Intracranial aneurysms associated with moyamoya disease in children: clinical features and long-term surgical outcome

Peng Liu, MD, Xian-li Lv, MD, Ai-hua Liu, MD, Cheng Chen, BS, Hui-jian Ge, MD, Heng-wei Jin, MD, Xin Feng, MM, Ming Lv, MD, You-Xiang Li, MD, Lian Duan, MD, PhD

PII: S1878-8750(16)30313-8
DOI: 10.1016/j.wneu.2016.05.039
Reference: WNEU 4100

To appear in: World Neurosurgery

Received Date: 15 March 2016
Revised Date: 13 May 2016
Accepted Date: 14 May 2016


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Intracranial aneurysms associated with moyamoya disease in children: clinical features and long-term surgical outcome

Peng Liu¹,²,³#, MD; Xian-li Lv¹,³#, MD; Ai-hua Liu¹,³, MD; Cheng Chen², BS; Hui-jian Ge¹,³, MD; Heng-wei Jin¹,³, MD; Xin Feng¹,³, MM; Ming Lv¹,³, MD; You-Xiang Li¹,³*, MD; Lian Duan²*, MD, PhD

Peng Liu and Xian-li Lv contributed equally to this work.

1: Department of Interventional Neuroradiology, Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, China
2: Department of Neurosurgery, 307 Hospital, PLA, Beijing, PR China
3: Beijing Engineering Research Center for Interventional Neuroradiology

* Corresponding author to Lian Duan and You-Xiang Li.

Lian Duan MD, PhD

Affiliation: Department of Neurosurgery, 307 Hospital, PLA 8 Dong-Da Street, Fengtai District Beijing 100071 (PR China)

Email: duanlian307@sina.com; Tel: 86-10-66947156; Fax: 86-10-62177976
You-Xiang Li MD

Affiliation: Beijing Neurosurgical Institute, Beijing Tiantan Hospital, Capital Medical University, No.6, Tiantan Xili, Dongcheng, Beijing, 100050, P.R.China

E-mail: liyouxiang307@sina.com; Tel: 86-10-67098847; Fax: 86-10-67098847

Key words: Pediatric, Intracranial, Aneurysm, Long-term, Surgical outcome

Running head: Intracranial aneurysms associated with moyamoya disease in children

Funding: This article is supported by the Commission of Beijing Municipal Science and technology, municipal clinical special application study, special fund project (No. Z14110000211441); National Natural Science Foundation (81171078 and 81471166).

Abbreviations: mRS=modified Rankin Scale; ICA=internal carotid artery; EDAS=encephalo-duro-arterio-synangiosis; DSA=digital subtraction angiography.

Conflict of interest statement: The authors claim that none of the material in the paper has been published or is under consideration for publication elsewhere.
Abstract

BACKGROUND: Moyamoya disease (MMD) in children was rarely associated with intracranial aneurysms. The purpose of this study was to report the clinical characteristics and long-term surgical outcomes of pediatric intracranial aneurysms accompanied with MMD.

METHODS: Between October 2002 and October 2013, 9 pediatric MMD patients (aged ≤17 years) with intracranial aneurysms were treated in our department. Clinical and angiographic features, treatment selection as well as the follow-up information were obtained and analyzed. The efficacy of vascularization and the changes of intracranial aneurysms were evaluated with digital subtraction angiography (DSA). We also collected 7 previously published literature to analyze the characteristics of this rare condition.

RESULTS: In our series of 9 patients, seven were male. The mean age was 11 ± 3.4 years (range 5 to 16). Seven patients presented with intracranial hemorrhage as the initial manifestation, while two patients with transient ischemic attacks. The most common aneurysm location was the posterior choroidal artery (4, 44.4%). One anterior choroidal artery aneurysm was completely embolized with onyx. One posterior choroidal artery aneurysm failed due to the inaccessibility to the parent artery. Bilateral encephalo-duro-arterio-synangiosis (EDAS) surgery was performed for all the children. During the follow-up period of 6.4±2.2 years (range 3 to 11), spontaneous occlusion of aneurysm was observed in four children, including one child with middle cerebral artery aneurysm, one with lenticulostrate artery aneurysm, and two with posterior choroidal artery aneurysm. Good or fair vascularization were observed in all the 9 children with DSA follow-up. No patients suffered intracranial hemorrhage during the follow-up period.

CONCLUSIONS: The long-term survey showed EDAS surgery could effectively increase the cerebral blood flow and maintain good outcomes in children, which may further result in the disappearance of the intracranial aneurysms and decrease the
incidence of recurrent hemorrhage.

**KEY WORDS:** Pediatric, Intracranial, Aneurysm, Long-term, Surgical outcome

**INTRODUCTION**

The incidence of intracranial aneurysms in moyamoya disease (MMD) has been estimated to be 3-14% in adults. (25) A large number of cases in the adult population have been reported, whereas such association is very uncommon in children. To our knowledge, aneurysm associated with MMD can be classified into two types, which includes the major artery aneurysm (60%) and blood flow secondary to the arterial stenosis (40%; choroidal, moyamoya vessels, meningeal vessels). (5)

The aneurysms on the major artery aneurysm usually present with subarachnoid hemorrhage, while aneurysms on the peripheral arteries with intracranial or intraventricular hemorrhage. (5,9,14,23,31) Additionally, a minor proportion of children present with an incidental finding or manifested with symptoms of transient ischemic strokes.

During the past decades, the natural history as well as the treatment selection of these aneurysms in pediatric MMD patients have been rarely reported and remained controversial. (8,19,22,26,28,30) Our former article reported the abnormal dilation of anterior choroidal artery and posterior communicating artery maybe the major cause of hemorrhage in children absent of intracranial aneurysms. However, children with the intracranial aneurysms were not included in the study. (12) Previous data showed that blood flow modification after revascularization could lead to spontaneous regression and disappearance of these aneurysms. (4,9,21)

The purpose of this study was to report the characteristics and long-term follow-up outcomes of pediatric intracranial aneurysms with MMD.

**MATERIALS AND METHODS**
**Study population**

The study protocol was approved by the research ethics committee at Beijing Tiantan Hospital and 307 Hospital PLA, formal written consent was obtained from all the patients. Between October 2002 and October 2013, 469 pediatric MMD patients were treated in our hospital. Among them, 9 (two females and seven males) pediatric MMD patients accompanied with intracranial aneurysms with an incidence of 1.9% (9/469). Clinical, radiographic features as well as the treatment selection were retrospectively reviewed for each patient. The diagnosis of MMD met the current criteria. Intracranial hemorrhage was confirmed with computed tomography and cerebral infarction with magnetic resonance imaging (MRI).

**Endovascular treatment**

Two children underwent endovascular treatment under general anesthesia after giving informed consent. Both the two procedures consisted of transarterial embolization using Onyx (ev3, Irvine, California, USA) with the patient under general anesthesia. Vascular access was obtained via a transfemoral approach using a 6 French guiding catheter. Firstly, diagnostic angiography was performed to delineate the vascular architecture of the lesions. Following the diagnostic angiogram, using a roadmapping technique, a Marathon microcatheter was coaxially navigated through the guiding catheter into a selected feeding artery. Progression of the microcatheter was aided by the use of a microguidewire (Mirage 008, ev3 or Traxcess-14, Microvention) to reach to or as close as possible to the aneurysm sac.

Inter-operative heparinization was achieved by adding 3000 IU of heparin to 500 mL of 0.9% wt/vol sodium chloride infusion solution and was administered through the guiding catheter during the procedure. Bolus infusions of heparin were not administered; thus, any anticoagulation that may have occurred from the flush solutions was not reversed at the end of the procedure.
Surgical treatment

As to the 9 children, all underwent bilateral encephalo-duro-arterio-synangiosis (EDAS) procedure by one neurosurgeon in our department. All the nine children underwent bilateral EDAS of the superficial temporal artery. One patient was performed with the EDAS of the left occipital artery due to the involvement of posterior cerebral artery during the follow-up period.

Clinical follow-up

Neurological outcome was assessed using modified Rankin’s scale (mRS). The development of collateral circulation through the EDAS was assessed by DSA according to the system that was described by Matsushima et al. (15) where “good” indicates that the postsurgical collateral vessels achieved vascularization of two-thirds of the middle cerebral artery (MCA) distribution, “fair” indicates that the postsurgical collateral vessels achieved vascularization of one-third to two-thirds of the MCA distribution, and “poor” indicates that the postsurgical collateral vessels achieved very little or no vascularization.

RESULTS

The age of 9 patients ranged from 5 to 16 years with a mean age of $11 \pm 3.4$ years. Seven (77.8%) of the 9 patients presented with intracranial hemorrhage as the result of rupture of the aneurysms. Hunt and Hess scale I was observed in six patients, scale II in one patient. In two patients (22.2%), the aneurysm was an incidental finding and presented with transient ischemic attacks. Of the 7 children (77.8%) with ruptured aneurysms, six children presented with intraventricular hemorrhage, one with subarachnoid hemorrhage.

In our series of 9 patients, the most common aneurysm location was the posterior choroidal artery (44.4%) in 4 children. The other locations of the aneurysms were as follows: one anterior communicating artery, one posterior communicating artery, one
anterior choroidal artery, one lenticulostriate artery, and one middle cerebral artery. There was no case of multiple aneurysms. The mean aneurysm size was 3.1±0.9mm, with a range from 2.2 to 5.1mm. As to the morphology of aneurysm, 8 were round-shaped and one was elliptical-shaped.

**Surgical treatment and Follow-up angiographic findings**

Endovascular treatment with Onyx was successfully performed in one child with anterior choroidal artery aneurysm, and the immediate angiography showed complete occlusion of the aneurysm sac (Figure 1). The 6-month follow-up angiography showed no occurrence of aneurysm sac. Endovascular treatment failed in one child with posterior choroidal artery aneurysm due to the inaccessibility to the parent vessel of aneurysm sac.

All patients underwent DSA follow-up (mean interval, 6.5±1.1 months; range, 5 to 9 months). The postoperative DSA results showed that “good” collateral circulation in 6 children and “fair” collateral circulation in 3 children. As to the child treated with EDAS of the left occipital artery, the 6-month DSA follow-up showed minor formation of collateral vessels in the posterior circulation. In addition, moyamoya vessels was decreased in 5 patients (55.6%) and was unchanged in 4 patients (44.4%).

During the long-term follow-up period, spontaneous regression and disappearance of aneurysms were found in four children. One child with lenticulostriate artery aneurysm manifested progression of MMD and accompanied with the spontaneous disappearance of aneurysm sac three months after the onset of hemorrhage prior to the EDAS surgery (Figure 2). Another child with middle cerebral aneurysm disappeared at the period of 6 months after the ipsilateral EDAS surgery (Figure 3). In addition, two posterior choroidal artery aneurysms in two children disappeared at the interval of 2 years (Figure 4) and 4 years after the bilateral EDAS surgery, respectively.

**Clinical follow-up outcome**
Over a mean follow-up of 6.4±2.2 years (range, 3 to 11 years), no children had an episode of recurrent intracranial hemorrhage. Three children complained of ischemic symptoms such as intermittent headache, transient amaurosis and limb weakness and numbness, and the other children did not complain of any discomfort. All the children had no disability (mRS 0 and 1) with no neurological deterioration.

**DISCUSSION**

After reviewing the literature, only nine pediatric MMD children with intracranial aneurysms have been reported (Table 1). (8,19,22,26,28,30) Including our 9 cases, aneurysms in 10 children (55.6%) were located in the anterior circulation, and 8 (44.4%) in the posterior circulation. Our study showed the distribution of the aneurysm location was quite different from that seen in the general pediatric population. (1) We found the AChA and the moyamoya vessels were the most common location in the anterior circulation, while in the posterior circulation the PChA were the most common location. As shown in our series, all the aneurysms were less than 7 mm in diameter. It was generally believed that this aneurysmal lesion arising from the peripheral artery was the direct cause of bleeding in moyamoya disease. Apart from the two children presented with TIAs, the location of the seven ruptured aneurysms were all consistent with that of the intracranial aneurysms.

As to the 9 aneurysms in our cohort, we could not determine the pathological features based purely on the aneurysm location or the imaging features and all the aneurysms in our study manifested a stable status. Contrary to our study, some studies depicted the peripheral artery aneurysm as a false aneurysm, (16,20,31) since the histology study showed the aneurysm wall was composed of collagen fibers and fibrin without elastic fibers. (16) These pseudoaneurysms had a tendency to undergo an early increase in size. (3,20,31) Repeated bleeding and subsequent aneurysm enlargement have been reported as early as 5 days after the initial rupture. (3) In the case reported by Tanaka et al, (27) the aneurysm on a moyamoya vessel became enlarged 2 months later and then disappeared. The author reported that there was interruption of the
internal elastic membrane in the aneurysm wall removed from the posterior choroidal artery. (27) Additionally, true aneurysms associated with MMD have also been reported, which were located at the AChA. (10,17)

Previous reports as well as our experience suggested that hemodynamic stress was involved in the development of such aneurysms. (2,24) Rupture occurred due to persistent hemodynamic stress on dilated, fragile moyamoya vessels. (4,6,7,11,18,29) To prevent rebleeding, there were several options available for the management of these aneurysms, such as surgical obliteration, (18) endoscopic treatment, (11) extra-intracranial revascularization surgery, (4,9,21,29) endovascular surgery, and observation (that is, expectation of a spontaneous regression).

Since the fragile moyamoya vessels, interruption of anastomotic channels, poor tolerance to retraction and ischemia, and poor reserve capacity of hemodynamics could be the obstacles for the clipping procedure, surgical clipping was not suggested in our study. Endovascular treatment is less invasive and has shown good results for major artery aneurysms associated with MMD in adults. However, as to the aneurysms located in the perforating artery or the choroidal artery, endovascular treatment remains challenging. (13) As to the seven peripheral aneurysms, selective onyx embolization was successfully performed only in one child with AChA aneurysm. The other child with PChA aneurysm failed due to the restricted microcatheter access to the parent vessel.

We performed EDAS surgery for all the children. The rationale for performing revascularization in these cases was based on the hypothesis that additional sources of collateral blood flow through indirect anastomoses could decrease the hemodynamic stress on the delicate collateral network of vessels and, thus, decreased the risk of aneurysm rupture and de novo aneurysm formation. In previous reports, some aneurysms disappeared even very small collateral circulation developed. (21) Although only three aneurysms (one cerebral middle artery and two posterior choroidal artery) disappeared in our series after revascularization surgery, our study
showed that the other four untreated aneurysms remained a stable status and no children suffered rebleeding as well as development of de novo aneurysm. However, we must admit the fact that longer time DSA follow-up and more detailed study are needed to find out the specific answers for all the questions haunted in the misery of intracranial aneurysms in pediatric MMD patients.

CONCLUSIONS

The long-term survey showed EDAS surgery could effectively increase the cerebral blood flow and maintain good outcomes in children, which may further result in the disappearance of the intracranial aneurysms and decrease the incidence of recurrent hemorrhage.

REFERENCES


**Figure legends:**

Figure 1. An eleven-year-old boy with MMD suffered a sudden onset of intracranial ventricular hemorrhage with predominance of hematoma in the left ventricle (A); The lateral angiogram of the left internal carotid artery showed the presence of an anterior choroidal artery aneurysm (arrow) (B); The superselective angiogram through a Marathon microcatheter showed the aneurysm was associated with a pial vessel (arrow) (C). The post-procedural lateral angiogram of the left internal carotid artery showed the complete occlusion of aneurysm sac (arrow) (D).

Figure 2: A ten-year-old boy suffered a sudden onset of intracranial ventricular hemorrhage (A); The lateral angiogram of the left internal carotid artery confirmed the diagnosis of the MMD and the presence of a lenticulostriate artery aneurysm (arrow) (B, C); Three months after the onset of intracranial hemorrhage, pre-operative left internal carotid artery angiogram showed the spontaneous disappearance of the aneurysm sac accompanied with the progression of the MMD (arrow) (D).

Figure 3: A nine-year-old boy presented with intermittent limb numbness was admitted at our hospital. The angiogram of the bilateral internal carotid artery confirmed the diagnosis of the MMD and the presence of a cerebral middle artery aneurysm located on the moyamoya vessels (arrow) (A, B). After the bilateral EDAS surgery, the 6-month bilateral ICA angiogram follow-up showed the resolution of the aneurysm sac (arrow) (C, D); The pre-operative bilateral external carotid artery (ECA) angiogram showed there was no spontaneous formation of collateral circulation (E, F); The 6-month bilateral ECA angiogram follow-up showed the development of extensive collateral circulation (G, H).

Figure 4. A seven-year-old boy with MMD suffered a sudden onset of intracranial ventricular hemorrhage (A); The right vertebral artery angiogram confirmed the presence of a posterior artery aneurysm (arrow) (B, C, D); Two years after the bilateral EDAS surgery, the follow-up angiogram showed the good collateral formation in the left hemisphere and the disappearance of the posterior artery aneurysm (arrow) (E, F).
Table 1: Summary of previous reports of intracranial aneurysms associated with moyamoya disease in children

<table>
<thead>
<tr>
<th>Author/year</th>
<th>No. of cases</th>
<th>Age/sex</th>
<th>Initial symptoms</th>
<th>Aneurysm site</th>
<th>No. of aneurysms</th>
<th>Treatment (aneurysm)</th>
<th>Treatment (MD)</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pool/1967</td>
<td>1</td>
<td>7 months/female</td>
<td>Fever, tetraplegia</td>
<td>MCA</td>
<td>1</td>
<td>Conservative</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Takahashi/1980</td>
<td>1</td>
<td>10 years/female</td>
<td>TIA</td>
<td>Moyamoya vessel</td>
<td>2</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>8 years/female</td>
<td>TIA</td>
<td>PCA</td>
<td>1</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Yamada/1981</td>
<td>1</td>
<td>10 years/female</td>
<td>ICH</td>
<td>Moyamoya vessel</td>
<td>1</td>
<td>Conservative</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>11 years/male</td>
<td>ICH</td>
<td>Moyamoya vessel</td>
<td>1</td>
<td>Conservative</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Okuma/1980</td>
<td>1</td>
<td>10 years/female</td>
<td>Convulsions</td>
<td>Moyamoya vessel</td>
<td>1</td>
<td>Conservative</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Konishi/1985</td>
<td>1</td>
<td>13 years/male</td>
<td>IVH</td>
<td>AChA</td>
<td>1</td>
<td>Conservative</td>
<td>Conservative</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Waga/1985</td>
<td>1</td>
<td>6 years/female</td>
<td>TIA</td>
<td>PChA</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral STA-MCA</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Johann/2008</td>
<td>1</td>
<td>7 years/female</td>
<td>Hemineglectence</td>
<td>PChA</td>
<td>1</td>
<td>Conservative</td>
<td>Multiple bur-hole technique</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Present case 1</td>
<td>1</td>
<td>5 years/male</td>
<td>SAH</td>
<td>PComA</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral EDAS</td>
<td>Present</td>
</tr>
<tr>
<td>Present case 2</td>
<td>1</td>
<td>9 years/male</td>
<td>TIA</td>
<td>AComA</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral EDAS</td>
<td>Present</td>
</tr>
<tr>
<td>Present case 3</td>
<td>1</td>
<td>9 years/male</td>
<td>TIA</td>
<td>MCA</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral EDAS</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Present case 4</td>
<td>1</td>
<td>16 years/female</td>
<td>IVH</td>
<td>PChA</td>
<td>1</td>
<td>Onyx embolization (failure)</td>
<td>Bilateral EDAS</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Present case 5</td>
<td>1</td>
<td>15</td>
<td>IVH</td>
<td>PChA</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral EDAS</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Present case 6</td>
<td>1</td>
<td>7</td>
<td>IVH</td>
<td>PChA</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral EDAS</td>
<td>Present</td>
</tr>
<tr>
<td>Present case 7</td>
<td>1</td>
<td>11</td>
<td>IVH</td>
<td>AChA</td>
<td>1</td>
<td>Onyx embolization</td>
<td>Bilateral EDAS</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Present case 8</td>
<td>1</td>
<td>10</td>
<td>IVH</td>
<td>Lenticulostriate artery</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral EDAS</td>
<td>Disappeared</td>
</tr>
<tr>
<td>Present case 9</td>
<td>1</td>
<td>9</td>
<td>IVH</td>
<td>PChA</td>
<td>1</td>
<td>Conservative</td>
<td>Bilateral EDAS</td>
<td>Present</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; MCA = middle cerebral artery; PCA = posterior cerebral artery; PChA = posterior choroidal artery; AChA = anterior choroidal artery; AComA = anterior communicating artery; EDAS = encephalo-duro-arterio-synangiosis.
Highlights

1. We reported so far the largest number of pediatric MMD patients accompanied with intracranial aneurysms;
2. The long-term survey showed EDAS surgery could effectively increase the cerebral blood flow and maintain good outcomes in MMD children with intracranial aneurysms;
3. EDAS surgery may further result in the disappearance of the intracranial aneurysms and decrease the incidence of recurrent hemorrhage.
Conflict of Interest

All authors have read and approved this paper and due care has been taken to ensure the integrity of the work. No part of this paper has published or submitted elsewhere. No conflict of interest exits in the submission of this manuscript, and we declare that we have no Conflict of Interest.

With Best Regards

Sincerely Yours

Dr. Youxiang Li and Peng Liu

Department of Interventional Neuroradiology
Beijing Neurosurgical Institute,
Beijing Tiantan Hospital, Capital Medical University.
Tiantan Xili 6,Dongcheng District, Beijing, China
Abbreviations

Moyamoya disease, MMD;
Digital subtraction angiography, DSA;
Emission Computed Tomography, ECT
Encephalo-duro-arterio-synangiosis, EDAS
Modified Rankin Scale, mRS