Chapter

Clinical Aspects of Moyamoya Disease

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Abstract

Moyamoya disease is a chronic progressive, non-atherosclerotic, occlusive intracranial vasculopathy involving major cerebral arteries around the circle of Willis. MMD occurs frequently in East Asian populations but the disease can affect the American and European ethnicities as well. Knowledge of clinical aspects of Moyamoya disease (MMD) is important in view of distinctive clinical presentation observed in children and adults. MMD has bimodal age of distribution, with peaks in the first and last decades of life. Childhood MMD is characterised by Ischemic manifestation (Transient ischemic attack, Cerebral Infarction), whereas adult MMD presents with hemorrhagic manifestations (Intracerebral haemorrhage, Intraventricular bleed). Refractory headache, seizure and ophthalmological abnormalities are other clinical presentations of MMD. A high index of clinical suspicion and an eye to recognise the common as well as unusual manifestations of the disease and inciting events may prevent delay in the diagnosis. A thorough knowledge about the varied clinical presentation would aid clinician for early diagnosis and management of this rare entity. The present article provides extensive review on the clinical aspects of MMD amongst adults and paediatric population, on the basis of previous articles and research studies.

Keywords: Moyamoya disease, Moyamoya syndrome, clinical features

1. Introduction

Takeuchi and Shimizu Takeuchi first described Moyamoya disease, in 1957 [1]. The term "Moyamoya" was coined to this illness due to its angiographic appearance of "something hazy, like a puff of cigarette smoke" (Moyamoya in Japanese) [1] "Moyamoya disease" (MMD) and "Moyamoya syndrome" (MMS) are both chronic cerebrovascular diseases affecting distal internal carotid and proximal portions of the anterior and middle cerebral arteries [2]. Though Moyamoya disease and Moyamoya syndrome are used synonymously, a subtle distinction separates these two entities. Moyamoya vasculopathy in those with underlying risk factors are described under the umbrella term "Moyamoya syndrome", thus a wide variety of conditions can incite a Moyamoya vasculopathy, however, if a similar angiographic appearance is evident in those with no risk factors, except for an underlying genetic predisposition, it is entitled as "Moyamoya disease" [2]. One more distinction is the" bilateral "angiographic appearance pathognomonic for Moyamoya disease, whilst" unilateral "vasculopathy always qualifies to a Moyamoya syndrome, even without an underlying associated risk factor [2].

2. Literature research strategy

We searched PubMed from 1968 to January 2021 with the words "Moyamoya disease", "Moyamoya syndrome", "population-based", "epidemiology", "risk factors", "genetics", "clinical aspects",clinical features of Moyamoya, seizure and Moyamoya, headache and Moyamoya, paediatric Moyamoya, Adult Moyamoya, stroke and Moyamoya, neuropsychological profile of Moyamoya, Research studies on Moyamoya, Case reports of Moyamoya. Relevant articles were also searched in the national and International journals where the full article could be retrieved. Clinical manifestation and underlying pathophysiology was reviewed in the searched article to provide an extensive review ofclinical aspects of Moyamoya disease.

2.1 Epidemiology

This disease entity was believed to affect Asian heritage, given their genetic predisposition. However, it is now a well-known fact that this disease entity can affect American and European ethnicities [3]. This disease has a bimodal distribution of age-specific incidence rates with two peaks in the age groups of 5 years in children andmid-40s in the adults [3, 4]. It is twice more common in females as in males [3]. The incidence estimates of 0.35–0.54/100,000 are found in the Japanese and Korean populations [5]. An incidence of 0.086 cases per 100,000 persons inAmericans, incidence-rate ratios are 4.6 for Asian Americans, 2.2 for blacks, and 0.5 for Hispanics [6].

2.2 Etiopathogenesis

Moyamoya disease has a genetic aetiology, as mentioned above. Many studies where total genome search linkage was performed found an association between the disease and markers located at 3p24.2–26 chromosome [7], a possible connection of the marker D6S441 located on chromosome 6 which also has HLA gene [8], linkage to chromosome 17 have also been reported.

Moyamoya syndrome is associated with many conditions, as described below: [8].

Chromosomal/Genetic disorder	**Neurofibromatosis, "Down's syndrome, Turner syndrome**
Haematological disorders	Sickle cell anaemia, Thalassemia, Aplastic anaemia
Infectious disease	Leptospirosis, Tuberculous meningitis
Neoplasms	Craniopharyngioma, Wilms tumour
Drug abuse	Phenobarbital
Autoimmune diseases	"Behcet's disease, "Sjögren's syndrome, systemic lupus erythematosus (SLE), Henoch Scholein Purpura (HSP) and 'Graves' disease
Others	Cardiomyopathy, Polycystic kidney, Pulmonary sarcoidosis, Irradiation, Trauma, Renal artery stenosis

A role of fibroblast growth factor, prostaglandin, and activation of cox2 in the vascular smooth muscle, EBV DNA and propionibacteria have all been proposed as a possible mediator of the neovascular response [9].

2.3 Natural history

Disease progression can be slow, with overlapping intermittent events, or it can be a fulminant course, with rapid neurologic decline [10]. It has been reported that symptomatic progression is observed for five years, and delay in the rap initiation may have catastrophic consequences [10].

3. Diagnostic criteria

Various guidelines have been published over time and again. In 1996 and 1997 Japan published diagnostic criteria for the pathology and treatment of MMD [11]. In 2012, Japan published the latest guidelines based on 1997 guidelines [11].

Though cerebral angiography remains the gold standard for the diagnosis (**Table 1**), novel guidelines added a staging based on scores of magnetic resonance (MR) angiography (MRA) [12].

Stenosis or occlusion at the end of ICA and/or the initial segment of the ACA and/or MCA.

At least two obvious shadows of the blood flow are displayed on the same scan level at the basal ganglia region, suggesting the existence of an abnormal vascular network.

The above manifestations are bilateral, but bilateral lesions may be staged differently.

The total score was the sum total of MRA results and each side (right and left were scored individually) as shown in the **Tables 2** and **3**.

As per the new guidelines, other diseases viz. atherosclerosis, autoimmune diseases, meningitis, brain tumours, Down syndrome, Recklinghausen's disease, head injury and cerebrovascular damage after head irradiation, should be excluded [12].

Pathological findings suggestive of MMD are fibrocellular thickening of arterial intima, waviness of internal elastic lamina, thinning of the media, variable stenosis and occlusion of the implicated vessels, presence of anastomotic and perforating branches around the circle of Willis and pial reticular conglomerate of small blood vessels [12].

Definitive MMD: Either angiographic or MRA appearance of vessels bilaterally with the exclusion of alternative diagnosis [13].

Stage	Cerebral angiographic findings
I	Narrowing of the carotid fork
II	Initiation of the moyamoya (dilated major cerebral artery and a slight moyamoya vessel network)
III	Intensification of the moyamoya (disappearance of the middle and anterior cerebral arteries, and thick and distinct moyamoya vessels)
IV	Minimization of the moyamoya (disappearance of the posterior cerebral artery, and narrowing of individual moyamoya vessels)
V	Reduction of the moyamoya (disappearance of all the main cerebral arteries arising from the internal carotid artery system, further minimization of the moyamoya vessels, and an increase in the collateral pathways from the external carotid artery system)
VI	Disappearance of the moyamoya (disappearance of the moyamoya vessels, with cerebral blood flow derived only from the external carotid artery and the vertebrobasilar artery systems)

Table 1.
Stages and cerebral angiographic findings.

Scoring for each artery	
Score	**MRA Findings**
Internal carotid artery	
0	Normal
1	Stenosis of C1
2	Discontinuity of the C1 signal
3	Invisible
Middle cerebral artery	
0	Normal
1	Stenosis of M1
2	Discontinuity of the M1 signal
3	Invisible
Anterior cerebral artery	
0	Normal A2 and blood vessels distal to A2
1	Signal decrease A2 and its distal blood vessels
2	Invisible
Posterior cerebral artery	
0	Normal P2 and blood vessels distal to P2
1	Signal decrease P2 and its distal blood vessels
2	Invisible

Table 2.
Classification and scoring based on the MRA findings.

MRA total score	**MRA stage**
0–1	1
2–4	2
5–7	3
8–10	4

Table 3.
Total score calculated individually for the right and left side.

Probable MMD: Either angiographic or MRA appearance of vessels unilaterally with the exclusion of alternative diagnosis [13]. Unilateral MMD may progress to bilateral MMD in 10 to 39% of the cases.

If the autopsy is performed with no previous angiography, pathological findings similar to those mentioned above may serve in the diagnosis of MMD [13].

Quasi MMD or Rui MMD:Evidence of stenosis or occlusion of distal ICA or proximal MCA or ACA with abnormal vascular network either unilateral or bilateral, in association with an underlying disease [13]. Concurrent occurrence of congenital disease is common in children, and acquired disorderis common in adults.

Unstable MMD: Defined as "rapid progression or repeated stroke". It is a clinically challenging condition. It is more prevalent in patients younger than threeyears and those with an associated underlying disease. It is a possible risk factor associated with perioperative ischemic complication [14].

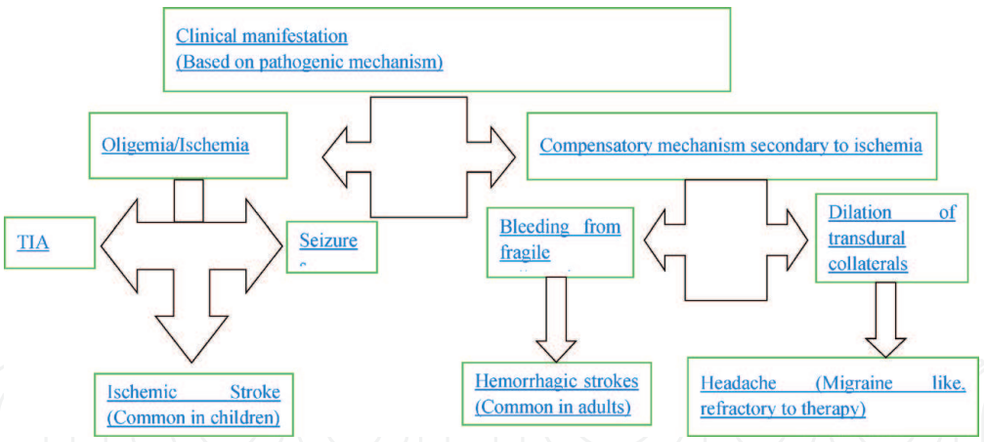

Figure 1.
Flow chart showing the clinical manifestation of Moyamoya disease based on underlying pathogenic mechanism.

Moyamoya disease/syndrome symptoms can be broadly categorised into two, by the underlying mechanism (**Figure 1**). The first category of symptoms is oligemia like transient ischemic attack (TIA), stroke, and oligemia like transient ischemic attack (TIA), stroke, and seizures. Amongst the ischemic symptoms, completed strokes are more common in children, a possible explanation being their inability to identify and complain about TIAs [11]. The second category of symptoms are due to the compensatory mechanisms' harmful consequences to ischemia like a haemorrhage from fragile collateral vessels and headaches from dilated transdural collaterals [10].

"Initial attacks" of MMD [12].

The research committee has identified nine types of initial episodes of MMD.

Hemorrhagic type.

Epileptic type.

Infarction type (can be same side or alternating hemiplegia).

TIA type.

Frequent TIA type (two or more attacks per month).

Headache type.

Asymptomatic type.

Other types.

Details unknown type.

4. Clinical manifestations in children

Moyamoya disease presents with ischemic symptoms in children, an incidence of 68% and adults usually present with a hemorrhagic stroke, about 42% [10].

Amongst the ischemic symptoms, completed strokes are more common in children, a possible explanation being their inability to identify and complain about TIAs [15]. They can be transient or fixed. Most commonly occur in the territory of the internal carotid artery and proximal middle and anterior cerebral arteries [10].

Underlying mechanism:

Progressive stenosis of the internal carotid and middle cerebral arteries are responsible for most of the symptoms [10].

Maximally dilated cortical vessels in patients with chronic ischemia, constrict in response to the decreased carbon dioxide due to hyperventilation, resulting in reduced cerebral perfusion and thus exacerbating the symptoms [16].

Precipitating factors: [16].

Crying (In the paediatric population).
Hyperventilation (In paediatric population).
Exercise.
Anaesthesia.
Dehydration.
Altitude.
Eating a hot meal.
Focal Symptoms: [10].
Hemiparesis.
Dysarthria.
Aphasia.
Visual deficits.
Chorea.
Non-focal symptoms: [10].

Headache: Approximately 20% of the paediatric patients under the age of 14 years suffer from headache. Likely explanantion for the headache was the reduction of cerebral blood flow or cerebral blood flow reserve and diffusive cortical inhibition [17]. Dilatation of meningeal and leptomeningeal collateral vessels may stimulate dural nociceptors. Every refractory headache, especially in the paediatric population should be thoroughly worked up for moyamoya disease [17] Headaches can be migraine-like episodes which may respond to revascularization surgery or remain refractory to surgery [17].

Cognitive impairment, learning disability, and attention deficits.
Seizures.
Syncope.

Personality change, mistaken for a psychiatric illness like schizophrenia, acute transient psychosis, and mania [18].

Symptoms and signs which serve as biomarkers in MMD/MMS:

Orthostatic intolerance (also termed "orthostatic dysregulation"): [19] Orthostatic intolerance is defined as" a disturbance in the physiological adjustment mechanism compensating for physical stresses, such as standing, and causes a variety of symptoms associated with hemodynamic or autonomic nervous system compromise". These symptoms can have a potential impact on the quality of life of paediatric MMD patients. In a study done by H. Uchino et al., 59% of children 10–15 years old suffered from orthostatic intolerance. These symptoms usually go unnoticed, and thus a thorough history from the patients and their caretakers become mandatory.

Symptoms which are suggestive of orthostatic intolerance:
Frequent headache.
Susceptibility to vertigo & dizziness on standing.
Fatigue.
Difficulty while getting out of bed.
Motion sickness.
Palpitation &/or dyspnea after mild exercise.
Tendency for fainting in the standing position.
Anorexia.
Occasional umbilical colic (severe abdominal pain).
Nausea on taking a hot bath or encountering unpleasant experiences.
Absent from school due to the above symptoms.
Pallor.

Fundus: Retinovascular anomalies and "morning glory disk" an enlargement of the optic disk should compel the clinician to look for moyamoya vasculopathy [20]. Morning glory syndrome or Morning glory disc anomaly is an unusual

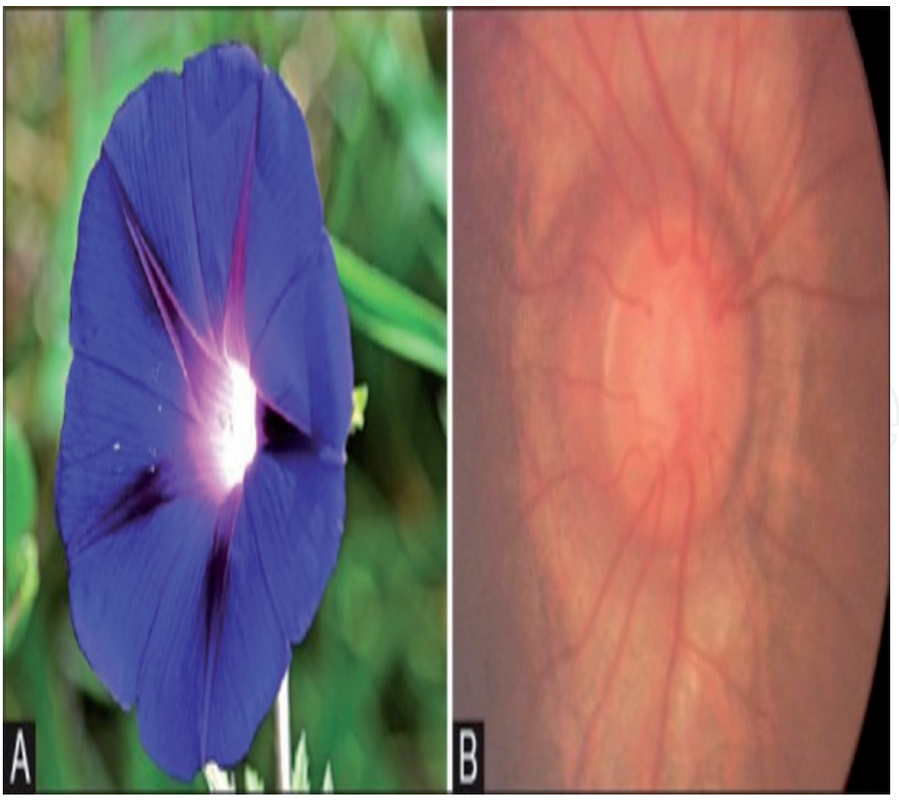

Figure 2.
*Showing morning glory disc [courtesy:Indian J Radiol imaging. 2018 Apr-Jun] [22]. MRI brain CISS sequence of orbit region may further confirm funnel-shaped excavation of the posterior globein morning glory syndrome of Moyamoya disease (**Figure 3**) [22].*

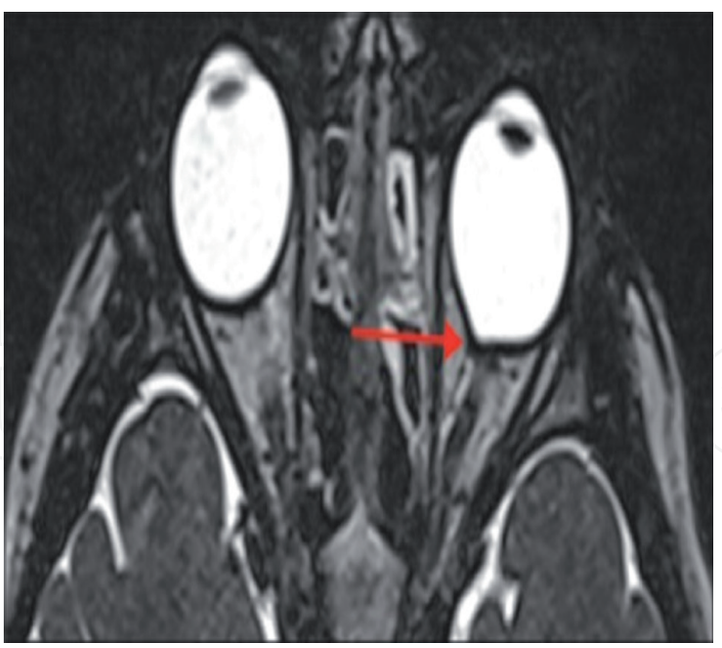

Figure 3.
Showing funnel-shaped excavation of posterior globe [courtesy: Indian J Radiol imaging. 2018 Apr-Jun] [22].

congenital optic disc anomaly characterised by a funnel-shaped excavation of the posterior globe that incorporates the optic disc [21]. Kindler described it in 1970 because it resembled the morning glory flower. The disc itself is enlarged, and orange or pink in colour within a surrounding area of peripapillary chorioretinal pigmentary changes. Alteration of lamina cribrosa and posterior sclera due to embryonic developmental defect leads to this fundus's flowery appearanace.

Presence of this sign indicates an association with systemic or intracranial vasculopathies such as MMD. Morning glory disc occurs in 50% of patients with the MMD (**Figure 2**).

Sequelae of MMD: [16].

Refractory headaches.

Recurrent TIAs.

Posterior cerebral artery (PCA) involvement.

Recurrent intracranial aneurysms.

Unstable MMD.

In children with MMD, recurrent ischemias can result in cerebral atrophy and thus emanate the onset of learning difficulties, cognitive impairment and mental retardation.

5. Clinical manifestations in adults

Hemorrhagic manifestations are more common in adults than in children. These haemorrhages are seen in 42% of the adults. The location of the bleeding can be intraventricular, intraparenchymal or subarachnoid.

Underlying mechanism:

Rupture of fragile collateral vessels as a result of chronic oligemia [23].

Development of cerebral aneurysms at the apex of the basilar artery and posterior communicating artery, areas of increased shear stress due to shifting circulatory pattern at the base of the brain is another source of haemorrhage [24].

Quasi MMD is common in adults, and the manifestations may range from asymptomatic to catastrophic haemorrhage and rebleeding with a moribund prognosis [13].

Ischemic symptoms are more common in the paediatric population, as described above. Amongst the ischemic symptoms transient ischemic attacks(TIA) are more common in the paediatric population with an incidence of 81% and infarctions are experienced by adults in approximately 51% [25].

Reason for the above observation could be due to better development of leptomeningeal collaterals (LMCs) in children than adults [25]. Various factors have been implicated in this observation: [25].

Ageing: Significant decrease in LMCs and increased tortuosity and vascular resistance in leptomeningeal vessels.

Concomitant diseases in adult MMD patients like hypertension may have an effect on the development of collaterals.

Focal cerebral ischemia may stimulate cytokines' secretion, such as angiogenic peptides and vascular endothelial growth factor (VEGF). These cytokines levels are lower in adults.

Associated underlying conditions are commonly observed in adults with MMD.

Clinical clues for associated disorders: [10].

History of radiotherapy	Head and neck malignancies like optic gliomas, craniopharyngiomas, and pituitary tumours
Endocrine insufficiency	Neurofibromas or tumours compressing hypothalamic–optic pathway and pituitary stalk
Visual field defects	Tumours compressing hypothalamic–optic pathway, Strokes involving the visual pathway
Anaemia	Sickle cell anaemia, Thalassemia, Aplastic anaemia
Acute abdomen, bone crises	Sickle cell anaemia

Neurocutaneous markers	Neurofibromatosis, Down's syndrome,Turner syndrome
Refractory hypertension	Renal Artery Stenosis
Fever	Leptospirosis, CNS tuberculosis
Recurrent falls (Especially in the Paediatric population)	TIAs
Systemic symptoms like cutaneous rash, joint pains	SLE, Sjogren syndrome and HSP

Special Precautions to be exercised:

EEG: Hyperventilation may precipitate an acute oligemic episode, thus caution has been exercised in patients with suspected moyamoya disease. Specific alterations in MMD/MMS have characteristic changes in EEG, consisting of the gradual decrease in frequency and amplitude activation after hyperventilation. These EEG changes are referred to as re-build-up phenomenon [2].

Anaesthesia and postop care.

Travelling to high altitudes.

Exercise.

6. Conclusion

A vast constellation of symptoms constitutes a repertoire in MMD. They may facilitate the diagnosis or add more confusion to the diagnosis. Fundus examination and characteristic angiogram findings clinch the diagnosis of MMD. A high index of clinical suspicion and an eye to recognise the disease's common and unusual manifestations and inciting events may prevent delay in the diagnosis. Early recognition of illness with prompt treatment may halt the progression and allay catastrophic neurological deficits.

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