ORIGINAL COMMUNICATION

Profile of precipitating factors and its implication in 160 Indian patients with Moyamoya angiopathy

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Abstract

Introduction Moyamoya angiopathy (MMA) has been known to manifest with myriad of neurological manifestations, often in association with various precipitating factors. This is the first study to systematically analyze the precipitating triggers to neurological symptoms done on the largest cohort of MMA in India.

Methods A single-centered, cross-sectional observational study, recruiting 160 patients with consecutive angiographically proven MMA over a period of 5 years (2016–2021), was undertaken to evaluate the profile of immediate precipitating factors in temporal association to the neurological symptoms, along with their clinical and radiological characteristics. SPSS 25 was used for statistical analysis.

Results Among the 160 patients (Adult-85, children-75), precipitating factors were seen in 41.3%, significantly higher in children (52%) than adults (31.8%) (p value: 0.011). The commonest triggers included fever (18.8%), emotional stress (8.1%), heavy exercise and diarrhea (6.3% each). Cold bath triggered MMA symptoms in 1.3%. Fever (p value: 0.008) and persistent crying (p value: 0.010) triggered neurological symptoms more commonly in children than in adults. Amongst MMA patients with precipitating factors, the commonest MMA presentation included cerebral infarction type (37.9%) and TIA (31.8%). The majority of precipitating factors that preceded an ischemic event were BP-lowering ones (54.7%).

Conclusion Neurological symptoms of MMA are commonly associated with several precipitating factors, including the lesser known triggers like cold bath. The frequency and profile precipitating factors varies with the age of presentation and type of MMA. It can serve as an early clue to the diagnosis of MMA and its careful avoidance can be largely beneficial in limiting the distressing transient neurological symptoms.

Keywords Moyamoya angiopathy · Precipitating factor · Moyamoya disease · Spicy food · Fever

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Introduction

Moyamoya angiopathy (MMA) is a chronic, progressive intracranial vasculopathy characterized by steno-occlusive lesions of intracranial anterior circulation large vessels with compensatory collateral formation [1–4]. Chronic cerebral hypoperfusion secondary to both occlusion and steal phenomenon leads to ischemic presentation in MMA, and is seen in both adults and children [5–7]. The neurological manifestations in MMA has been closely described in association with several precipitating factors like fever, diarrhea, heavy exercise, crying and hyperventilation, spicy food intake and hot bath [8, 9]. Recently, the precipitation of MMA following Covid-19 vaccination has also been described [10]. However, literature pertaining to the exact frequency of precipitating factors and its clinical implication is sparse. Ours is the first study to systematically analyze the specific triggers to neurological symptoms in MMA, done in the largest cohort of MMA patients in India. We also herein report cold bath as a trigger to neurological symptoms in MMA, which to the best of our knowledge has not been described previously.

Methodology

A descriptive, observational, cross-sectional study was undertaken from a single, tertiary-care-centre (Bangur Institute of Neurosciences, Kolkata) over a period of 5-years (2016–2021) recruiting 160 consecutive angiographically proven MMA patients with bilateral disease. Each patient was scrutinized for clinical and radiological characteristics. Perfusion study in the form of Single-photon emission computerized tomography (SPECT) was done for cerebral blood flow and cerebrovascular reserve index. All of them were systematically questioned regarding any precipitating factor which occurs in temporal association to the neurological symptoms in the patient (Table 1). The documentation was based on the history given by patient's kin (for children with MMA) or self-recollection for adult patients. The precipitating factor was considered if it occurred within 15 min prior to onset of neurological symptoms. Exception was made for fever and diarrhea as precipitating factors, for which latency was considered as within hours. Fever was defined as oral temperature greater than 37.7 °C (> 99.9 °F). Diarrhea was defined as 3 or more loose stools per day. For rest of the precipitating factors, standardization was not possible due to cultural and social heterogeneity. Their mere presence or absence from a qualitative history was considered for the study. Thorough investigations were done to identify any secondary cause of MMA. All additional work-up was done depending on the clinical need case-to-case basis. All patient with history of precipitating factors were followed up for 6 months and reassessed in terms of frequency and duration of episodes of perfusion-dependent transient neurological symptoms (TIA, vascular type headache, transient EPS like chorea) in comparison to their status at diagnosis and any new onset fixed neurological symptom (fixed motor weakness, visual symptoms excluding amaurosis fugax, cognitive decline, fixed extra-pyramidal symptoms). SPSS 25 was used for statistical analysis. Data were summarized by routine descriptive statistics, namely mean and standard deviation for numerical variables that are normally distributed, median and inter-quartile range (IQR) for skewed numerical variables and counts and percentages for categorical variables. Numerical variables were compared between two groups by Student's independent samples t test, if normally distributed, or by Mann–Whitney U test, if otherwise. For multiple group comparison of skewed variables, Kruskal–Wallis ANOVA was used followed by Dunn's test for post hoc comparisons between two individual groups. Fischer's exact test or Pearson's Chi-square test were employed for intergroup comparisons of categorical variables. Analyses were two-tailed and statistical significance level was set at $p < 0.05$ for all comparisons. The study was undertaken following the consent of institutional ethical committee.

Table 1 Questionnaire regarding the precipitating factor occurring in temporal association to the neurological symptoms

Did you have neurological symptoms (TIA, vascular type headache, transient or fixed EPS like chorea, fixed motor weakness or cognitive and behavioral symptoms) following occurrence of-	
1. Fever	Yes/no
2. Exercise	Yes/no
3. Spicy food	Yes/no
4. Hot bath	Yes/no
5. Cold bath	Yes/no
6. Crying	Yes/no
7. Emotional stress	Yes/no
8. Diarrhea	Yes/no

Results

Among the 160 MMA patients, all the patients had bilateral disease, 85 had adult-onset MMA and 75 had childhood-onset MMA. The presence of immediate precipitating factor was seen in 66 (41.3%) out of the 160 MMA patients, significantly higher among children (52%) than adults (31.8%) (p value 0.011). The commonest triggers included fever (18.8%), emotional stress (8.1%), heavy exercise and diarrhea (6.3% each). The precipitation of MMA symptoms in temporal relation to fever and persistent crying was significantly higher in children than adults (p-value 0.008 and 0.010 respectively). Amongst the MMA cohort with presence of precipitating factor, mean age of onset of first neurological symptoms was 15.9 ± 15.9 years (median 9.0 years, range 3.5–24.3 years), followed by mean interval of 32.2 ± 58.6 months (median 12.0 months, range 0.0–36.0 months) and ultimately final diagnosis occurred at the mean age of 18.6 ± 16.3 years (median 12.0 years, range 4.8–31.5 years). The presence of one and two precipitating factors were seen in 72.7% and 19.7% patients with triggers respectively, while three or more triggers were seen in 7.6%, no significant differences in adult or child was noted. There was no instance of simultaneous occurrence of two or more trigger in any of our patient. The commonest MMA types associated with precipitating factors were cerebral infarction and TIA comprising of 37.9% and 31.8% of MMA cohort with triggers respectively. Baseline bihemispheric cerebral hypoperfusion was noted in 77.3%, while absence of hypoperfusion was noted in 4.5% of MMA patients with trigger. A presence of precipitating factor lowering blood pressure

(BP) (fever, hot bath) was noted in 54.7% of ischemic events (p value 0.579), compared to presence of precipitating factor known to elevate blood BP (exercise, emotional stress) which was seen in of 28.3% of ischemic events (p value 0.080), amongst the MMA cohort with triggers. Hemorrhagic event was seen in only 2 out of the 66 patients with triggers. Results of base-line characteristics are summarized in Tables 2, 3, 4.

Reassessment at follow-up after 6 month period revealed, among the 66 MMA patients with history of precipitating factor, none of them had any new onset of fixed neurological symptom, while 28 (42.4%) of them had decrease (either in frequency or severity or both)in their perfusion-dependent transient neurological symptom (TIA or headache).

Case presentation: A 5-year-old boy from rural Bengal presented to us with five episodes of transient left hemiparesis with slurring of speech and one episode of right fixed hemiparesis in the last 10 months. On detailed history-taking, the mother revealed that all the episodes have occurred during or immediately following bath in cold water. Magnetic resonance imaging (MRI) brain revealed T2/FLAIR multiple foci of white matter signal changes in the right subcortical, periventricular region with cystic changes. Magnetic resonance angiography (MRA) showed occlusive changes involving bilateral distal ICA, proximal MCA and right ACA, with collateral formation, suggestive of MMA. Brain SPECT revealed reduced perfusion with significantly impaired cerebral vascular reserve in bilateral ACA and MCA territories. The patient's kin was counseled in details regarding the avoidance of cold water bath. The patient had no further TIA or new-onset fixed neurological deficit at 6 month follow-up period.

Discussion

MMA can be considered as a model of hemodynamic insufficiency, wherein depending on the adequacy of collateral status, reduced cerebral perfusion pressure and ultimately decreased blood flow may occur distally. Despite

Table 2 Frequency of precipitating factors in the whole cohort

	Overall ($n=160$)	Adult ($n=85$)	Child ($n=75$)	p value
Precipitating factor				
Present	66 (41.3%)	27 (31.8%)	39 (52.0%)	0.011
Absent	94 (58.7%)	58 (68.2%)	36 (48.0%)	

Table 3 List and frequency of precipitating factors among children and adult:

	Overall ($n=160$)	Children ($n=75$)	Adults ($n=85$)	p value
Precipitating factor history				
1. Fever	30 (18.75)	21 (28.00)	9 (10.59)	0.008
2. Heavy exercise	10 (6.25)	5 (6.67)	5 (5.88)	1.000
3. Spicy food	12 (7.50)	9 (12.00)	3 (3.53)	0.068
4. Hot bath	8 (5.00)	5 (6.67)	3 (3.53)	0.476
5. Cold bath	2 (1.25)	2 (2.67)	–	0.218
6. Crying	6 (3.75)	6 (8.00)	–	0.010
7. Emotional stress	13 (8.13)	3 (4.00)	10 (11.76)	0.087
8. Diarrhea	10 (6.25)	5 (6.67)	5 (5.88)	1.000

Table 4 Baseline clinical characteristics, number of precipitating factor in each patient, distribution of precipitating factor in relation to the type of MMA presentation and perfusion status at base-line in the cohort of MMA patients with history of precipitating factor:

	Overall ($n=66$)	Adult ($n=27$)	Child ($n=39$)	p value
1. Sex ratio (male:female)	1:2	1:2.9	1:1.6	0.288
2. Area of residence				
Rural	69.7%	70.4%	69.2%	
Urban	30.3%	29.6%	30.8%	
3. Mean age at onset of first neurological symptoms (years)	15.9 ± 15.9 Median with range: 9.0 (3.5–24.3)	32.0 ± 12.8 Median with range: 32.0 (19.0–42.0)	4.8 ± 3.0 Median with range: 4.0 (2.5–6.5)	
4. Mean age at diagnosis (years)	18.6 ± 16.3 Median with range: 12.0 (4.6–31.5)	34.0 ± 13.2 Median with range: 37.0 (21.0–45.0)	7.9 ± 7.1 Median with range: 6.0 (3.5–11.0)	
5. Latency: First appearance of neurological symptoms to confirmed diagnosis (months)	32.2 ± 58.6 Median with range: 12.0 (0–36.0)	25.1 ± 48.8 Median with range: 12.0 (0–24.0)	37.2 ± 64.7 Median with range: 12.0 (0–36.0)	
6. Number of precipitating factors				
(a) One	48 (72.7%)	22 (81.5%)	26 (66.7%)	0.334
(b) Two	13 (19.7%)	3 (11.1%)	10 (25.6%)	
(c) Three or more	5 (7.6%)	2 (7.4%)	3 (7.7%)	
7. Presence of precipitating factor according disease presentation type				
(a) TIA	21 (31.8%)	8 (29.6%)	13 (33.3%)	0.751
(b) Cerebral infarction	32 (48.5%)	9 (33.3%)	23 (59.0%)	0.040
(c) Hemorrhage	2 (3.0%)	2 (7.4%)	0	0.084
(d) Headache	11 (16.7%)	8 (29.6%)	3 (7.7%)	0.019
8. Cerebral Perfusion status at baseline				
(a) Bihemispherical hypoperfusion	51 (77.3%)	19 (70.4%)	32 (82.1%)	0.359
(b) Unihemispherical hypoperfusion	12 (18.2%)	7 (25.9%)	5 (12.8%)	
(c) No hypoperfusion	3 (4.5%)	1 (3.7%)	2 (5.1%)	

autoregulatory vasodilation and increased oxygen extraction fraction acting as compensatory mechanisms, impaired hemodynamics lends a major risk of future cerebrovascular events in these patients [11]. Kraemer et al. observed evidence of syncope in 6.5% of its MMA patients hinting towards a heightened intolerance to orthostatic maneuvers in MMA [6]. MMA often manifests itself, in the face of transient changes in cerebral hypoperfusion caused by various triggering factors, with wide array of paroxysmal and fixed neurological symptoms, depending on the severity and duration of changes in the already compromised cerebral perfusion [7, 12–14]. A history of immediate precipitating factor was observed in 41.3% of MMA in our cohort, more frequently in children than adults (p-value 0.011). Thus, it is a frequent finding in MMA. But it is commonly overlooked, possibly due lack of awareness on the part of treating physician of its high incidence and its clinical implication in MMA [5]. Also, younger patients fail to appreciate these triggers themselves, only to be picked up by their vigilant guardians later in the course of the disease and it is also not infrequent for the patients to think that these triggers are unrelated.

Dynamic cerebral autoregulation (CA) normally maintain cerebral blood flow (CBF) homeostasis in normal population. However, it has been seen that dynamic CA is limited in MMA and dynamic, short (± 10–20% of mean arterial pressure) blood pressure (BP) changes can markedly affect CBF (± 10–15%), making them susceptible to hypoperfusion or hyperperfusion related cerebral insults. Thus, maintenance of a strict BP becomes imperative in this population to avoid neurological complications [15]. It may be interesting to note the triggers known to elevate BP like emotional stress and exercise preceded the hemorrhagic events among the two cases in our cohort. Similarly, BP lowering precipitating factors was commoner amongst patients with ischemic events in temporal association than BP elevating factors in our cohort, although statistical significance could not be reached. The development of the pathological collateral systems provides an alternate route for cerebral perfusion in MMA. But it is often insufficient to compensate reduced

cerebral perfusion. This is more conspicuous in children than adult MMA, thus making them further vulnerable to changes in BP and precipitating factors known to alter the cerebral perfusion [15–17].

Fever and increased body temperature can potentiate symptoms of MMA related to hemodynamic stress. Our findings resonate with the observation by Das et al., wherein Covid-19 infections precipitated MMA symptoms [14, 18, 19]. It has been seen that there is a marked drop of central blood-pressure post bath in hot water that can persist for 45–60 min. This can further lead to decompensation of already compromised cerebral circulation and seems to be the major drive in precipitation of neurological symptoms following hot bath [20, 21]. Cold water bath related potentiation of MMA symptoms may be hypothesized to the fact that a abrupt fall in skin temperature can lead to powerful cardio-respiratory changes called as the "cold shock" response, this leads to hyperventilation and subsequent decrease in cerebral blood flow (CBF). Besides, corroborative evidence suggests that repeated cold exposure can modulate endothelial nitric oxide (NO) synthase and bioavailability of NO and impair endothelial vasodilatory function [22–24]. Chen et al. described a case of MMA precipitated following whole body cryotherapy and linked the events mechanistically as cryotherapy induced cerebral autonomic dysregulation and vasoconstriction, potentially through transient hyperventilation [25].

Crying as a precipitating factor was significantly commoner in children with MMA, conforming to previous reports. It may be presumed due to the essential differences in susceptibility to ischemia of brain of children and adults. Thus, even a moderate decrease in cerebral perfusion can potentiate ischemic symptoms in children, who have higher cerebral oxygen consumption in comparison to adults. Besides, a child is more prone to crying in response to uncomfortable situation due to its intellectual and emotional immaturity. Other less plausible explanations could be more severely compromised cerebral circulation and possibility of better vasoconstrictive response to hyperventilation in children compared to adults [26].

Hyperventilation-induced intracranial vasoconstriction subsequent decrease in cerebral perfusion is a result of hypocapnia. Crying and intake of spicy food causes precipitation of ischemic symptoms chiefly by the mechanism of hyperventilation. Besides, spicy food can lead to increased blood flow through external carotid artery (ECA) to oral glands and mucosa causing a "steal phenomenon" to the anterior cerebral circulation, previously being compensated by collaterals from ECA. Further, spicy food intake causes increased body temperature [9, 26–29]. Previous studies have shown exercise induced hyperthermia can lead to decrease in middle cerebral artery (MCA) velocity [30]. Its extrapolation may be reasonable in cases of spicy

food intake as well. Exercise, on the other hand, also causes increased hemodynamic demand [9, 31, 32]. Diarrhea and dehydration can lead to decrease in systemic pressure and subsequently diminution of cerebral perfusion [33]. An already compromised cerebral circulation in MMA, is thus often decompensated by this mechanisms leading to manifestation of ischemic symptoms [5, 7, 8].

Acute emotional stress is proposed to enhance the risk of ischemic stroke by excessive sympathomimetic activity and complex interactions of altered coagulation and inflammatory states [34–37]. It has been speculated that stress can cause endothelial dysfunction with decreased NO production leading to loss of anti-coagulant and pro-fibrinolytic properties [34–36]. This becomes particularly important in individuals with pre-existing vessel lumen compromise. Besides, it can cause alteration of immune system by increasing IL-8, pro-inflammatory TNF- α and unaltered induction of anti-inflammatory cytokine IL-10, which is already known to be implicated in worsening of MMA [34, 38–42]. Also, several studies have shown that sympathetic activity can decrease CBF or attenuate CBF increases, but under normal physiological condition neurogenic control has lesser influence over cerebral autoregulation in comparison to vasomotor, metabolic and chemical mechanism. However, in chronic ischemic states, these dominant mechanisms are often overwhelmed and a dysautoregulation secondary to accentuation of neurogenic, sympathetic control of CBF occurs [43]. A similar pathophysiology might be underpinning the precipitation of transient symptoms in MMA secondary to emotional stress leading to sympathetic stimulation.

Certain symptoms in MMA like limb-shaking TIA (LS-TIA) and focal motor seizures are difficult to tell apart. A reliable clinical clue is the history of temporal association of symptom onset to triggers causing cerebral hypoperfusion which usually points towards the diagnosis of LS-TIA [8, 44–46].

It was noticed that 4.5% of the patient did not document any evidence of cerebral hypoperfusion on baseline imaging. They were only decompensated on exposure to precipitating factors leading to manifestation of transient neurological symptoms. Though a very minor fraction, these patients can greatly benefit from detailed elicitation and attribution of these triggers to an underlying occlusive vasculopathy, which can aid in early diagnosis and better prognostication. It was further observed that careful avoidance of the specific precipitating factors led to decrease of transient neurological symptoms, in either severity or frequency or both, among 42.4% patients with history of precipitating factors and none of them had new onset fixed motor neuro-deficit over a follow-up period of 6 months. This is likely due to reduction of transient worsening of the cerebral perfusion in the absence of triggers. Behavioral therapy promoting avoidance of preventable triggers can be useful. Physical measures aiding

in blood pressure regulation, drinking adequate fluids and occasional use of compression hosiery can greatly aid in maintenance of blood volume and subsequently cerebral perfusion. This undermines the importance of meticulous elicitation of history of such triggering factors which can greatly aid in decreasing the distressing neurological symptoms while a definite therapy for MMA is awaited. This is especially important in countries like India, where the health-care system is not robust and MMA patients have to travel great distances to avail centers with facilities for revascularization surgery [5, 7, 8, 45].

This is the first study to explore the effects of triggering factors in MMA patients. The potential limitation includes a single-centered observational study. A perfusion study at follow-up period could have further strengthened the observations. However, the strength lies in the relatively large cohort of MMA patients included in the study.

Conclusion

MMA is frequently associated with triggers that can cause transient cerebral hypoperfusion, more common in children than adult-onset MMA. Certain precipitating factor can affect an age group more commonly, crying more commonly potentiated ischemic symptoms in children. It can be an early clue to diagnosis in MMA, even before the setting of cerebral hypoperfusion. A careful avoidance of these factors can help alleviate distressing transient neurological symptoms, which is especially beneficial in resource-limited setting.

Declarations

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