

ORIGINAL ARTICLE

Clinical and radio-angiographic features of paediatric moyamoya disease in Bangladesh

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ABSTRACT

Background: Moyamoya disease is a cerebrovascular arteriopathy of unknown origin characterized by progressive stenosis followed by occlusion of the cerebral arteries. Studies on moyamoya disease, especially in children in Bangladesh, are rare. We aimed to determine the clinical and neuroimaging features of moyamoya disease, particularly angiographic features.

Methods: Forty children diagnosed with moyamoya disease were consecutively recruited from Bangabandhu Sheikh Mujib Medical University Hospital, Dhaka, Bangladesh. Each patient underwent a medical history and physical examination focusing on stroke, magnetic resonance imaging, and magnetic resonance angiography scans of the brain. In some instances, electroencephalogram and digital subtraction angiography were also performed.

Results: Of the 40 patients, 22 experienced their first-ever stroke (median age, 84 months), and 18 had recurrent strokes (median age, 90 months). Common symptoms included hemiparesis, headache, seizure, and speech disorder. The commonly affected vessels were the internal carotid and middle cerebral arteries. Cortical involvement was found in 82.5% of cases. Bilateral involvement was observed in 37.5% of the patients, most of whom were in the Suzuki stage III.

Conclusion: Hemiparesis, headache, seizure, and speech disorder were the common manifestations. Most patients reported late (Suzuki stages III and IV), indicating an advanced stage. Early detection is necessary, considering the severity of the disease and its inherent tendency for recurrence.

Keywords: Moyamoya disease, paediatric stroke, radio-angiographic characteristics

INTRODUCTION

Moyamoya disease is an angiopathy where there is progressive occlusion of the internal carotid artery and/or its branches, causing recurrent strokes in children. In this condition, there is compensatory development of collateral blood vessels in the brain, which is pathognomonic. These collateral blood vessels have a 'puff of smoke' appearance on conventional angiographic imaging, which is encapsulated in the term 'moyamoya' in Japanese.^{1,2} This disorder was first described in 1957 in Japan and was called "moyamoya disease" by Suzuki and Takaku in 1969.³ The etiopathogenesis of MMD is not known precisely. However, there are infectious, inflammatory, and genetic basis.^{4,5}

Moyamoya syndrome defines characteristic arterial changes that are associated with comorbid medical conditions like neurofibromatosis, Down syndrome, and

sickle cell disease.^{6,7} Moyamoya disease is an important cause of paediatric stroke, both ischemic and hemorrhagic. The prevalence of moyamoya disease in Japan is 0.35 to 0.94 per 1,000,000 people.^{8,9} The prevalence is almost double in females compared to males. There is a bimodal distribution of age; the first peak is between 5 to 9 years and second peak is between 45 to 49 years.

The clinical manifestation of moyamoya disease exhibits distinct variations in adults and children. Adult patients predominantly experience cerebral infarctions and intracranial hemorrhages, whereas paediatric cases are more frequently associated with ischemic events. Moreover, clinical manifestations vary according to geographical distribution.¹⁰⁻¹³ Children with moyamoya disease present with diverse manifestations, thus underscoring the imperative of early diagnosis for effective management. Identifying the risk factors and

HIGHLIGHTS

1. Moyamoya disease in Bangladeshi children is not very uncommon.
2. Almost half of the children with moyamoya disease had recurrent strokes.
3. Hemiparesis, headache, seizure, and speech disorder were the common manifestations.
4. Eight in every ten patients had cortical involvement.
5. More than half of the patients presented in Suzuki stages III and IV, indicating late diagnosis. Measures for an early diagnosis are necessary.

clinical features of both initial and recurrent cerebrovascular events is crucial. This study has been done to identify the clinical manifestations, neuroimaging profile, and risk factors of moyamoya disease in children.

METHODS

This cross-sectional study was done under the Department of Paediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, and data were collected from March 2019 to March 2021. Children under 18 years diagnosed with moyamoya disease through magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain were recruited. Patients' age, age at onset of neurological events, clinical manifestations, familial medical history, prior treatment interventions, and neuroimaging data (MRI and MRA) were documented. MRI findings were evaluated by expert radiologists. Additionally, electroencephalogram (EEG) results were collated. The therapeutic approaches administered to the patients were recorded. The diagnostic criteria for moyamoya disease adhered to the guidelines set by the International Paediatric Stroke Study, focusing on arteriopathy criteria that involve the narrowing or blockage of the distal segments of one or both internal carotid arteries, accompanied by a network of telangiectatic collateral vessels beyond the obstructed arteries.¹⁴

The MRA findings were categorized using Suzuki staging as follows: Stage I- narrowing of the carotid fork; Stage II: initiation of the moyamoya, dilated anterior cerebral artery (ACA), middle cerebral artery

(MCA) and narrowed internal carotid artery (ICA) bifurcation with moyamoya change; Stage III: intensification of the moyamoya, further increase in moyamoya change of the ICA bifurcation and narrowed ACA and middle cerebral artery (MCA); Stage IV: minimization of the moyamoya, moyamoya change reducing with occlusive changes in ICA and tenuous ACA and MCA; Stage V: reduction of the moyamoya, further decrease in moyamoya change with occlusion of ICA, ACA and MCA; Stage VI: disappearance of the moyamoya, ICA essentially disappeared with the supply of brain from ECA. A recurrent stroke was defined as a distinct acute onset focal neurological deficit occurring >24 hours after the initial stroke. Data regarding recurrent stroke, including clinical features, age, risk factors, and neuroimaging features, were included.

Statistical analysis

Data were analyzed using SPSS version 23. The median (interquartile range) for continuous variables and number (percent) for categorical variables were presented. To compare the first and recurrent stroke groups chi-square test (for categorical variables) and Mann–Whitney U test (for continuous variables) were used. $P < 0.05$ was considered as statistically significant.

RESULTS

Out of 40 children with MMD, 22 had the first stroke, and 18 had recurrent stroke. The median age of the children in the first stroke group was 84 months, while in the recurrent stroke group was 90 months. More than half (54.5%) of the first stroke group and two-thirds (66.7%) of the recurrent stroke group were boys. The median onset of the disease in the first and recurrent stroke groups was 27 and 54 months, respectively. No significant statistical difference was found among these two groups (**TABLE 1**).

TABLE 1 Demographic characteristics of children with moyamoya disease (n=40)

Characteristics	Total	First stroke (n=22)	Recurrent stroke (n=18)	P
Age, months ^a	-	84 (36-129)	90 (51-108)	0.91 ^c
Age at onset, months ^a	-	27 (12-69)	54 (38-93)	0.09 ^c
Sex ^b				
Male	24 (60.0)	12 (54.5)	12 (66.7)	0.44 ^d
Female	16 (40.0)	10 (45.5)	6 (33.3)	

^aMedian (interquartile range); ^bNumber (percent); ^cMann–Whitney U test; ^dChi-square test

The most predominant clinical features observed were hemiparesis, seizure, headache, and speech disorder. Other features were cranial nerve palsy, cognitive impairment, developmental delay and regression, and loss of consciousness. The comparison between first and recurrent stroke groups showed no significant difference in clinical features, except for developmental regression and loss of consciousness (**TABLE 2**).

TABLE 2 Clinical characteristics of children with moyamoya disease (n=40)

Clinical characteristics	Total (n=40)	First stroke (n=22)	Recurrent stroke (n=18)	P
	Number (%)	Number (%)	Number (%)	
Hemiparesis	36 (90.0)	20 (90.9)	16 (88.9)	0.99 ^a
Headache	16 (40.0)	6 (27.3)	10 (55.6)	0.07
Seizure	26 (65.0)	13 (59.1)	13 (72.2)	0.39
Type of seizure				
Focal seizure	18 (45.0)	7 (31.8)	11 (61.1)	0.16 ^a
Generalized seizure	9 (33.5)	7 (31.8)	2 (11.1)	
No seizure	13 (32.5)	8 (36.4)	5 (27.8)	
Speech disorder	20 (50.0)	10 (45.5)	10 (55.6)	0.53
Cranial nerve palsy	15 (37.5)	7 (31.8)	8 (44.4)	0.41
Cognitive impairment	15 (37.5)	6 (27.3)	9 (50.0)	0.14
Developmental regression	12 (30.0)	2 (9.1)	10 (55.6)	0.001
Developmental delay	11 (27.5)	7 (31.8)	4 (22.2)	0.42 ^a
Loss of consciousness	8 (20.0)	1 (4.5)	7 (38.9)	0.01 ^a
Movement disorder	3 (7.5)	1 (4.5)	2 (11.1)	0.58 ^a
Dystonia	3 (7.5)	1 (4.5)	2 (11.1)	0.58 ^a
Choreoathetosis	1 (2.5)	0 (0)	1 (5.6)	0.45 [*]
Hypertension	1 (2.5)	0 (0)	1 (5.6)	0.45 [*]

^aFisher's exact test

Brain MRI scans were generally abnormal across the cases. In the group with recurrent strokes, all patients showed abnormal MRI results, whereas in the first stroke group, two individuals had normal brain MRIs. Eight in every ten patients had cortical involvement, while others had putamen, globus pallidus involvement. Cortical atrophy and fluid void were present in one-fourth of the patients. The internal carotid artery was the commonest artery which was involved. EEG results indicated that 18 patients exhibited focal discharges, while 8 had generalized discharges (**TABLE 3**).

At diagnosis, 57.5% of the patients were in Suzuki stage III, and 27.5% were in stage II, indicating the disorder's identification in an advanced stage, which may predict

adverse outcomes. Most of the patients had Suzuki stage III involvement in MRA, while in the first episode of stroke, 25% had stage III, 22.50% had stage II

TABLE 3 Investigation profile of children with moyamoya disease (n=40)

Investigation profile	Total (n=40)	First stroke (n=22)	Recurrent stroke (n=18)	P
	Number (%)	Number (%)	Number (%)	
Magnetic Resonance Imaging of brain				
Normal	2 (5.0)	2 (9.1)	0 (-)	0.49 ^b
Abnormal	38 (95.0)	20 (90.9)	18 (100)	
Magnetic Resonance Imaging areas of involvement ^a				
Cortical involvement	33 (82.5)	16 (72.7)	17 (94.4)	0.11
Thalamic involvement	1 (2.5)	1 (4.5)	0 (-)	0.99 ^b
Putamen involvement	3 (7.5)	3 (13.6)	0 (-)	0.24 ^b
Globus pallidus involvement	1 (2.5)	1 (4.5)	0 (-)	0.99 ^b
Cortical atrophy	10 (25.0)	3 (13.6)	7 (38.9)	0.14 ^b
Fluid void	10 (25.0)	4 (18.2)	6 (33.3)	0.30
Magnetic Resonance Angiography				
Internal carotid artery	19 (47.5)	8 (36.4)	11 (61.1)	0.12 ^b
Middle cerebral artery	16 (40.0)	12 (54.5)	4 (22.2)	
Anterior cerebral artery	4 (10.0)	2 (9.1)	2 (11.1)	
Posterior cerebral artery	1 (2.5)	0 (-)	1 (5.6)	
Side of involvement				
Unilateral involvement	25 (62.5)	10 (45.5)	15 (83.3)	0.01
Bilateral involvement	15 (37.5)	12 (54.5)	3 (16.7)	
Renal involvement (artery stenosis)				
Yes	2 (5.0)	1 (4.5)	1 (5.6)	0.99
No	38 (95.0)	21 (95.5)	17 (94.4)	
Electroencephalogram				
Generalized epileptic discharge	8 (20.0)	7 (31.8)	1 (5.6)	0.03 ^b
Focal epileptic discharge	18 (45.0)	6 (27.3)	12 (66.7)	
Normal	14 (35.0)	9 (40.9)	5 (27.8)	

^aMultiple response; ^bFisher's exact test

involvement, while in recurrent strokes, 32.50% patients had stage III and 7.50% had stage IV involvement (**FIGURE 1**). MRI of brain fluid attenuated inversion recovery (FLAIR) image showing periventricular hyperintensity in one patient with MMD (**FIGURE 2A**) and MRI of brain T2 image showing multiple flow voids in periventricular areas suggestive of development of collateral blood vessels (**FIGURE 2B**). MRA of the brain shows non-visualization of internal carotid artery branches on both sides (**FIGURE 3A**). MRA of the brain shows multiple collaterals of internal carotid artery branches, giving the characteristic “puff of smoke” appearance (**FIGURE 3B**).

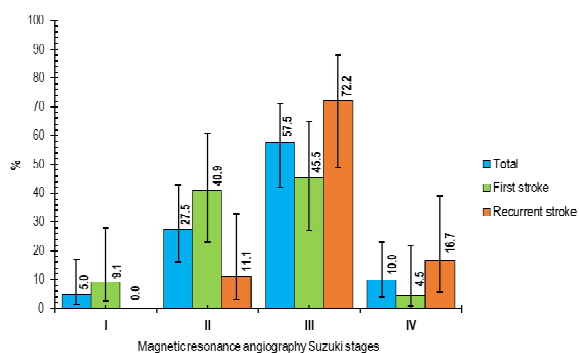


FIGURE 1 Magnetic resonance angiography Suzuki stages of children with moyamoya disease (n=40)

DISCUSSION

Moyamoya disease is a chronic, occlusive disorder of cerebral vessels causing stroke in children and adults. It is an important cause of recurrent stroke in the

(5–18%).^{18, 19} The clinical features in children may differ from adults. For instance, ischemia is often observed in children, while hemorrhage is common in adults. Infarction constitutes 70–80% of moyamoya disease cases in children in previous studies.^{20, 21} The features in our children like infarction, headache, hemiparesis, seizure, and difficulty in speech were observed by Kim et al.²² and Lee et al.² The predominant type of seizure in this study was focal seizure. There are studies that reported both focal and generalized seizures, probably because of hypoperfusion.²³

Cognitive impairment is an important issue to address in children with moyamoya disease. It is important to know that the recurrence causes more cognitive decline compared to first-ever strokes. Hsu et al. discovered that cognitive impairment was related to temporal lobe lesions in children.²⁴ Kurokawa et al. in their study

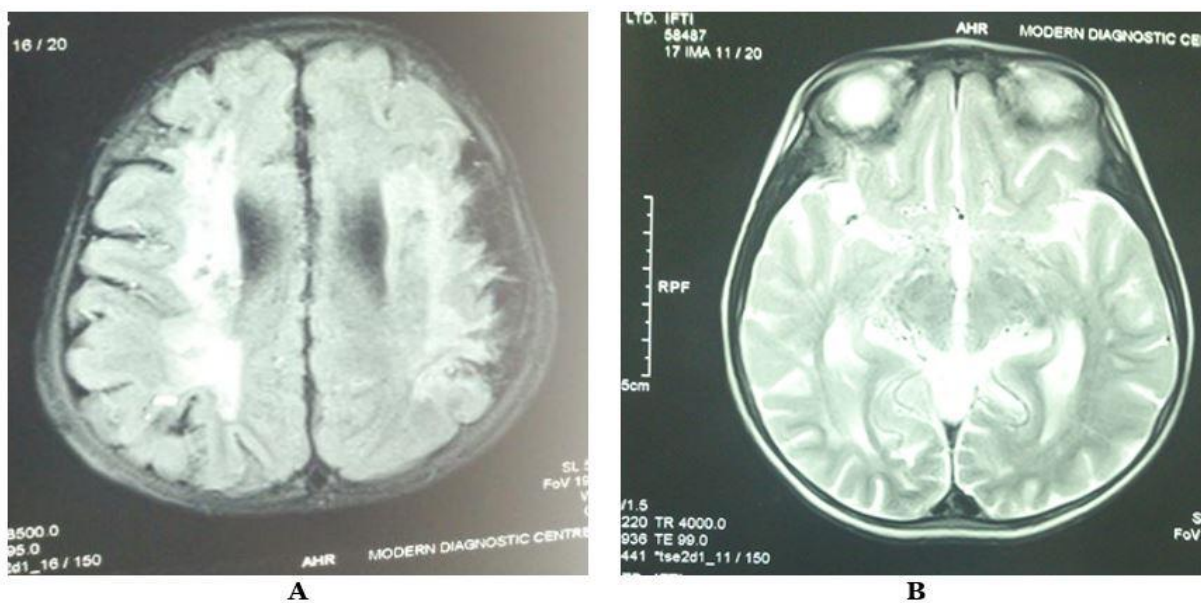


FIGURE 2 Magnetic resonance imaging (A and B) of children with moyamoya disease.

paediatric population.^{15–17} The study's key finding was loss of consciousness, and developmental regression was significantly high in recurrent moyamoya disease. None of the patients in the recurrent group had a normal brain MRI. This warrants the necessity of neuroimaging for an early diagnosis. Most patients reported to the hospital in Suzuki stages III and IV.

In the current study, 45% had a recurrence in contrast to the findings of Zhao M et al. (7.4%), and Chiu D et al.

found that four years after moyamoya disease onset, many children revive with normal intelligence levels. But it declines again in the course of time. Normal intelligence levels may be dropped in one-third of the patients after 10–15 years.^{25, 26} Therefore, a comprehensive assessment of cognitive function and early measures are needed to restore cognitive functions among the victims of moyamoya disease.

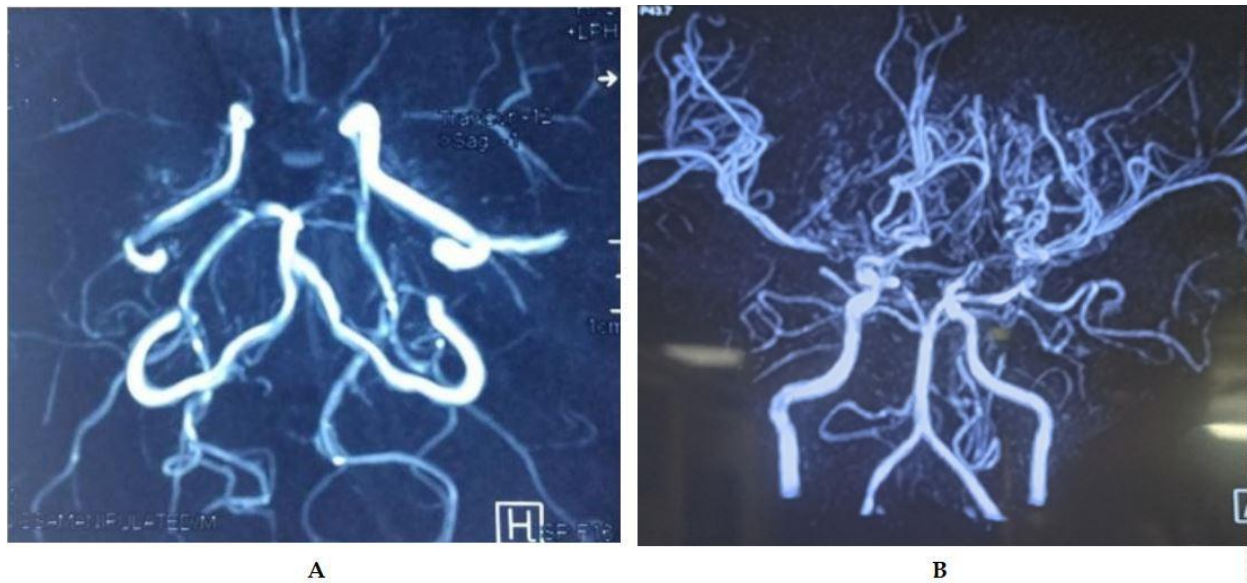


FIGURE 3 Magnetic resonance angiography (A and B) of children with moyamoya disease.

Developmental status is affected in children with moyamoya disease. Williams et al. in their study, showed that children with moyamoya disease scored significantly lower than the test standardization samples on all indices of intelligence and ratings of executive functioning. Moreover, children with bilateral disease and stroke scored significantly lower than those with unilateral disease in respect of intellectual function and verbal comprehension.²⁷ This should be taken into consideration during the management planning.

There are certain characteristic signs of moyamoya disease in MRI of the brain. First, there is the Ivy sign, which refers to the appearance of the brain on postcontrast T1-weighted or FLAIR images where prominent leptomeningeal collaterals with slow blood flow and post-contrast enhancement give an Ivy-type appearance.²⁸ The abnormal moyamoya vessels: lenticulostriate, thalamoperforating, leptomeningeal, and dural arteries, appear as multiple tortuous flow voids on T1 and T2 weighted sequences. There are multiple foci of microbleeds and also prominent deep medullary veins "brush sign" on susceptibility sequences.²⁹ In our study cases, 38 patients had abnormal MRI of the brain. The most affected area was the cortex. Other areas involved were the thalamus, putamen, and globus pallidus. One-fourth had a fluid void in our series.

MRA is a relatively time-consuming, safer, and noninvasive modality of investigation with no requirement for contrast medium and radiation exposure. However, it may miss very small stenotic lesions.³⁰ In a study by Yamada et al., MRA diagnosed stenosis in more than 80% of the cerebral vessels. Both MRI and MRA are very sensitive (up to 100%) and specific (up to 93%).^{31, 32} Bilateral involvement was another feature in four in ten patients, but Yamada et al. found it in 64% of the patients.³²

The Suzuki grading system is well accepted for categorizing moyamoya disease. It indicates the intrinsic compensatory reorganization of stenosis of the ICA, subsequent development of moyamoya vessels, compensatory development of trans-dural/trans-cranial anastomosis from the external carotid artery system, and finally, disappearance of moyamoya vessels at the late stage.^{33, 34} In this study more than half of the cases presented in Suzuki stage III which reflected the wide gap of time to diagnose the cases. It also indicates that some of the features of MMD were ignored. Therefore, measures are necessary to promote early detection and treatment.

A seizure in moyamoya disease is an important tool for diagnosing focal or generalized epileptic discharge. In a similar study, Frechette et al. found that 90% of EEGs

were abnormal in patients with moyamoya disease. The majority of them had focal epileptic discharges.³⁵

Conclusion

Although rare, moyamoya disease is an important cause of childhood stroke. Cerebral infarction, headache, hemiparesis, dysarthria, and seizure are common manifestations. Recurrence of stroke is very common in paediatric moyamoya disease. MRI and MRA are important diagnostic tools. The cortex of the brain is the most common site of stroke occurrence. Patients in our series reported to the hospital very late, having Suzuki stages III and IV. Therefore, an early detection is necessary, considering the severity of the disease and its inherent tendency for recurrence.

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Author Contributions

Conception and design: KF, MMR, SA. Acquisition, analysis and interpretation of data: KF, MMH. Manuscript drafting and revising critically: KF, MMR, MMH, SA. Approval of final version of the manuscript: KF, MMR, MMH, SA. Guarantor accuracy and integrity of work: KF, MMR, MMH, SA.

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Conflict of Interest

The authors have no conflict of interest to declare.

Ethical Approval

The parent of all subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (Memo no: BSMMU/2019/11856).

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