	Retrospective review	3/4	2/2	3/3	8/9	Good
Smith et al., 2009[11]	Retrospective review	3/4	1/2	3/3	7/9	Fair
Griessenauer et al., 2015[12]	Retrospective review	2/4	1/2	3/3	6/9	Fair
Hall et al., 2016[13]	Retrospective review	3/4	1/2	3/3	7/9	Fair
Kennedy et al., 2014[14]	Retrospective review	4/4	1/2	3/3	8/9	Good

CTT was 49 (40.2%). The presenting symptoms for both medically and surgically managed patients included stroke (48%), transient ischemic attack (20%), seizure (6%), and incidentally discovered vasculopathy (10%). Presenting symptoms were not reported for 16% of included patients (Figure 2). All surgical interventions in this study were indirect revascularization including EDAS (35.6%), PS (56.2%), and EMAS (8.2%) (Figure 3). For all comers, 61% of patients presented with bilateral disease (laterality of disease was reported in 67% of studies).

Of the 73 patients who underwent indirect revascularization, the preoperative medical course was outlined for 61. Of those 61 patients, 84% were on a chronic transfusion protocol before surgery. An average of 46.5% of patients who were undergoing a transfusion protocol had major events (stroke or transient ischemic attack) while undergoing therapy. The length of time on transfusion therapy to cerebrovascular event for these patients was not reported. The average length between initiation of transfusion therapy and surgery was 5.2 years for the 2 studies that reported these data. All surgical interventions performed were indirect revascularizations (Table 3).

For patients that underwent indirect revascularization surgery, a total of 1 perioperative (1.4%) and 4 postoperative strokes (5.5%) were reported, with an average clinical follow-up of 44 months. In 83% of the study patients, a stroke while on CTT prompted surgical intervention. The average radiographic follow-up across studies was 17.8 months, with 100% of the grafts found to be patent (Table 3). The stroke rate in the postoperative group was significantly lower than that in the preoperative group ($P = 0.00215$).

The 4 studies that examined outcomes of only surgical patients strongly leaned toward the efficacy of surgical intervention when weighing the rates of complications with those of recurrent stroke and disease progression.[9-12] In Smith et al.,[11] comparing medical and surgical groups, there were no repeat strokes in the revascularization group, manifesting significant differences between the study groups. In total, 112 patients underwent CTT either exclusively or preoperatively. Of those 112 patients, 63 ultimately received surgical intervention. An additional 10 patients underwent surgical revascularization without having previously received transfusion therapy for a total of 73 patients who underwent

Table 2. Demographics and General Characteristics of Included Studies

Study	All Comers						
	Number of Patients	Average Age (Range) at Presentation (years)	Male (%)	Presenting CVA	Presenting TIA	Seizure	Incidentally Found
Fryer et al., 2003[9]	6	9 (6–17)	66.7	3 (50)	2 (33)	1 (16.7)	0 (0)
Hankinson et al., 2008[10]	12	NR	33.3	6 (50)	2 (16.7)	3 (25)	1 (8.3)
Smith et al., 2009[11]	12	11.3 (3–22)	50	10 (83)	11 (92)	3 (25)	0 (0)
Griessenauer et al., 2015[12]	48	NR	41.7	NR	NR	NR	NR
Hall et al., 2016[13]	27	6.8	55.6	26 (96)	0 (0)	0 (0)	4 (14.8)
Kennedy et al., 2014[14]	17	NR	47.1	7 (41.2)	4 (23.5)	3 (17.6)	3 (17.6)
Total	122	9	46.7	52 (70)	19 (25.6)	10 (13.5)	8 (10.8)

Values are number of patients (%) or as otherwise indicated.
CVA, cerebrovascular accident; TIA, transient ischemic attack; NR, not recorded.

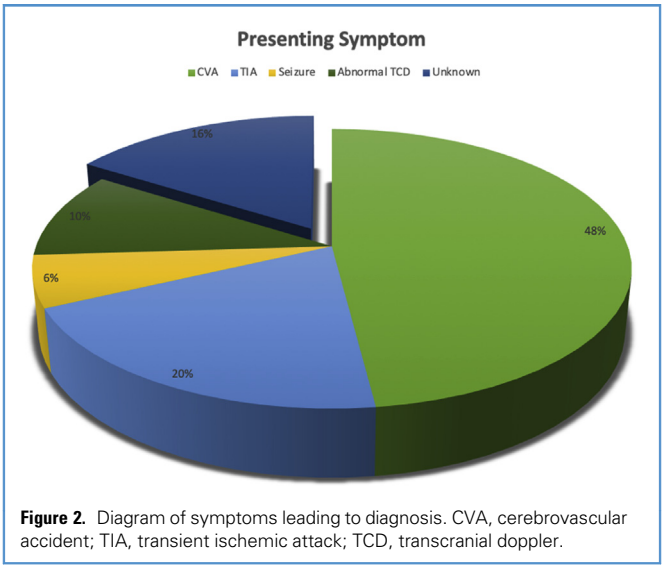

Figure 2. Diagram of symptoms leading to diagnosis. CVA, cerebrovascular accident; TIA, transient ischemic attack; TCD, transcranial doppler.

either EDAS, PS, or EMAS. Sixty-four patients had strokes before undergoing surgery, 24 of whom were on optimal transfusion therapy at the time of their cerebrovascular event. Five patients had postoperative strokes (Table 4). This calculates to a preoperative stroke rate, while on optimal transfusion therapy, of 1 stroke per 13.65 patient-years. This figure was calculated by the number of preoperative patients on optimal transfusion therapy multiplied by the average amount of time from initiation of CTT to surgical intervention (63 patients × 5.2 years = 327.6 preoperative patient-years) and then divided by the number of preoperative strokes while on optimum medical therapy (327.6 patient-years/24 preoperative strokes on CTT = 13.65). The postoperative stroke rate was calculated as 1 stroke per 53.3 patient-years. Again, this number was calculated using the number of patients who underwent surgical revascularization multiplied by the average length of follow-up (73 patients undergoing surgery × 3.65 years = 266.5 patient-years) and then divided by the number of postoperative strokes for these patients (266.5 patient years/5 postoperative strokes = 53.3). In summary, the stroke rate for CTT was 1 stroke per 13.65 patient-years, whereas the stroke event rate for revascularization was lower at 1 stroke per 53.3 patient-years.

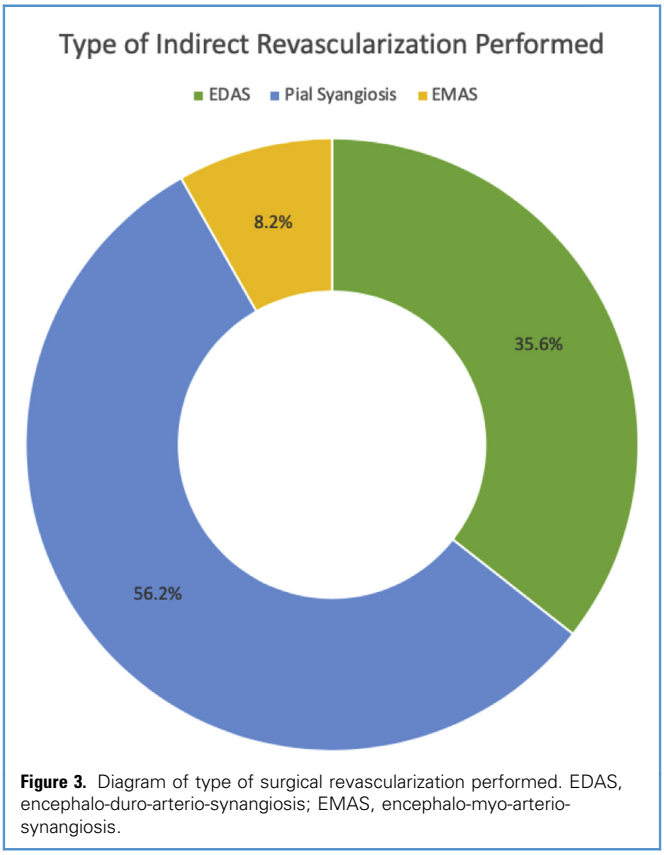

Figure 3. Diagram of type of surgical revascularization performed. EDAS, encephalo-duro-arterio-synangiosis; EMAS, encephalo-myo-arterio-synangiosis.

DISCUSSION

In summary, a systematic review of the available literature yielded only 6 studies in which medical and/or surgical outcomes were evaluated for patients with SCA-induced MMS. The current standard practice is enrollment in a screening and CTT regimen with progression to surgical evaluation if there is worsening of the vasculopathy or repeat neurologic insults, which can happen many years after presentation. Patients presenting for treatment have most often already undergone a cerebrovascular insult, and although not consistently reported, the preoperative stroke rate was higher than the post-revascularization stroke rate (1 per 13.65 patient-years vs. 1 per 53.3 patient-years, respectively). Finally, there is agreement across the research that indirect revascularization is a safe and effective treatment which results in low rates of recurrent stroke and high rates of collateralization.

The most important finding of this review is the percentage of patients on transfusion therapy who suffer neurologic insults before transition to a surgical intervention, which has been demonstrated to be safe and effective at reported clinical and radiographic follow-up. In the same vein, there was found to be a paucity of data about direct revascularization despite the increasingly large body of literature supporting its use over indirect revascularization in adult MMS.[15]

Table 3. Types of Surgical Intervention and Outcomes for Each Study

	Intervention		Immediate Postoperative Outcomes				Long-Term Outcomes			
Study	Type of Surgery	Bilateral (%)	Complications	TIAs	CVAs	Deaths	Average Length of Follow-Up (months)	TIAs	CVAs	Deaths
Fryer et al., 2003[9]	EDAS (100%)	66	0 (0)	0 (0)	0 (0)	0 (0)	33	0 (0)	1 (17)	0 (0)
Hankinson et al., 2008[10]	EDAS (100%)	58	2 (18)	0 (0)	0 (0)	0 (0)	47	1 (8.3)	1 (8.3)	0 (0)
Smith et al., 2009[11]	Pial synangiosis (100%)	17	2 (18)	0 (0)	1 (8.3)	0 (0)	49	0 (0)	0 (0)	0 (0)
Griessenauer et al., 2015[12]	EDAS (57.2%); EMAS (42.8%)	NR	2 (14)	0 (0)	0 (0)	0 (0)	34	0 (0)	1 (7.1)	0 (0)
Hall et al., 2016[13]	Pial synangiosis (100%)	64	4 (33)	0 (0)	0 (0)	0 (0)	NR	2 (17)	0 (0)	0 (0)
Kennedy et al., 2014[14]	Pial synangiosis (100%)	59	3 (11)	0 (0)	0 (0)	0 (0)	57	1 (5.8)	1 (5.8)	0 (0)

Values are number of patients (%) or as otherwise indicated.
TIA, transient ischemic attack; CVA, cerebrovascular accident; EDAS, encephalo-duro-arterio-synangiosis; NR, not recorded; EMAS, encephalo-myo-arterio-synangiosis.

This study represents a large systematic review of the available literature regarding SCA-induced MMS and the treatment strategies available to these patients. It reaffirms what smaller studies have found: revascularization procedures for these patients provide a decrease in postoperative stroke rates. This study highlights that surgical intervention is associated with significantly lower rates of negative outcomes compared with patients who remain on CTT. What remains unanswered by any of the literature is the optimal timing for ipsilateral and contralateral surgery in the context of specific risk factors including SCA severity, radiographic appearance (Suzuki score), and type of surgical intervention to be performed.

The limitations of the included studies are the retrospective nature of the research and the small sample sizes. Additionally, the external validity of the current review is limited by 2 factors. First, because the average age of presenting patients was 9 years, the findings of this review are of limited use to adult patients seeking treatment. Second, the body of MMS literature not published in English was not included here, limiting the results of this review regarding patients of Asian descent. Finally, the studies reviewed were not standardized in terms of who was offered revascularization, when revascularization was offered, or for how long they were followed postoperatively, limiting the ability to draw conclusions from the rates of complications and recurrent strokes.

Surgical interventions remain unexplored by randomized controlled trials despite the mounting evidence in observational studies for their benefit. At this time, many questions about treatment remain unanswered, including which type of surgery to perform and the timing of said intervention. Based on the review of all available data on this topic, we advocate for earlier radiographic evaluation with angiography to appreciate the extent of the disease in patients known to be at risk with scheduled repeat examinations and an early discussion regarding the potential need for surgical intervention to prevent a CVA. In an effort to assist with these discussions and management decisions, future research should focus on a prospective registry to compare ongoing

Table 4. Pre- and Postoperative Outcomes for Medical and Surgical Interventions

	Study Groups				
Study	Chronic Transfusion Therapy	Surgical Intervention	Preoperative CVA	CVA on Optimum Transfusion Therapy	Postoperative CVA
Fryer et al., 2003[9]	6	6	7	1	1
Hankinson et al., 2008[10]	7	12	10	5	1
Smith et al., 2009[11]	12	12	10	7	1
Griessenauer et al., 2015[12]	48	14	14	NR	1
Hall et al., 2016[13]	27	12	11	6	0
Kennedy et al., 2014[14]	12	17	12	5	1
Total	122	73	64	24	5

CVA, cerebrovascular accident; NR, not recorded.

medical management versus direct and/or indirect revascularization.

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