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Sickle Cell Anemia With Moyamoya Disease: Outcomes After EDAS Procedure

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Moyamoya disease is a relatively uncommon neurovascular complication of sickle cell anemia. We report a case series of six patients with sickle cell anemia who developed moyamoya disease and underwent encephaloduroarteriosynangiosis procedures. These six patients presented with either cerebrovascular accidents, transient ischemic attacks, or seizures, and subsequent magnetic resonance imaging scans were suggestive of moyamoya-like changes in the cerebral vasculature. Conventional cerebral angiography was used to confirm the diagnosis in all six patients. Four of six patients manifested a cerebrovascular accident before surgery, and two of these patients were compliant on a transfusion protocol at the time of their cerebrovascular accident. Bilateral (n = 4) or unilateral (n = 2) encephaloduroarteriosynangiosis procedures were performed without any complications. The patient who was stroke-free preoperatively had a cerebrovascular accident 2 weeks after the procedure; otherwise, all patients have remained free of neurovascular complications with an average follow-up of 33 months. Collateral anastomoses between external and internal carotid arteries were established by magnetic resonance angiography in three patients. The encephaloduroarteriosynangiosis procedure is a safe and effective treatment option in patients with sickle cell anemia who develop moyamoya disease.

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Introduction

In pediatric patients with sickle cell anemia, cerebrovascular complications such as cerebral infarction and intracranial hemorrhage have been reported to occur by age 20 in approximately 11% of patients [1]. This high incidence has been attributed to many factors including a microvasculopathy involving the arterioles and capillaries [2], impaired cerebral autoregulation [3,4], and a large vessel vasculopathy with intimal hyperplasia [5,6]. In some patients with sickle cell anemia, a large vessel vasculopathy is accompanied by a proliferation of a fragile network of vessels at the base of the brain in an angiographic pattern resembling moyamoya disease [4,6-9].

Moyamoya disease is a rare, chronic occlusive cerebrovascular disorder characterized by two important features: progressive bilateral stenosis of the arteries of the Circle of Willis and formation of small capillary-sized vessels that provide collateral blood flow. Angiographically, these abnormal reticular vessels look like a puff of smoke, which brings about a hazy, or moyamoya ("misty" in Japanese) appearance. These vascular changes commonly result in ischemic strokes in children and cerebral hemorrhages in adults [10]. In addition to the idiopathic presentation, the moyamoya angiographic pattern appears to be a nonspecific response to various underlying conditions, including sickle cell anemia [11], neurocutaneous syndromes such as neurofibromatosis [12], bacterial meningitis [13], tuberculosis [14], use of oral contraceptives and cigarette smoking [15], atherosclerosis [16], tetralogy of Fallot and blood overtransfusion [12], Fanconi's anemia [17], periarteritis nodosa and other connective tissue abnormalities [18], prior cranial irradiation therapy [19], Down's syndrome [20,21], and head and neck infections [19].

Currently, patients with sickle cell anemia who have had a cerebrovascular accident or who have exhibited

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evidence of large vessel vasculopathy by transcranial Doppler ultrasonography are treated with chronic transfusion therapy [22]. Transfusions have not only been described to significantly decrease the risk of subsequent infarction [22,23], but significant improvement in neurologic function after cerebrovascular accident has also been noted following transfusions [24]. Chronic transfusion therapy, however, is not without risk. Iron overload and hemosiderosis are potential complications, which may require cessation of treatment [25]. Furthermore, the beneficial effects of blood transfusions in preventing cerebral infarcts in children with sickle cell anemia seem to continue only as long as the patient remains on transfusion therapy [2]. Relapses occur when transfusions are stopped, even before the percentage of HbS begins to increase [26].

Surgical interventions, including direct and indirect vascularization procedures, alleviate many of the ischemic symptoms in patients with idiopathic moyamoya disease who have evidence of reduced perfusion reserve by positron emission tomography or single-photon emission computed tomography scan [27,28]. Questions remain, however, as to the safety and efficacy of these surgical techniques in patients with sickle cell anemia and moyamoya disease [18]. While there have been many reported cases of surgical revascularization in idiopathic moyamoya disease, to our knowledge there is only one report of a patient with sickle cell disease undergoing an encephaloduroarteriosynangiosis (EDAS) procedure [18]. In this series, we report outcomes for six patients with both sickle cell anemia and moyamoya disease who underwent EDAS procedures.

Table 1. Preoperative patient characteristics

Patient	Gender	Age: Symptom	Preoperative Angiogram
1	M	7: Focal seizure 7: TIA	Complete occlusion of bilateral A1 segments, mild narrowing of L supraclinoid ICA (figure 1A)
2	M	6: CVA 6: Focal seizure 7: CVA 16: TIA*	R MCA occluded; high grade stenosis of L MCA and ACA
3	F	6: CVA 10: Focal seizure 10: CVA*	R ICA, proximal MCA and ACA stenotic; L M1 segment stenotic and hypoplastic L A1 segment (figure 1B)
4	F	17: TIA 17: CVA	L ICA occluded, L ACA stenotic; R ICA, MCA and ACA uninvolved
5	M	7: CVA 12: CVA	R ICA occluded; L ICA stenotic with complete occlusion of L MCA
6	M	10: TIA 11: Focal seizure 12: Focal seizure	L and R ICA occluded, large R PCOM supplying R ACA and MCA distribution

* Events occurred while compliant on transfusion therapy.

Abbreviations:
ACA = Anterior cerebral artery
CVA = Cerebrovascular accident
ICA = Internal carotid artery
L = Left
MCA = Middle cerebral artery
PCOM = Posterior communication artery
R = Right
TIA = Transient ischemic attack

Materials and Methods

Patient Population

Six patients with sickle cell disease and moyamoya disease who underwent EDAS procedures between 1996-2000 at Children's Hospital of New York, Columbia-Presbyterian Medical Center were identified prospectively. Four of the patients are black (2 males, 2 females), and two patients are Hispanic (both males). Their ages ranged from 6 to 17 years at the time of their presentation (Table 1). All six patients presented with a neurologic event—either a cerebrovascular accident, transient ischemic attack, or seizure—and underwent a comprehensive preoperative evaluation that included magnetic resonance imaging and magnetic resonance angiography (MRA) imaging, trans-cranial doppler studies, single-photon emission computed tomographic scans, and cerebral angiography.

Operative Intervention

All patients underwent either single (n =2) or bilateral (n =4) EDAS procedures. Originally described in detail by Matsushima et al. [29,30], the goal of the operation is to facilitate the formation of spontaneous anastomoses between the external and internal carotid arteries. In brief, the donor scalp artery (most commonly the superficial temporal artery) is exposed and freed, maintaining the surrounding connective tissue and galea underneath. This continuous fibrovascular bundle is then transplanted through a small craniotomy with dural and arachnoid opening and sutured to the pia of the posterior frontal lobe, taking care to leave both the proximal and distal ends of the donor artery untouched. Spontaneous anastomoses can then develop between cortical, dural, and scalp arteries.

Perioperative Management and Anesthetic Considerations

Optimal anesthetic management for children with moyamoya and sickle cell anemia balances the need to minimize the cerebral metabolic oxygen consumption rate while maintaining adequate cerebral blood flow. All of the patients in our series were admitted the night before surgery to optimize hydration prior to surgery. Intraoperative electroencephalogram monitoring was performed to assist in patient assessment, and arterial blood gas measurements repeatedly conducted to monitor CO_2 and avoid hypocarbia. Tagawa and coworkers reported a marked reduction in regional cerebral blood flow when the Pa_{CO_2} declined below 29 mm Hg [31]. Hyperventilation-induced hypocarbia may be causing constriction of normal cerebral vessels and a "steal" from the moyamoya collateral vessels. Furthermore, every attempt was made to maintain intraoperative normothermia. Hyperthermia causes an increase in cerebral oxygen consumption and can precipitate neurologic deficits, while hypothermia can induce a sickle cell crisis. Postoperatively, attention was given to maintain adequate levels of analgesia to reduce pain and crying, which can lead to an increase in cerebral oxygen consumption, hyperventilation, hypocarbia, and vasoconstriction [32].

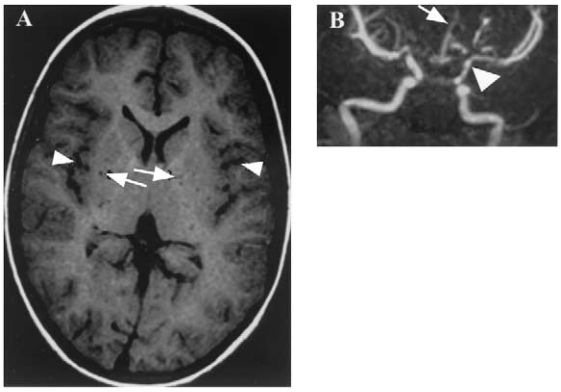

Figure 1. (A) FSE-weighted axial magnetic resonance imaging (TR= 3000, TE=14) of Patient 1 indicating vessel flow voids in the basal ganglia (white arrows) and enlarged flow voids of cortical vessels (white arrowheads). (B) MRA of the same patient. The internal carotid arteries appear normal up to the area above the carotid siphon, at which point there is more narrowing on the left side (white arrowhead) compared with the right side, extending into the M1 segments, with marked focal stenosis of the A1 segments, although the anterior cerebral artery remains patent (white arrow).

Postoperative Monitoring

Patients underwent a combination of neuroimaging tests within the first year following the EDAS procedure. Four of six patients received a postoperative magnetic resonance imaging scan. These scans were compared with preoperative images to determine if there had been any new "silent" infarcts. To visualize the grafted vessels, one patient underwent a cerebral angiogram and three patients underwent magnetic resonance angiography with surface coils.

Results

Characteristics of Sickle Cell Patients With Moyamoya Disease

Presenting neurologic events in our six patients included cerebrovascular accident (n = 3), seizure (n = 1), and transient ischemic attack (n = 2). The average age at the time of the presenting neurologic event was 9 years old (range 6-17). There were a total of 16 neurologic events (mean 2.7; range 2-4; [Table 1]), including seven cerebrovascular accidents, five seizures, and four transient ischemic attacks (Table 1). Cerebrovascular accident was the most common neurologic event, affecting four of six patients (67%) preoperatively. Four patients manifested a seizure (67%), all of which had an apparent focal onset. All patients were treated with chronic transfusion therapy. Two of these patients manifested neurologic events while on optimum transfusion therapy (Patients 2 and 3). Patient 5 had been placed on transfusion therapy but because of noncompliance missed three consecutive months during which period he had a cerebrovascular accident (Table 1).

Radiographic Findings

Patients were given the diagnosis of moyamoya disease after careful review of magnetic resonance imaging/magnetic resonance angiography scans performed following a neurologic event. The findings on magnetic resonance imaging that were suggestive of moyamoya disease included flow voids in the basal ganglia and enlarged cortical vessels (Fig 1A). Magnetic resonance angiography was useful in identifying the diseased large vessels (Fig 1B), but the small caliber moyamoya vessels were often difficult to see. Cerebral angiography was performed in all patients to verify the diagnosis, and provided the added benefit of viewing the donor artery as the external carotid artery was also imaged during the angiography.

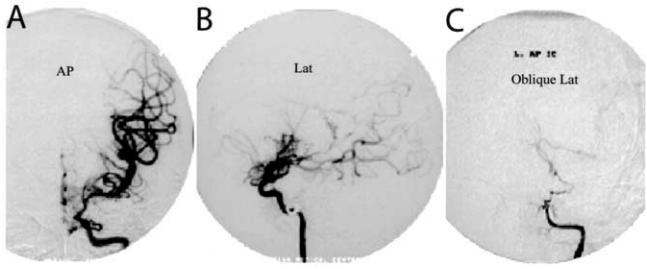

Figure 2. Preoperative cerebral angiography of moyamoya disease in patients with sickle cell anemia. (A) Left internal carotid artery injection in Patient 1, with narrowing of the internal carotid artery just before the bifurcation, a nearly absent A1 segment, but with relatively preserved flow to the middle cerebral arteries. (B) An angiogram of Patient 3, the left internal carotid artery is visible, but there is virtual absence of any distal middle carotid artery branches, the A1 segment is hypoplastic, and there is evidence of shunting to the posterior circulation. (C) Figure 2C shows complete occlusion of the left internal carotid artery with a short branch anastomosing with the middle cerebral artery in Patient 6. Abbreviations: AP = anterior-posterior; Lat = lateral.

Moyamoya disease can involve any of the vessels of the circle of Willis, although typically the anterior circulation is preferentially involved. The distribution of involvement in the anterior circulation illustrated two predominant patterns, differentiated by involvement of the internal carotid artery. Two patients (1 and 2; 33%) predominantly manifested involvement of the anterior carotid artery and/or middle carotid artery with relative sparing of the internal carotid artery, while the remaining four patients (3, 4, 5 and 6; 66%) developed internal carotid artery stenosis or occlusion, with 4 of 8 internal carotid arteries completely occluded. All patients in our series manifested involvement of the anterior circulation, with five of six patients demonstrating bilateral involvement, and only one patient, Patient 4, showing unilateral involvement (Table 1). Patient 6 manifested only anterior circulation involvement on his initial angiogram; however, a postoperative angiogram performed 1.5 years after the initial angiogram revealed posterior circulation involvement. Angiograms of three patients are illustrated in Figure 2.

Clinical and Radiographic Outcome

A total of 10 EDAS procedures were performed on 6 patients. There were no perioperative complications. Patients who underwent EDAS procedures on both sides (four of six patients) underwent two separate operations

Table 2. Postoperative follow-up

Patient	Months*	Events*	Neuroimaging (Interval Post-EDAS)
1	29	1†	MRI (8 weeks): increased signal on FLAIR images in R frontal lobe white matter. MRA‡: anastomotic branches between transplanted STA and MCA on L > R sides.
2	31	0	MRI (1 year): no evidence of any new infarcts. MRA‡: short intracranial branches from STA to MCA on L > R sides.
3	28	0	MRI (7 months): no evidence of any new infarcts. MRA‡: STAs patent with filling of perisylvian branches of MCA.
4	36	0	No follow-up imaging.
5	31	0	Head CT (5.5 months): performed after minimal head trauma showed no new infarcts.
6	43	0	MRI (4 months): no evidence of any new infarcts. Cerebral angiogram (1.5 years): B ICA occlusions, L MCA branches filled by large L meningeal and STA arteries (Fig 3), large R PCOM with supply of R MCA and ACA

* Post-EDAS.
† Patient 1 had a CVA 2 weeks after an ipsilateral EDAS procedure.
‡ With surface coils.

Abbreviations:
ACA = Anterior cerebral artery
B = Bilateral
CVA = Cerebrovascular accident
ICA = Internal carotid artery
L = Left
MCA = Middle cerebral artery
MRA = Magnetic resonance angiography
PCOM = Posterior communication artery
R = Right
STA = Superficial temporal artery
TIA = Transient ischemic attack

spaced approximately 4 weeks apart. The average length of monitoring was 33 months (range 28-43 months; Table 2). Only one postoperative neurologic event has taken place in this series of patients to date. Patient 1 underwent a right-sided EDAS procedure and 2 weeks later had an episode of left face and arm weakness that resolved completely within 3 days. A subsequent magnetic resonance imaging revealed a new lesion in the central nervous system territory corresponding to his symptoms.

Postoperative neuroimaging studies consisted of magnetic resonance angiography with surface coils (three patients) or cerebral angiography (one patient) within the first year. Two patients (Patients 4 and 5) were noncompliant with postoperative magnetic resonance imaging imaging studies, although Patient 5 had a head computed tomogram during a visit to the emergency room for minimal head trauma (Table 2). To assess patency of the graft and growth of collaterals, a magnetic resonance angiogram with surface coils was performed in patients

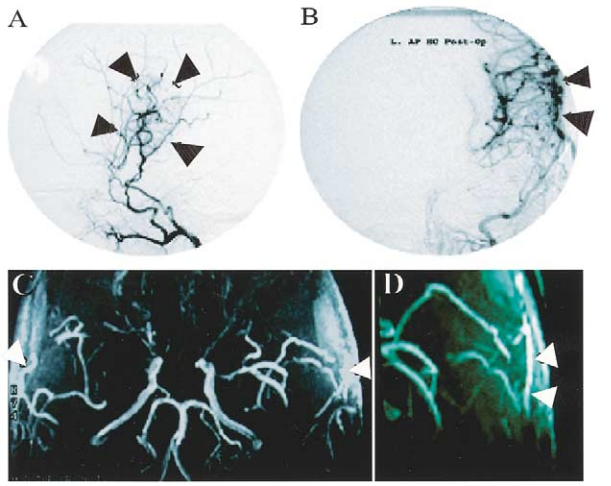

Figure 3. Postoperative angiogram (A, B) and magnetic resonance angiogram with surface coils (C, D). (A) Lateral view of left external carotid artery injection 1.5 years after a left EDAS procedure (Patient 6). The arrowheads outline an area with the grafted vessel in the center surrounded by smaller collateral vessels. (B) In the same patient, an AP view of left external carotid artery injection shows the donor superficial temporal artery vessel (arrowheads) with collateral vessels connecting with branches of the middle cerebral artery. (C) Birdseye view of magnetic resonance angiogram with surface coils illustrate internal carotid arteries and vertebrobasilar system medially, and transplanted superficial temporal arteries (arrowheads) laterally in a patient 11 weeks post left-sided EDAS procedure and 8 weeks post right-sided EDAS procedure. (D) Magnified view of right superficial temporal artery (arrowheads) in same patient from (C). Note the small collateral vessels from the transplant. Abbreviations: AP = anterior-posterior.

one through three. A representative magnetic resonance angiogram is revealed in Figure 3. Magnetic resonance angiography with surface coils demonstrated patency of graft vessels and growth of collateral and anastomotic vessels in all three patients. Collateral formation was visible as early as 6 weeks postoperatively, as seen in Patient 1. Patient 6 underwent conventional cerebral angiography, which illustrated robust growth of collateral vessels in and around the grafted vessel (Fig 3).

Discussion

Although cases of moyamoya disease have been reported worldwide, the vast majority of cases have occurred in Japan [33]. Epidemiologic studies of moyamoya disease have revealed that while moyamoya disease can present at any age, the majority of cases occur in children under the age of 10 years [10]. Childhood moyamoya disease typically presents with signs of ischemia, whereas adult patients are more likely to present with hemorrhage [10, 34]. Angiographically, the moyamoya changes appear to progress rapidly in early childhood, and then more slowly through late childhood and adolescence [35]. Ischemic symptoms such as seizures, transient ischemic attacks and cerebrovascular accidents occur when the cerebral blood flow and perfusion reserve become insufficient, and can occasionally be induced by hyperventilation or crying. As the developing brain has greater metabolic demands than the mature brain, clinical symptoms are much more likely

to occur in early childhood. In most cases, the disease remains relatively stable throughout adolescence, as there appears to be little angiographic progression and the metabolic demands of the cerebrum have declined from early childhood [35]. Presumably as a result of atherosclerotic changes, adults who have managed to remain asymptomatic throughout childhood then present with the hemorrhagic type of moyamoya disease [35].

The initial symptomatology of patients with sickle cell anemia and moyamoya disease was similar to that seen in moyamoya disease: five of six patients in this series presented under the age of 10 years with a variety of ischemic symptoms including seizures, transient ischemic attacks, and cerebrovascular accidents. However, the incidence of cerebrovascular accident was much greater in patients with sickle cell anemia and moyamoya disease. It has been reported that 39% of patients under the age of 15 with moyamoya disease have cerebrovascular accidents [27], while six of six patients in this series manifested at least one cerebrovascular accident. The most likely explanation for this relates to effects that the hematologic abnormalities of sickle cell anemia have on the cerebral vasculature. In neurologically asymptomatic individuals with sickle cell anemia, the cerebral vasculature is characterized by a relative hyperemia combined with a reduced perfusion reserve capacity [36]. The combination of moyamoya-like large vessel stenosis along with an already reduced cerebral perfusion reserve capacity likely accounts for the increased incidence of cerebrovascular accidents observed in patients with sickle cell anemia and moyamoya disease.

Medical treatment for moyamoya disease, including steroids, vasodilating agents, anti-platelet agents, and heparinoids, have been disappointing [18,37]. In general, moyamoya patients with ischemic symptoms and poor perfusion on a cerebral blood flow study (single-photon emission computed tomography or positron emission tomography) are good candidates for direct or indirect bypass procedures [28,34,38,39]. The EDAS procedure was chosen because it has several major advantages over the other surgical procedures, namely superficial temporal artery-middle cerebral artery (STA-MCA) bypass and encephalo-myo-synangiosis (EMS). The EDAS procedure is rapid, technically relatively easy to perform, and associated with a low morbidity mainly because the recipient vessel is not divided, interrupted, or clamped at any time during the operation [29]. EDAS permits neovascularization to develop over a larger area of the brain than observed with direct anastomosis [40,41] and has been revealed to cause cessation of symptomatic attacks much sooner than the natural course of the disease [42]. In contrast, STA-MCA bypass, which involves the direct anastomosis between the superficial temporal artery and the middle cerebral artery, is often not feasible in children because of the small caliber of both the donor and recipient vessels [30]. Moreover, cerebral vessels have to be interrupted during the course of the procedure, which can be potentially harmful for tissues with borderline vascularization [18,43] and lead to more serious postoperative complications [44,45]. EMS likewise carries numerous disadvantages: it requires a large incision and a significant craniectomy with subsequent risk of impairment of the spontaneous anastomoses between intracranial and extracranial arteries; extensive scarring and adhesions can form between the muscle and brain, leading to a higher postoperative occurrence of seizures [30]; and cosmetic results are often poor. Additionally, some authors have reported more rapid revascularization and better cerebral blood flow and angiographic assessments with EDAS when compared with EMS [46]. To date, there have been no controlled prospective studies comparing direct and indirect revascularization procedures, and retrospective studies comparing differences in outcomes between direct and indirect anastomosis have not proven to be statistically significant [10].

Some would argue that sickle cell anemia is a relative contraindication to an indirect bypass procedure as occlusion of the small anastomotic branches would occur in the postoperative period during the time of a sickle cell crisis [18]. This did not appear to be the case as we were able to confirm graft patency in four of six patients using either invasive (angiography) or noninvasive (magnetic resonance angiography with surface coils) techniques. The two patients who have not had confirmation of graft patency by radiographic means have not manifested any clinical events postoperatively. Other criticisms of the EDAS procedure have questioned the adequacy of the blood supply offered by the EDAS procedure [44,47-49] and emphasized the potential for continued ischemic events during the time required for brain revascularization [50]. Matsushima et al., however, reported that clinical improvements in 25 patients undergoing EDAS began as early as 4 days (mean 10 days), with nearly half of the patients (12 of 25) having improved deficits or diminished attacks within 3 weeks [42]. These clinical data correlate with recent reports that indicated collateral vessels and retrograde filling of the middle carotid artery branches at about 1 month after indirect bypass by angiography [51] or magnetic resonance angiography [9,34]. In our series, the only clinical event that occurred post-EDAS, a cerebrovascular accident, occurred on the side ipsilateral to an EDAS procedure 2 weeks postoperatively. This time frame is too short for adequate revascularization to have occurred from the EDAS procedure, and is not likely to be due to failure of the EDAS procedure. Furthermore, subsequent magnetic resonance angiography with surface coils revealed that the graft was patent, and there was evidence of anastomotic vessels between the graft vessel and distal perisylvian branches of the middle carotid artery.

We recommend screening of all children with sickle cell anemia who present with focal ischemic symptoms with magnetic resonance imaging and magnetic resonance angiography. Although cerebral arteriography has tradition-

ally been regarded as essential for a definitive diagnosis of moyamoya disease [52], magnetic resonance imaging and magnetic resonance angiography are now accepted to provide sufficient diagnostic information for a firm diagnosis of moyamoya disease [35,52-54]. Definitive angiography should be reserved for those patients for whom surgery would be considered on the basis of magnetic resonance angiography evaluation. We believe that when moyamoya disease is detected, surgery should be considered as early as possible for all patients, given the potential severe neurologic deterioration that is possible in children with moyamoya disease. Our data, in addition to the patient report of Vernet et al. [18], indicate that EDAS is a safe and effective procedure in patients with sickle cell anemia and moyamoya disease.

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