ORIGINAL ARTICLE

Clinicoradiological Profile of Childhood Moyamoya Disease: Indian Study of 30 Children with Literature Review

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ABSTRACT

Introduction: Moyamoya disease is an uncommon cerebrovascular disease characterized by progressive steno-occlusive changes in terminal internal carotid arteries (ICAs) and their main branches, associated with development of moyamoya vessels.[1] We present the largest case series of childhood moyamoya disease from India.

Materials and methods: Thirty patients of childhood Moyamoya disease, whose diagnosis was confirmed by magnetic resonance imaging (MRI), MR angiography (MRA), and digital subtraction angiography (DSA), were studied for various spectrum of clinical and radiological manifestations.

Results: Of the 30 patients evaluated (mean age: 6.71 years; F:M ratio 1.15:1), majority (96.66%) presented with ischemic symptoms, whereas only one (3.33%) had hemorrhagic stroke. Ischemic stroke with hemiparesis was the most common presenting feature (66.66%); rarer manifestations of moyamoya disease like headache, seizures, cognitive decline, visual loss, and bihemispherical transient ischemic attacks (TIAs) were also seen as presenting features. Radiologically, other than ischemic and hemorrhagic stroke, normal parenchyma with abnormal flow voids was the uncommon pattern seen on MRI brain, seen in 23.33%; 1 patient had isolated corpus callosal infarct. On angiography, 21 (70%) had bilateral ICA disease, 5 (16.66%) had unilateral ICA disease, and 4 (13.33%) had bilateral ICA with associated posterior circulation involvement.

Conclusion: Other than seizures and strokes, headache, cognitive decline, bihemispherical TIAs and isolated corpus callosal involvement were the unusual presentations found in this study. Radiologically, unilateral affection and posterior circulation involvement were also found. It is important to be familiar with the usual and unusual clinical manifestations and MRI/MRA findings in moyamoya disease to make an early diagnosis leading to a good prognosis.

Keywords: Childhood moyamoya disease, Early diagnosis, Myriad presentations, Neuroradiological spectrum.

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INTRODUCTION

Moyamoya disease was first described in the Japanese literature in 1957 by Takeuchi and Shimizu as a case of "hypoplasia of the bilateral internal carotid arteries."[2] However, it was not until 1969 when Suzuki and Takaku[3] coined the term "moyamoya" signifying "something hazy, like a puff of cigarette smoke" to describe the angiographic appearance that would both describe and define the illness.

Moyamoya disease is a cerebrovascular arteriopathy of unknown origin characterized by progressive stenosis and, ultimately, occlusion of the distal intracranial ICAs and the proximal branches of the anterior and middle cerebral arteries. The resulting ischemia leads to the formation of multiple collaterals from the leptomeninges as well as both the external and intracranial ICAs. It is the dilated basal collateral vessels arising from the intracranial ICAs that lead to the characteristic angiographic appearance simulating a puff of smoke, termed as moyamoya.[4]

The incidence of moyamoya disease is high in countries in East Asia, such as Japan and Korea. In Japan, the annual prevalence and incidence have been estimated to be 3.16 to 10.5 and 0.35 to 0.94 per 100,000 respectively.[5,6] The annual incidences in the USA and Europe have been reported to be about 10% of that in Japan.[7] There is a bimodal age distribution of moyamoya disease, with the first peak occurring in the pediatric population, typically in the first decade of life, and a second peak between 30 and 40 years of age.[8] Moyamoya is found in both females and males; however, there is a clear female preponderance, with affected females outnumbering males nearly 2:1.[9] Familial occurrence is seen in 6 to 12% of cases.[4,10,11]

Childhood moyamoya disease accounts for around 6% of cases of pediatric ischemic strokes and differs significantly from adult moyamoya disease.[12,13] Firstly, in contrast to adults who often present within the setting of intracranial

hemorrhage (<46%),[14] children affected with moyamoya disease typically exhibit signs and symptoms of cerebral ischemia secondary to TIAs and/or cerebral infarctions. Secondly, following a TIA, children have a much higher rate of completed infarcts when compared with their adult counterparts. This tendency is likely due to immature verbal skills in younger children making it difficult to communicate symptoms associated with TIAs, delaying the diagnosis of moyamoya and increasing likelihood of completed stroke upon presentation.[15] This signifies the importance of early diagnosis of childhood moyamoya disease.

MATERIALS AND METHODS

This is a cross-sectional observational study of 30 consecutive patients of moyamoya disease below 15 years of age, conducted at a tertiary care hospital in Eastern India between September 2010 and December 2014. All the patients underwent brain imaging in the form of computed tomography (CT), MRI, followed by cerebral angiography (MRA/DSA) to confirm the diagnosis (Fig 1). Diagnosis was made based on features of angiographic findings studied by the visualization of both the carotid and vertebrobasilar circulation. Secondary causes of moyamoya syndrome (prior radiotherapy to the head or neck for tumors, including craniopharyngiomas, pituitary tumors, optic gliomas; genetic disorders including Down's syndrome, neurofibromatosis type 1, tuberous sclerosis, sickle cell disease, and other hemoglobinopathies; autoimmune disorders including Grave's disease; vasculitis; congenital cardiac anomalies; renal artery stenosis; infections including tuberculous meningitis and leptospirosis; and fibromuscular dysplasia) were ruled out by relevant investigations. Enrolled patients were studied for demographic, clinical, and radiological profile.
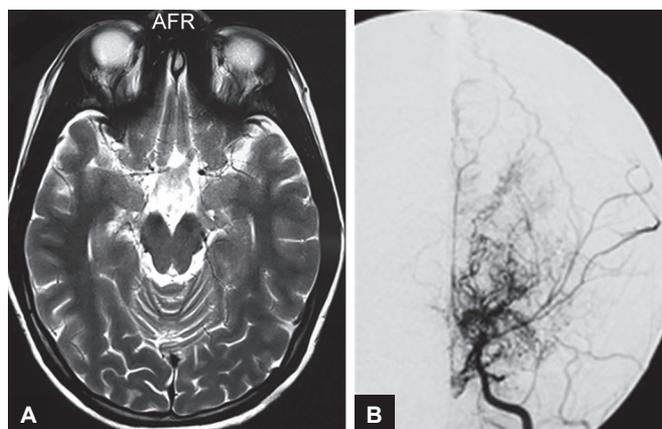
Figs 1A and B: Imaging in a child presenting with history of migrainous headache for 1 year duration. (A) MRI brain T2 sequence, showing normal brain parenchyma with attenuated flow voids of middle cerebral arteries. (B) The digital subtraction angiography of this patient showing narrowing of supraclinoid internal cerebral artery with a puff of smoke appearance suggestive of moyamoya disease

RESULTS

Totally, 30 patients of childhood moyamoya disease were studied.

Table 1 summarizes the demographic and clinical profile of the patients (n = 30).

Seven (23.33%) patients had presentations other than hemiparesis—headache in 1, headache + seizure in 1, recurrent TIA in 2, cognitive decline, bihemispherical TIA, and visual loss in 1 each.

Table 2 summarizes the radiological profile of the patients (n = 30).

Table 1: Demographic and clinical profile of the patients

Demographic characteristics		
Age-wise distribution		
• Mean age	6.71 years	
• Age range	6 months to 15 years	
• Age groups		
0–5 years	6 (20%)	
5–10 years	15 (50%)	
10–15 years	9 (30%)	
Sex-wise distribution		
• Females	16 (53.33%)	
• Males	14 (46.66%)	
• Female:male ratio	1.15:1	
Familial	Nil	
Clinical characteristics	*Frequency*	*As presenting feature*
• Hemiparesis	20 (66.66%)	
• Recurrent TIAs	14 (46.66%)	2 (6.66%)
• Headache	12 (40%)	2 (6.66%)
• Seizures	8 (26.66%)	1 (3.33%)
• Cognitive decline	2 (6.66%)	1 (3.33%)
• Bihemispherical TIA	2 (6.66%)	1 (3.33%)
• Visual loss	1 (3.33%)	1 (3.33%)
• Recurrent stroke	12 (40%)	

Table 2: Radiological profile of the patients

MRI brain	
Types of stroke	
A. Ischemic stroke	22 (73.33%)
• Anterior circulation strokes	18 (60%)
• Posterior circulation (PC) strokes	2 (6.66%)
• Anterior circulation + PC strokes	2 (6.66%)
B. Hemorrhagic stroke	1 (3.33%)
C. Normal parenchyma (only abnormal flow voids seen)	7 (23.33%)
Pattern of involvement	
• Cortical involvement	29%
• Subcortical involvement	21%
• Cortical + subcortical involvement	46%
• Watershed zone infarcts	4%
Angiography	
• Unilateral ICA	5 (16.66%)
• Bilateral ICA with normal PC	21 (70%)
• Bilateral ICA with PC involvement	4 (13.33%)
• Isolated PC involvement	0
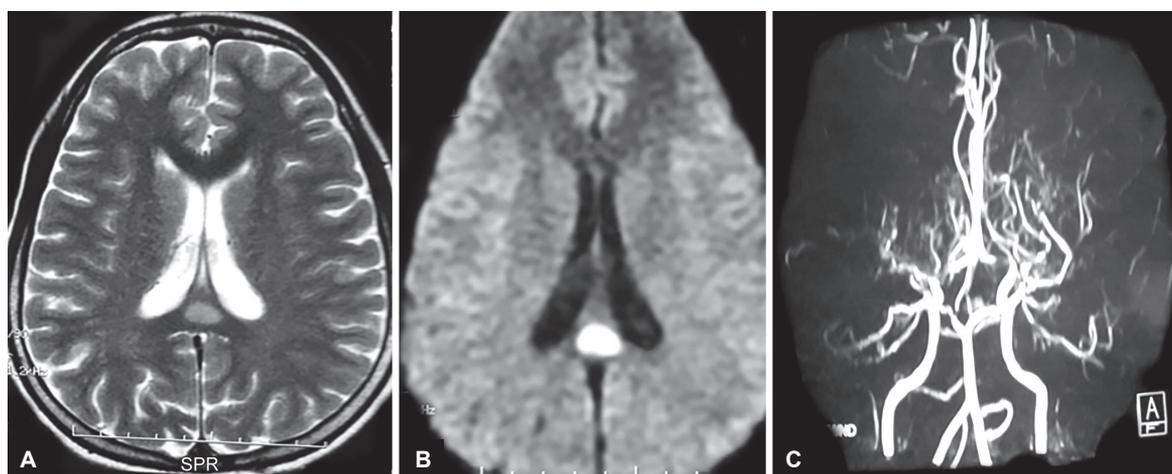
Figs 2A to C: Imaging in a child presenting with focal seizure. (A) MRI brain T2 axial sequence showing hyperintensity in the splenium of corpus callosum suggestive of infarct. (Boomerang Sign) (B) DWI image showing diffusion restriction suggestive of acute infarct. (C) MR angiography of cerebral vessels showing obliteration of bilateral ICA with narrowing of right PCA along with multiple moyamoya vessels

Table 2 shows that ischemic stroke was the presentation in 22 (73.33%) patients and hemorrhagic stroke was the presentation in 1 (3.33%) patient. Seven (23.33%) patients had normal brain parenchyma, and the only diagnostic clue in these patients was the presence of abnormal flow voids; 1 patient presented with isolated infarct in the splenium of corpus callosum (Boomerang sign)[16] (Fig. 2).

Staging of the moyamoya disease in this study, as per the Suzuki staging system,[17] is depicted in Graph 1.

DISCUSSION

Demographic Profile

The clinicoradiological profile of moyamoya disease patients, especially in the pediatric age group, has been reported in a very few studies in literature. Initially it was believed that moyamoya disease was restricted to Japan, but later, cases were reported from all over the world, especially from China, Korea, and India.[7] The study done by Suzuki and Kodama[17] included a total of 100 patients of which 46 were pediatric, whereas the study done by Mugikura et al[18] included 69 patients of childhood moyamoya disease. The study reported by Shoukat et al[19] from Pakistan included 13 patients of moyamoya disease with 7 pediatric cases.

There are only few studies from India, though there are case reports describing individual cases. Largest Indian study was done by Garg et al[20] with 44 patients over a 10-year duration, of which 18 were pediatric, whereas the retrospective study of Singhi et al[21] included 23 patients diagnosed with childhood moyamoya over 16 years. Chinchure et al[22] analyzed case records of 11 patients which include only adult-onset moyamoya disease, while Srivastava et al[23] reported a study of 26 patients of moyamoya disease over a span of 3 years of which 11 were less than 15 years of age. Our study includes 30 patients of childhood moyamoya disease over a span of 4 years, the largest case series of childhood moyamoya disease in India, and the second largest case series of moyamoya disease overall. The reason for this large number of cases in our study is probably because our institute is the only tertiary care hospital catering to the entire Eastern and North-eastern India, as well as to the patients coming from the adjoining Bangladesh.

Peak occurrence of childhood moyamoya disease as described in literature is in the age group of 5 to 9 years.[6] The mean age of patients in our study is 6.71 years with a range from 6 months to 15 years, with a maximum number of patients in the 5 to 10 years group (50%). This is in concordance with that reported in other studies. Mean age reported by Mugikura et al[18] was 6 ± 3 years
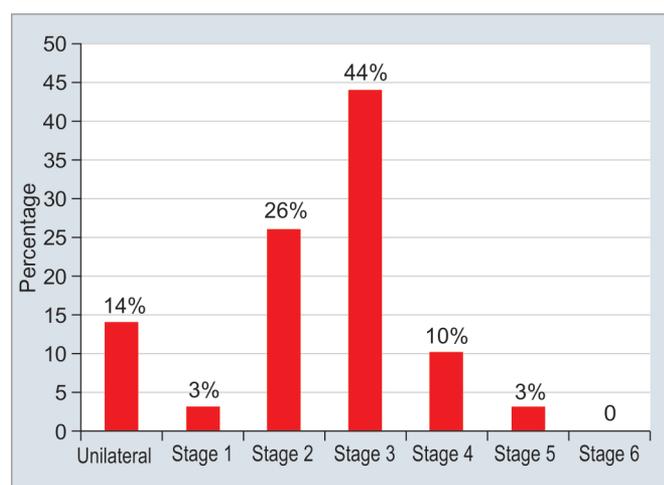
Graph 1: Stage-wise distribution at the time of diagnosis

while that reported by Singhi et al[21] was 3.3 ± 2.2 years. Srivastava et al[23] had a range of 5 to 14 years with maximum in the range of 5 to 10 years and none below 5 years of age. Youngest case reported in literature was 2 months old[24] and another 4 months old,[25] whereas that in our study was 6 months old. This signifies that moyamoya disease should be considered as an important differential diagnosis even in the first year of life.

Childhood moyamoya disease is said to be more common in females as compared with males with a ratio of 2:1.[9] Series from Garg et al[20] showed male predominance (68.2%); study from Chinchure et al[22] also showed slight male predominance (6 out of 11 patients), Duan et al[26] reported a 1:1 ratio, while Srivastava et al[23] reported a female predominance with a ratio of 3.3:1; all of these included adult cases as well. The study done by Singhi et al[21] (all cases of childhood moyamoya disease) reported a male predominance with male-to-female ratio of 3.6:1. In our study, there was a slight female preponderance with a female-to-male ratio of 1.15:1.

Most patients with moyamoya disease are sporadic cases, but in Japan 10 to 15%, whereas in the United States, 6% of the cases have a family history of the disease.[4,27,28] Duan et al[26] reported 5.2% of cases to be familial, whereas Srivastava et al[23] had no familial cases similar to our study. The female-to-male ratio in familial moyamoya disease is 5.0, which is much higher than that in sporadic cases (1.6). The mean age at onset of familial moyamoya disease (11.8 years) is lower than that in sporadic cases (30.0 years).[29] Among parent–offspring pairs, the age at onset of offspring (7.2 years) is lower than that of parents (30.7 years), suggesting a strong association with anticipation in familial moyamoya disease.[29] The presence of familial cases in many reports across literature suggests that genetic factors participate in the etiology of moyamoya disease.[29] Associations with loci on chromosomes 3, 6, 8, and 17 (MYMY1, MYMY2, MYMY3) as well as specific human leukocyte antigen haplotypes have been described.[30-35]

Clinical Profile

The difference in presentation between children and adults with moyamoya disease is striking. It has been suggested that adults are less able to form collateral vessels than children.[36] The medial striate arteries in fetuses of children and adults were examined and it was found that with aging, there was a reduction in the number of anastomoses and in the caliber of vessels. The disease process in children is dynamic and progressive, while in adults, it appears static and arrested and this may be the basis for the clinical dichotomy.[17]

In our study, ischemic stroke was the most common presentation seen in 73.33% of patients with hemiparesis as the most common presenting feature (63.33%); 23.33% of patients had presentation other than stroke, but their symptoms could be attributed to cerebral ischemia. So, a total of 96.66% patients had ischemic symptoms, whereas only 3.33% had hemorrhagic stroke as presentation. All patients in the studies conducted by Singhi et al[21] and all pediatric patients of Srivastava et al[23] had ischemic symptoms as presentation. Duan et al[26] had 97.7% pediatric patients with ischemic symptoms, while all 7 pediatric patients of Shoukat et al[19] had ischemic strokes.

The only patient with hemorrhagic stroke presented with basal ganglia bleed with intraventricular hemorrhage. Duan et al[26] had 2.3% incidence of hemorrhagic stroke in the pediatric population, whereas Shoukat et al,[19] Srivastava et al[23] and Singhi et al[21] had none. Historically, bleeding has been attributed to rupture of fragile collateral vessels associated with moyamoya as progressive stenosis of the ICA occurs.[37,38] Shifting circulatory patterns at the base of the brain have been implicated in the development of cerebral aneurysms (usually at the apex of the basilar artery and posterior communicating artery, areas of increased shear stress in moyamoya); this may be another cause of hemorrhage in moyamoya.[39,40]

Of the total patients, 23.33% had presentation other than stroke, which included TIAs and headache as presenting feature in 2 cases (6.66%) each, and seizures, cognitive decline, bihemispherical TIA, and visual loss as presentation in 1 case (3.33%), each as depicted in Table 1. Headaches arise from hypoperfusion-induced activation of pain-sensitive structures, such as both intracranial and extracranial vasculature, dura, orbital contents, and mucous membranes of the oral and nasal cavities.[41] Concomitantly, other mechanisms, such as dilation of the meningeal collaterals stimulating dural nociceptors and ischemia-induced lowering of the migraine threshold have also been suggested.[8,42] Disease bilaterality and duration of symptoms were the main factors associated with cognitive deficits, whereas age was not.[43] The role of a detrimental diffuse and prolonged ischemic–hypoxic mechanism in cognitive effects, similar to vascular cognitive impairment demonstrated in other brain hypoperfusion conditions in adults, has been suggested.[44] Our patient presenting with cognitive decline was found to have bilateral disease. Seizures, both focal and generalized, have been associated with moyamoya and are likely related to hypoperfusion.[45] Our patient presenting with visual loss was found to have occipital infarct. Other rare presentations reported in literature, but not found in our study, include choreiform movements[46] (attributed to any dysfunction of the basal ganglia–thalamocortical circuits, including infarctions

and mechanical compression by traversing dilated collateral vessels),[46,47] amourosis fugax, psychiatric manifestations, and subdural hemorrhage.[45] It is this group of patients presenting with features other than stroke, which require a strong suspicion of moyamoya disease so that an early diagnosis can be made and appropriate intervention initiated.

Radiological Profile

As discussed previously, 73.33% of patients presented with ischemic stroke. Out of this, anterior circulation stroke was present in 60%, posterior circulation stroke in 6.66%, whereas combined anterior and posterior circulation strokes were present in 6.66% cases; 1 patient presented with isolated infarct in the splenium of corpus callosum (Boomerang sign) (Fig. 2).[16] Most common pattern of infarcts was combined cortical plus subcortical, followed by cortical, subcortical, and watershed infarcts; 7 patients (23.33%) had normal brain parenchyma on MRI. These patients were suspected to have moyamoya disease based on abnormal flow voids seen on MRI brain (on the background of a relevant history and neurological examination) (Fig. 1A). These abnormal flow voids were in the form of either attenuation of the normal flow voids of middle cerebral artery/anterior cerebral artery/ICA or visualization of abnormal unusual flow voids at the base of brain, mainly around deep gray matter (Fig. 3A). When they were subjected to angiography, the classical moyamoya pattern was found.

Angiographically, posterior circulation is believed to be involved less frequently than anterior circulation.[48] Reason for this is that the pathology in moyamoya disease starts in the anterior circulation and then gradually spreads to involve posterior circulation in later stages; so, the posterior circulation acts as collateral
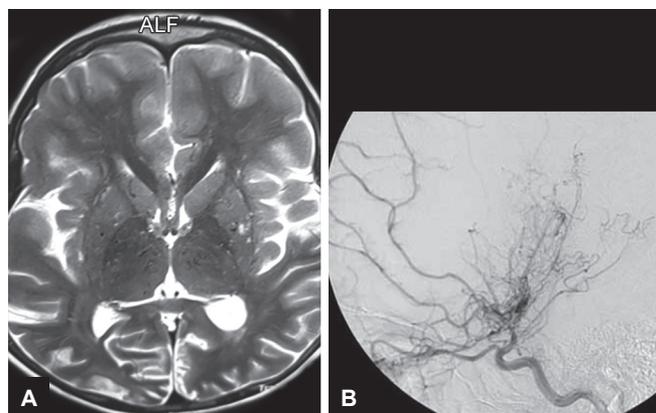

Figs 3A and B: Imaging in a child presenting with progressive cognitive decline. (A) MRI brain T2 axial view showing normal brain parenchyma with abnormal flow voids in the deep gray matter. (B) Digital subtraction angiography image showing obliteration of internal carotid artery with moyamoya vessels

pathway for the diseased anterior circulation till the later stage (Fig 4).[48]

In our study, bilateral ICA involvement with sparing of posterior circulation was the most common pattern found in 70% of our patients. Bilateral ICA with posterior circulation involvement was seen in 13.33%, unilateral ICA involvement in 16.66%, whereas isolated involvement of posterior circulation was not seen. Duan et al[26] and Chinchure et al[22] had 31.4% and 27.27% patients with posterior circulation involvement respectively. Posterior circulation was involved in 26.1% patients in the study done by Singhi et al[21] while in the series of Srivastava et al,[23] 50% of the patients had involvement of the posterior circulation.

Jayakumar et al[48] in their neuroradiological series regarding involvement of posterior circulation in moyamoya reported that though 90% of their patients had involvement of posterior circulation angiographically, and none of them had ischemic lesions in the posterior circulation territory.
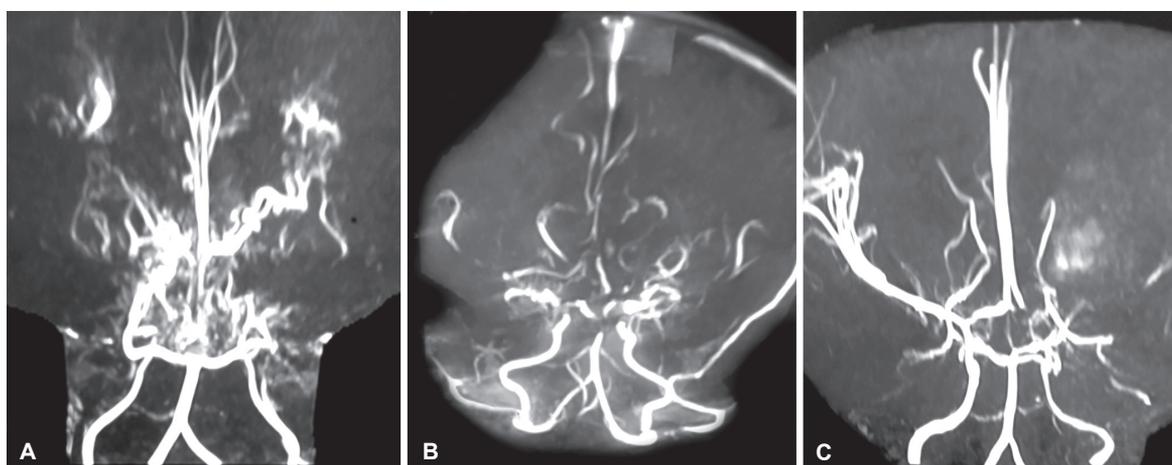
Figs 4A to C: Angiographic spectrum of moyamoya disease. (A) MR angiography of cerebral vessels showing bilateral ICA obliteration with preserved posterior circulation with multiple moyamoya vessels. (B) MR angiography of cerebral vessels showing bilateral ICA obliteration with obliteration of basilar and posterior cerebral arteries. (C) MR angiography of cerebral vessels showing unilateral ICA obliteration on left side with early narrowing of right ICA with preserved posterior circulation

But this was in total contrast with our study, where almost all patients with posterior circulation involvement angiographically had posterior circulation infarcts.

Bilateral involvement of ICA has been described as definite moyamoya disease whereas unilateral involvement of ICA has been described as probable moyamoya disease.[1] In our series, we had 16.66% cases with unilateral involvement. Duan et al[26] and Singhi et al[21] reported an incidence of 9.8 and 8.7% cases with unilateral moyamoya disease in their respective series.

There have been several reports of children presenting with unilateral moyamoya, and the obvious concern in these cases becomes contralateral progression of disease. The rate of progression of contralateral disease is variable. In the series of Smith and Scott,[8] 56% children with unilateral disease developed contralateral stenosis over a 6-month to 4-year follow-up period, whereas in the series of Kelly et al,[49] 38% went on to develop contralateral findings of moyamoya. It has been postulated that equivocal or mild stenosis in the contralateral hemisphere, congenital cardiac anomaly, Asian ancestry, and familial moyamoya syndrome were good predictors for the development of contralateral moyamoya.[49] Mean time to development of contralateral disease varies and has been reported as 12.7 months (5–22 months) to 3.1 years (0.5–7 years).[49,50]

In this series, 44% of children were diagnosed in stage 3 and 26% in stage 2 disease. This shows that most of the patients in our country are diagnosed when the disease has already evolved. This can be possibly due to inability of children to communicate their symptoms[15] as well as limited awareness of the myriad manifestations of moyamoya disease among the treating physicians, leading to a delayed diagnosis. None of the other studies have highlighted about the average stage of the disease at which the diagnosis was made.

CONCLUSION

To conclude, moyamoya disease is now a common disease entity and one should consider and rule out moyamoya disease in all patients with stroke, particularly in children. Children can have a myriad of presentations, which are significantly different from the adult population. Though ischemic strokes are most common, hemorrhagic stroke may also occur. The various atypical presentations in this study included seizures, cognitive decline, headache, bihemispherical TIAs, visual loss, and presentation at an age as young as 6 months. Though anterior circulation involvement was commoner, posterior circulation involvement as well as unilateral cases were also seen. Most of the patients were in stage 2 and stage 3 at the time of diagnosis.

The neurological status at the time of treatment is more predictive of long-term outcome than age, and a delay in diagnosis can lead to permanent neurological and cognitive deficits. Also, surgical revascularization procedures can improve the prognosis in such patients significantly. Here lies the importance of early diagnosis of moyamoya disease which can be the key prognostic factor. Hence, physicians should be aware of the spectrum of presentations, of moyamoya disease especially the atypical ones, which can aid in early diagnosis, early intervention and improved outcome in our pediatric population.

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