



Original Article

Seizure outcome in moyamoya after indirect revascularization in pediatric patients: Retrospective study and literature review

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ABSTRACT

Background: Moyamoya disease (MMD) is a unique cerebrovascular disorder characterized by progressive stenosis of anterior cerebral circulation. Moyamoya is not an uncommon disease in Saudi Arabia. Although a less common symptom of the disease, the incidence of seizure in MMD ranges from 6 to 30%. Indirect revascularization through Encephaloduroarteriosynangiosis technique is one of the surgical treatment options for MMD. In our cohort, we aim to evaluate seizure outcome in pediatric patients with moyamoya.

Methods: Eleven patients with seizure as primary presentation for MMD over a period of 10 years were included in the study. All patients underwent EDAS surgery. All patients underwent pre- and postoperative assessment of multiple factors contributing to seizure outcome. Patients were evaluated for surgery control clinically and radiologically.

Results: About 73% of MMD patients with seizures improved after EDAS surgery ($P < 0.0005$). Six patients out of 11 became seizure free. Patients with bilateral involvement of disease undergoing bilateral surgery had better seizure control than those undergoing unilateral surgery ($P < 0.07$).

Conclusion: Patients with controlled seizure before surgery are more likely to be seizure free after intervention. Seizure outcome is favorable after indirect surgical revascularization in pediatric moyamoya patients.

Keywords: Encephaloduroarteriosynangiosis, Indirect revascularization, Moyamoya, Pediatric epilepsy

INTRODUCTION

Moyamoya disease (MMD) was first reported in Japan by Takeuchi and Shimizu in 1957 and then identified as a distinct disease by professor Suzuki in 1968.^[21] It is a unique cerebrovascular disorder characterized by progressive stenosis of the terminal portion of the internal carotid artery (ICA).^[20] Moyamoya is a Japanese expression for a hazy cloud resembling a puff of smoke. It is used to describe the angiographic appearance of the flimsy network of collaterals that form to compensate for the ischemia caused by the narrowing of blood vessels supplying the brain.

Moyamoya is not an uncommon disease in Saudi Arabia, multiple cases were reported for moyamoya syndrome secondary to protein S deficiency, cranial radiation, systemic lupus erythematosus, Fanconi anemia, and in association with diabetic ketoacidosis.^[1-3,5,8]

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It is estimated to represent 5.8–20% of stroke etiology in Saudi pediatric patients.^[6,18] Indirect anastomosis was described by Matsushima *et al.* in 1981 using encephaloduroarteriosynangiosis (EDAS) technique.^[12]

Symptoms accompanying MMD include stroke, seizure, and headaches.^[7] The incidence of epilepsy in MMD is variable. It was reported between 6–12.5%,^[9] 20–30%,^[19] and 18.1%.^[11] It is reported that pediatric moyamoya patients undergoing EDAS show a more favorable outcome in patients presenting with seizure manifestations in comparison with those presenting with ischemic stroke or transient ischemic attacks (TIA).^[4] In this cohort, we aim to evaluate seizure outcome in moyamoya after EDAS in pediatric patients.

MATERIALS AND METHODS

Subjects

We selected patients who were diagnosed with moyamoya and underwent EDAS surgery at the Department of Neurosurgery, King Faisal Specialist Hospital and Research Center, Riyadh, between 2001 and 2011. The hospital research ethics board approved this study. Included patients had to be diagnosed with MMD with magnetic resonance imaging (MRI), magnetic resonance angiogram (MRA), and cerebral angiography findings of stenosis or occlusion in terminal intracranial ICA or proximal portions of anterior and middle cerebral artery with evidence of an abnormal vascular network. All included patients have seizure as a primary presenting symptom with postoperative follow-up period at our center of more than 5 years.

Retrospective review

We reviewed patient's charts and clinical notes and images for patient's sex, age at onset, age at first surgery, presentation of stroke and/ or seizure, developmental delay, cognitive impairment, seizure control, etiology, and radiological findings. Radiological findings were retrieved from multiple radiological reports reported by at least two experienced radiologists.

Clinical assessment and follow-up

Of all identified patients who underwent EDAS surgery and fit the inclusion criteria in the selected period, only patients who presented with seizures as a primary symptom and who were followed for more than 5 years were included in the study. Included patients were evaluated and managed by a pediatric epileptologist pre- and postintervention. We studied the etiology of moyamoya, either idiopathic or related to another pathology, presence, and type of stroke, pre- and postoperative seizure status, and the number of

anti-epileptic drugs (AED) to control seizures. Before the intervention, all patients were evaluated by MRI, MRA, and cerebral angiogram [Figures 1 and 2]. All patients underwent the same technique for EDAS by the same surgeon [Figure 3].

Statistical analysis

We assessed patients on pre- and postsurgery number of AED used and seizure control. Dividing the patients into two groups: improved seizure control and not improved seizure control. We looked at different variables including radiological findings and surgical interventions. Variables were analyzed with binominal tests and Chi-square. $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS for Windows, version 19.0.

RESULTS

A total of 22 patients were identified, 14 were having seizures at their initial presentation as a primary symptom, 11 patients were followed at least 5 years after surgery (5 males and 6 females) [Table 1].

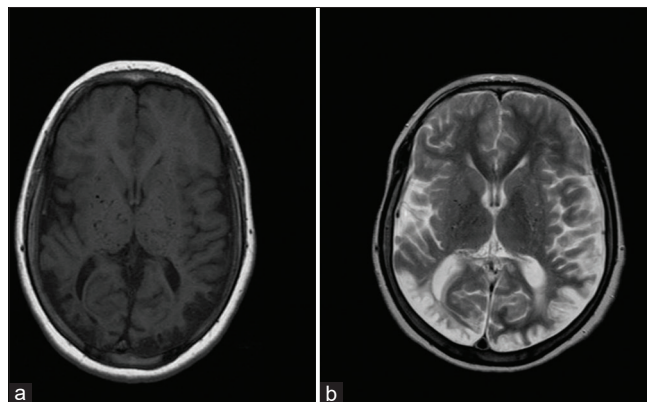


Figure 1: MRI brain (a: T1 and b: T2 weighted image) for a patient with Moyamoya.

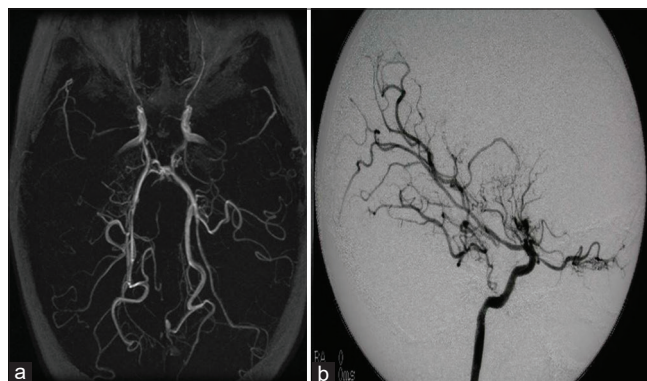


Figure 2: (a) MRA brain and (b) cerebral angiogram for a patient with moyamoya.

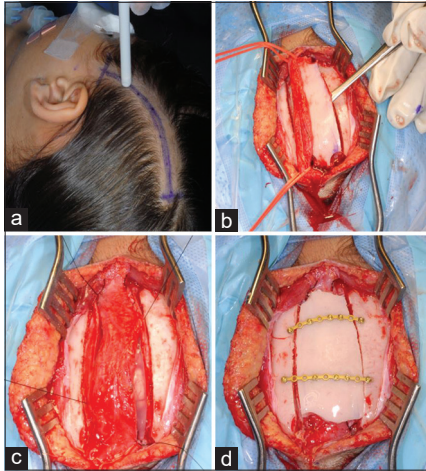


Figure 3: Surgical technique: (a) identify the superficial temporal artery using Doppler ultrasound. (b) After isolating the artery with facial small facial flap, a strip craniotomy was done. (c) The dura was opened and sutured to the flap. (d) Bone flap was fixed with plate and screws.

Table 1: Clinical features of 22 children with MMD.

Clinical feature	Value
Age at onset in years (range)	14.1±4.2 (0.9–15)
Age at first surgery in years (range)	15±4.9 (2–17)
Delay in years (range)	10±2.2 (0–10)
Female:male	05:06
Stroke at presentation	100% (22)
Seizure at presentation	63.6% (14)
Etiology	
Hematological disorder	31.8% (7)
Neurofibromatosis 1	4.5% (1)
Glycogen storage disease	4.5% (1)
Craniopharyngioma + radiation	4.5% (1)
Bilaterality	91% (20)
Posterior circulation involvement	59% (13)

Patients demographics

The mean age of our patients with MMD at the time of disease onset was 6 years (from 11 months to 15 years). All 22 patients had ischemic strokes, except 1 patient diagnosed with sickle cell anemia and glucose-6-phosphate dehydrogenase deficiency who had a hemorrhagic stroke. Of all the 22 patients, 14 patients presented with seizures as the primary symptom of their stroke. Only four patients out of the 11 patients had both developmental delay and cognitive decline with no other etiology.

Etiology

Ten of the 22 patients had a secondary etiology to Moyamoya, seven of them are hematological disorders. Two patients were diagnosed with sickle cell disease and one patient carried

sickle cell trait. Another patient had both sickle cell disease and G6PD deficiency. One patient with hypercoagulopathy, one patient with protein S deficiency, and one patient with alpha thalassemia. One patient had a craniopharyngioma that was resected and received radiotherapy before moyamoya diagnosis. One patient with glycogen storage disease and one patient with neurofibromatosis type 1.

Radiological findings

MRI, MRA, and cerebral angiography for all 22 patients showed bilaterality in 90% of patients before EDAS surgery. About 50% of patients showed posterior circulation involvement either at the time of diagnosis or with repeated images. ICA stenosis was noted in all patients, along with anterior and middle cerebral arteries.

All 22 patients had parenchymal changes on imaging, encephalomalacia, gliosis, and brain atrophy were noted. Most patients had large watershed infarcts. Degree of damage between patients with and without seizures was similar, involving large areas of the brain, sometimes a whole hemisphere.

Surgery status

EDAS was performed after finding the superficial temporal artery using Doppler ultrasound. A small strip craniotomy is done to allow for easy placement of the artery that is then sutured under the dura and the bone is fixed back to allow for healthy formation of collaterals. The procedure was performed by the same surgeon in the same technique for all patients.

Eight of the 11 patients with epilepsy underwent bilateral EDAS surgery by the same surgeon, at least 3 months apart and at most 2 years apart. Three patients underwent unilateral surgery for the more severely affected side.

Seizure status

Of the 11 patients with primary presentation of seizure who were followed for at least 5 years, eight patients were controlled on AEDs (7 patients on 1 AED and 1 patient on 2 AED), seizure was not controlled with AED in three patients. Postoperatively, 55% of patients became seizure free ($P = 0.02$). Eight patients improved (either weaned off AED completely or decrease the number of AED used). Five of those are no longer on AED. Three patients did not improve (either no change or improved for a short period).

MRI findings of all 11 patients showed multiple infarcts around watershed areas, large areas of atrophy, and gliosis. Patients with posterior circulation involvement were 5 out of 11, three of those improved. Five out of six patients with no posterior circulation involvement improved [Table 2].

Table 2: Clinical features of patients with improved seizure control compared to patients who did not improve after EDAS surgery.

Characteristic measure	Improved*	Did not improve**	P-value ($P < 0.05$)
EDAS surgery	8 of 11	3 of 11	0.0005
Posterior circulation involvement	3 of 5	2 of 5	0.4
Bilateral surgery	7 of 8	1 of 8	0.07
Patients with 1 AED presurgery	5 of 7	2 of 7	0.1
Patients not controlled or on more than 1 AED before surgery	1 of 4	3 of 4	0.1

*Weaned off AEDs, decrease seizure semiology, or decrease number of AED to 1. **No change in seizure outcome, or improvement for a short period only

Eight of 11 patients underwent bilateral EDAS surgery. Seven of those eight patients improved after surgeries. Three of 11 patients underwent unilateral EDAS surgery of the more affected side, one of those was weaned off AED.

DISCUSSION

Although seizure is one of the less common presentations of MMD, recent reports reveal different estimations of the number of pediatric patients presenting with seizure.^[16,17,22] In our study, approximately 63% (14 out of 22) of patients undergoing indirect revascularization surgery presented with seizure.

Mikami *et al.* found five statistically significant predicting factors for epilepsy in MMD: cerebrovascular accident (CVA), lesion diameter in T2-weighted image in brain MRI, age, seizure onset after stroke and cortical involvement, and hemorrhagic type of stroke.^[13] The age and presence of an abnormality in computed tomography (CT) scan were found to be a significant risk factor for epilepsy in moyamoya during a long-term follow-up study by Nakase *et al.*^[15] All 11 patients who presented with seizures had evidence of radiologically diagnosed stroke on investigations. All patients had significant brain damage (atrophy, gliosis, and multiple infarcts). All patients had an ischemic type stroke. Involvement of PCA has been linked with a poorer prognosis of MMD.^[10] In our study, nearly 45% of patients presenting with seizure had posterior involvement. Their outcome was not significantly linked to posterior involvement.

The duration of epilepsy before revascularization was identified as an independent factor for future seizure recurrence in pediatric MMD.^[11] In our study, a better outcome was observed in patients with controlled seizures. Patients with uncontrolled epilepsy preoperatively showed either no change or mild improvement in their seizure activity, despite a family history of epilepsy and multiple seizure semiology. No patient showed worsening or deterioration epilepsy wise.

In a single-center study on long-term clinical outcome after EDAS surgery, 67% of patients showed excellent, complete resolution of preoperative symptoms (such as TIA or seizures) and no fixed neurological deficits, with a more favorable

prognosis for patients presenting with symptoms at an older age (>3 years).^[22] Another study showed that younger age at onset (<5 years) is associated with better outcome of disease in terms of functionality and recovering from brain insults.^[14] Regarding seizure outcome in our patients, three out of four moyamoya patients who presented with seizures under the age of 3 years are seizure free and had an excellent overall outcome. One patient under three did not benefit from EDAS surgery, as she had a family history of seizures and was not controlled on 2 AED before surgery. Delay time (age of surgery – age of onset) was not a significant factor in seizure outcome in our study.

All patients in our study underwent indirect revascularization (EDAS) surgery. In a study by Ma *et al.*, there was no significant difference between direct and indirect revascularization in seizure outcome in pediatric moyamoya patients.^[11] To the best of our knowledge, there is no evidence of superiority of bilateral EDAS surgery as compared to unilateral surgery. All 11 of our patients with seizures had bilateral involvement and eight of them underwent bilateral surgery. Patients undergoing bilateral EDAS surgery had significantly better seizure outcome compared to patients with one EDAS surgery.

In the previous reports, it was reasonable for MMD to be subdivided into four types depending on the presentation, including an epileptic type.^[15] According to Mikami *et al.*, epilepsy in MMD is not an independent category of the disease, and is often associated with other clinical findings, and is a result of hemorrhagic or ischemic stroke and is not an independent category of the disease.^[13] Patients showing angiographic progression after successful revascularization are expected to improve epilepsy control significantly. However, when MMD patients undergoing EDAS surgery were divided based on their main clinical presentations into an ischemic group and epileptic group, patients in the epileptic group showed a more favorable outcome compared to the ischemic manifestation group, especially patients suffering from severe ischemic manifestations.^[4] All 11 patients in our cohort suffered an ischemic stroke and underwent successful indirect revascularization with improved seizure outcome. The study was done in a retrospective fashion, with a small sample size. Risk factors for seizure in moyamoya were not

discussed during the analysis. Detailed extend of stroke in those patients was not fully obtained given the retrospective collection of data. Seizure disorder is not an uncommon presentation in pediatric moyamoya. Patients with controlled seizure before surgery are more likely to be seizure free after the intervention. Seizure outcome is favorable after indirect surgical revascularization in pediatric moyamoya patients.

CONCLUSION

Pediatric Moyamoya patients with epilepsy will significantly benefit from EDAS. Patients with controlled seizures before surgery are more likely to become seizure free post operatively.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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