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Distinct presentation of Moyamoya disease in Iran

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Abstract

Moyamoya Disease (MMD) is a rare cerebrovascular disorder characterized by stenosis of the internal carotid arteries. To date, no studies have specifically described the characteristics of Moyamoya among Iranian populations. This study aims to examine the clinical characteristics of a case series of Iranian patients with MMD. This study prospectively identified all patients diagnosed with MMD at an institutional tertiary hospital in Tehran from 2010 to 2020. Data on demographic characteristics, disease presentations, past medical history, type of vascular lesion, treatment approaches, and outcomes during follow-up were collected. A total of 15 patients with MMD were included. Of these, 9 (60%) were female. Age distribution at diagnosis showed 6 patients were younger than 40 years. No familial patterns of MMD were observed. All patients experienced Cerebrovascular Accidents (CVA) at disease onset. A notable prevalence of comorbid conditions was observed, including hypertension (33.3%), diabetes mellitus (20%), and seizure disorders (20%). Vascular lesions were unilateral in 46.6% of patients and bilateral in 53.4%. Direct bypass surgery was performed in 40% of cases. The mean follow-up period was 16.3±1.2 months. During this time, 2 patients died and 1 experienced a new CVA. Residual symptoms were present in 13.3% of patients. This study shows distinct characteristics of MMD in an Iranian cohort, including a female predominance, frequent ischemic symptoms, and a high rate of bilateral occlusions. Further prospective studies are warranted to assess the efficacy of medical and surgical interventions in preventing recurrent symptoms in this population.

Key Words: Moyamoya disease, clinical presentation, stroke, cerebrovascular disorder.

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Moyamoya Disease (MMD) is a rare cerebrovascular disorder characterized by the progressive occlusion of the distal Internal Carotid Artery (ICA), the Middle Cerebral Artery (MCA), the Anterior Cerebral Artery (ACA), and the vessels around the circle of Willis, leading to cerebral ischemia.[1,2] In MMD patients, brain angiographies reveal a characteristic network of tiny blood vessels resembling a cloud or smoke, aptly named "Moyamoya," a Japanese term meaning "puff of smoke." This disease was first identified in Japanese literature. Predominantly, it affects children aged 5 to 9 years but is also observed in adults between 45 and 49 years.[2]

MMD's prevalence is notably higher in East Asian countries, such as Japan, China, and South Korea, likely due to significant genetic factors. The pathophysiology of MMD involves hyperplasia of Smooth Muscle Cells (SMCs) in the arterial wall's tunica media.[3] It is hypothesized to involve apoptosis in arterial wall cells via a caspase-dependent pathway.[4] Elevated levels of Vascular Endothelial Growth Factor (VEGF), Matrix Metalloproteinase (MMP), hepatocyte growth factor, and interleukin-1B have been observed in the bloodstream of MMD patients.[5] Additionally, structural and functional mitochondrial abnormalities in Endothelial Colony-Forming Cells (ECFCs) have been reported in these patients.[6] A distinct pattern of circular RNAs expression, influencing the pathogenesis of MMD through the Mitogen-Activated Protein Kinase (MAPK) signaling pathway, has been identified.[7] In East Asia, the p.R4810K variant of the Ring Finger Protein 213 (RNF213) is suspected to contribute to MMD development.[8]

For diagnosis, catheter-based Digital Subtraction Angiography (DSA) is considered the gold standard.[9] Magnetic Resonance Imaging (MRI) is also utilized for detecting acute ischemia or infarction, while perfusion MRI or Perfusion-Weighted Imaging (PWI) and Computed Tomogra-

phy (CT) perfusion are employed in both preoperative and postoperative assessments.[1]

Currently, there is no accepted treatment for MMD; however, antiplatelet drugs such as aspirin, cilostazol, and clopidogrel, along with surgical revascularization (both direct and indirect), are commonly used to prevent secondary complications.[10,11] Recent studies in diverse ethnic populations have highlighted significant epidemiological and clinical differences in MMD presentation, underscoring the need for region-specific research to inform diagnosis and treatment strategies. In the Middle East, particularly in Iran, there is scarce evidence on MMD in adults, including its clinical presentation, treatment, and long-term outcomes. This study aims to fill this gap by investigating adult MMD cases in Iran over a decade, comparing global data with our findings on demographic characteristics, clinical manifestations, treatment approaches, and long-term outcomes.

Materials and Methods

Study population

The study included consecutive patients diagnosed with MMD at Firoozgar General Hospital, an institutional tertiary hospital located in Tehran, Iran, from 2010 to 2020. Inclusion was based on clinical and radiographic criteria outlined in existing MMD guidelines.[12] Patients not meeting these criteria were excluded.

Data collection and treatment protocol

Patient electronical records were examined for demographic information (gender, age, ethnicity), clinical data (familial history, clinical presentations, past medical history, angiographic features), and treatment details. Patients were categorized based on symptom severity. Rapidly progressing cases underwent direct revascularization, while stable cases received medical management. Long-term outcomes were assessed via a telephone-based questionnaire.

Statistical analysis

Categorical variables were presented as number (percentage) while continuous variables were presented as mean ± standard deviation. All data were analyzed to identify patterns and correlations in clinical presentations, treatment effectiveness, and long-term outcomes among the Iranian MMD patient population.

Results

In this study, 15 MMD patients with a mean age of 41.00 ± 5.17. The sex distribution showed 9 females (60%) and 6 males (40%). The mean age was of the patients at the onset of disease was 40.65 ± 5.17. Regarding age at diagnosis, 6 patients were <40 years, while 9 were ≥40. In terms of familial background, parental consanguinity was noted in 3 (20%) patients. Considering Iran's multi-ethnic population, it's notable that all patients in this study were of Fars ethnicity, despite the country's diverse ethnic groups.[13]

At the disease onset, every patient had experienced a Cerebrovascular Accident (CVA). The neurological symptoms varied: 40% of patients presented with generalized symptoms including dysarthria, headache, nausea, and vomiting at admission, while 60% exhibited unilateral symptoms, predominantly hemiparesis and hemiplegia. Symptom frequency was as follows: hemiparesis (73.3%), dysarthria (40%), headache (33.3%), nausea and vomiting (33.3%), unilateral facial palsy (20%), photophobia (20%), loss of consciousness (13.3%), visual impairment (13.3%), quadriparesis (6.6%), and tics (6.6%) (Figure 1A).

The patients' medical histories revealed chronic hypertension as the most common comorbidity, followed by diabetes mellitus and seizure. Comorbidities were distributed as follows: hypertension (33.3%), diabetes mellitus (20%), seizure (20%), hypothyroidism (13.3%), migraine (6.6%), hyperthyroidism (6.6%), Down syndrome (6.6%), and thalassemia (6.6%), with a third of the patients having no significant past medical history (Figure 1B). It should be noted that hypertension and diabetes mellitus were only observed in patients aged ≥40. In terms of vascular lesions, 46.6% of patients had unilateral lesions, while 53.4% had bilateral lesions. The specific lesion distribution included right ICA (66.6%), left ICA (60%), right MCA (13.3%), left MCA (20%), right CCA (6.6%), and left CCA (6.6%) (Figure 1C).

Concerning treatment approaches, 60% of the patients received medical management, whereas 40% underwent direct bypass surgery, involving revascularization of the brain cortex with a temporalis muscle flap (Figure 2). The mean follow-up period for the patients was 68.3 ± 1.2 months, ranging from 31 to 140 months. The outcomes observed were complete resolution in 26.6% of patients, partial recovery in another 26.6%, ongoing symptoms in 13.3%, mortality in 13.3%, new-onset CVA in 6.6%, and 13.3% of patients were lost to follow-up (Figure 1D).

Discussion

Moyamoya Disease (MMD), a rare cerebrovascular condition characterized by stenosis or occlusion at the distal intracranial internal carotid arteries and their proximal branches, has been increasingly recognized in the Middle East. This region presents unique demographic and clinical profiles for MMD, as illustrated by several studies conducted in Middle Eastern countries.[14-20]

Prevalence and demographics

In Israel, Schwartzmann *et al.* (2024) reported on the characteristics of Moyamoya Disease (MMD) and Moyamoya Syndrome (MMS) in a cohort over 20 years. Their study found that patients with MMD were significantly younger than those with MMS, with a median age of 20 years for MMD and 40 years for MMS. The study noted no significant differences in clinical presentations or long-term outcomes between the two groups, with a recurrent stroke rate of approximately 25% in both, emphasizing the need for better risk stratification.[20]

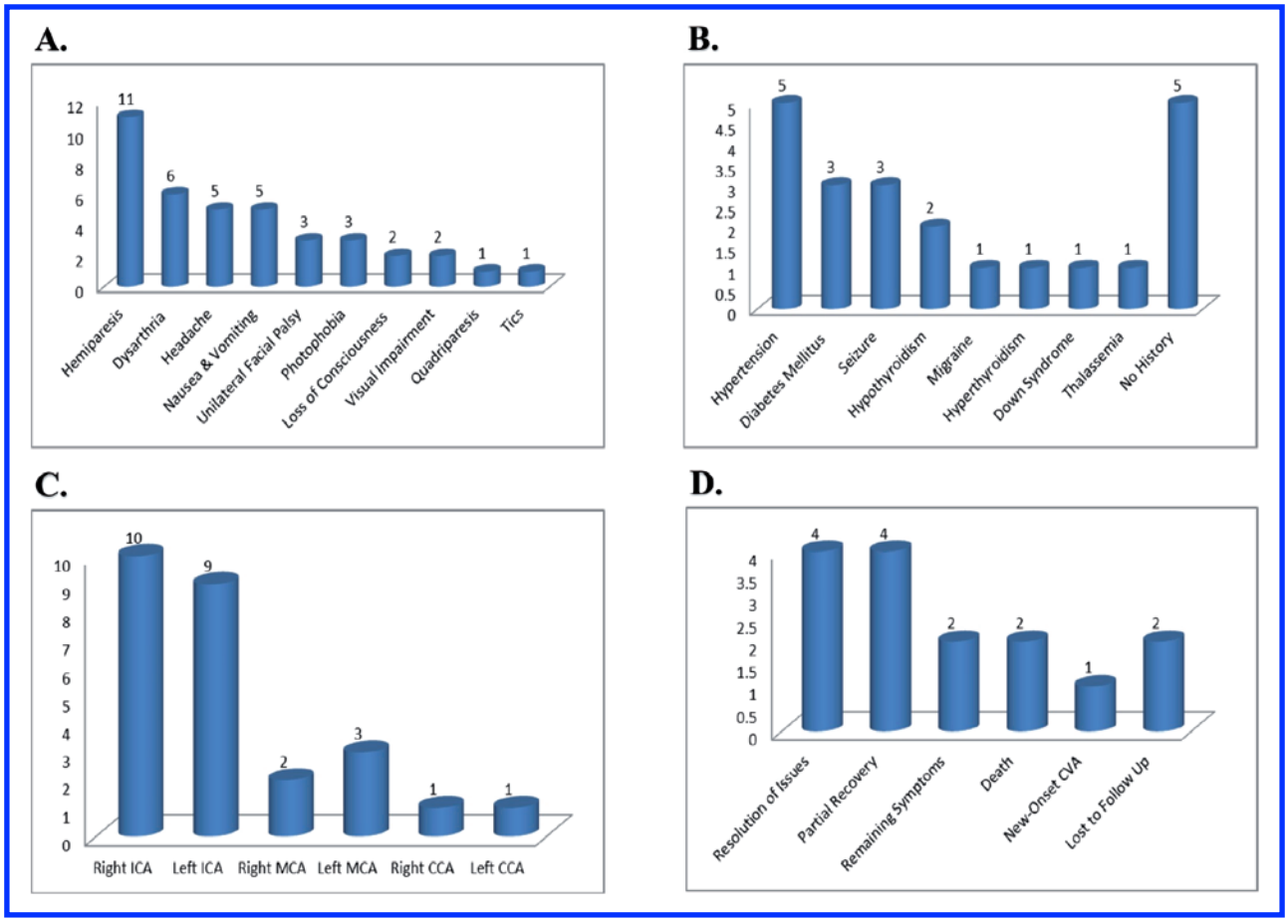

Figure 1. *Frequency of A) signs and symptoms, B) comorbidities, C) arterial lesions and D) patient outcomes in the studied cohort.*

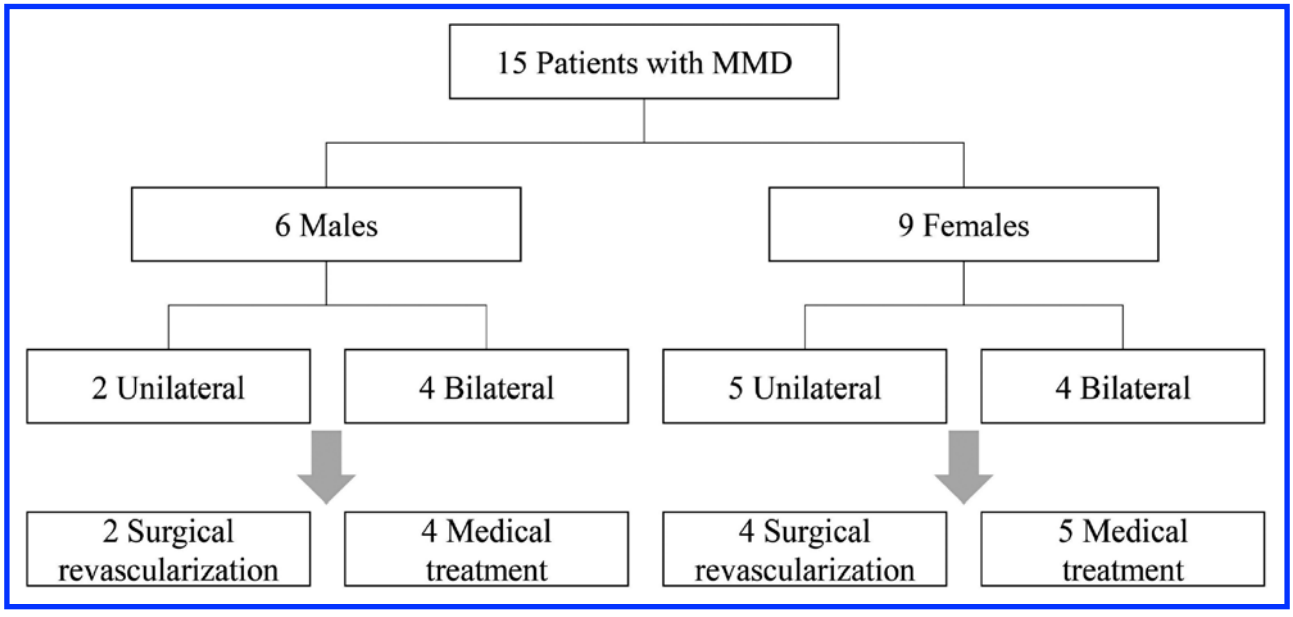

Figure 2. *Flowchart of interventional choices for patients recruited to the study.*

Similarly, Goren *et al.* (2021) highlighted surgical outcomes in Israeli patients, showing that Encephaloduroarteriosynangiosis (EDAS) with dural inversion is an effective treatment for MMD. Their study, which involved 54 patients, demonstrated favorable long-term outcomes, with 92.6% achieving a modified Rankin Scale score of 0-2 post-surgery.[19]

In Saudi Arabia, Saeed *et al.* (2016) and Salih *et al.* (2006) provided insights into pediatric MMD. Saeed *et al.* reported on 11 children with MMD, noting that surgical revascularization was performed in only a few cases due to varied clinical presentations, including associations with Down syndrome and sickle cell anemia.[18] Salih *et al.* observed MMS as a risk factor for stroke in children, identifying associations with conditions such as protein C and S deficiencies, sickle cell disease, and unique syndromes like Adams-Oliver syndrome and wrinkly skin syndrome.[15]

In Turkey, Tatli *et al.* (2012) and Sencer *et al.* (2000) provided data on pediatric and adult populations, respectively. Tatli et al. found no prothrombotic risk factors in their pediatric cohort, though outcomes were generally poor despite medical and surgical interventions.[17] Sencer *et al.* emphasized angiographic findings and surgical outcomes in their case series, noting successful revascularization in patients undergoing EDAS.[14]

Clinical presentations and challenges

Across the Middle East, MMD often presents with ischemic strokes and motor deficits, consistent with global findings. Shoukat *et al.* (2009) in Pakistan reported a predominance of strokes in their cohort, with bilateral vessel involvement noted in the majority of patients. Fever was an additional symptom noted among younger patients, a less commonly reported feature of MMD.[16]

The variability in clinical presentation and outcomes reflects both the diverse genetic backgrounds of Middle Eastern populations and the challenges in diagnosing and managing MMD. The association of MMD with other conditions, such as sickle cell disease and Down syndrome, highlights the need for comprehensive clinical evaluation and individualized management strategies.

Treatment and outcomes

Surgical revascularization, including both direct and indirect techniques, remains a cornerstone of MMD management in the Middle East. The outcomes reported by Goren *et al.*[19] and Sencer *et al.*[14] indicate that indirect procedures such as EDAS are effective in both pediatric and adult patients. However, the recurrence of ischemic events, as noted by Schwartzmann *et al.*,[20] highlights the need for ongoing monitoring and intervention.

Despite these advances, challenges persist in the early diagnosis and effective management of MMD, particularly in pediatric populations where disease progression can be rapid. The findings from these regional studies emphasize the importance of multidisciplinary approaches and the potential benefits of early surgical intervention.

Comparative studies and international perspectives on Moyamoya disease

The current study explored the characteristics of Moyamoya disease in an Iranian cohort, revealing a female predominance with a female-to-male ratio of 1.5:1, aligning with international findings. Notably, the age of onset varied, with a mean age of 40.2 years, slightly differing from studies on Japanese and Chinese populations.[21-23] Japanese studies have reported an age of onset of 10 to 14 years for children, the mean age of 41.4 years for non-surgical group of patients, and 42.5 years for surgical group of patients.[21,22] A Chinese study reported the mean age of 45.8 years for non-surgically treated MMD and 42.8 years for surgically treated MMD which their difference were not statistically significant.[23] All patients experienced ischemic stroke at onset, a higher rate than typically reported, underscoring potential regional differences in symptoms.[24,25]

Moyamoya disease's steno-occlusive nature profoundly impacts the anterior cerebral circulation, leading to reduced intracranial blood flow and collateral artery formation.[26] In our study, this was evidenced by the absence of posterior cerebrovascular abnormalities, aligning with European studies.[27,28] The genetic component, particularly the role of the ACTA2 mutation and the proliferation of SMCs and ECs, is a recognized pathophysiological mechanism.[29] However, unlike studies from Japan[21,22,30] and Germany,[31] none of our patients had a familial history, which might be attributed to the small sample size or distinct genetic patterns in the Iranian population.

The higher prevalence of Moyamoya syndrome, indicated by unilateral cerebral arteriography findings in 46.6% of our patients, differs from previous reports and highlights the need for a nuanced understanding of Moyamoya presentations.[30-33] These studies also confirmed the global trend of female predominance in Moyamoya disease, yet our findings regarding age of onset and symptomatology suggest regional variations. Therapeutic approaches in our cohort predominantly involved anti-thrombotic therapy,[34] reflecting the ischemic nature of the disease presentations in our patients. Direct bypass surgery was performed in 40% of the cases, indicating a balanced approach to management, considering the severity and progression of the disease.

Considering the lower prevalence of Moyamoya in Iran compared to East Asian countries,[35,36] our findings contribute to the understanding of its epidemiology in different ethnicities and regions. The absence of familial history in our patients, compared to higher prevalence in Japanese studies,[30] may indicate distinct genetic or environmental factors influencing the disease in the Iranian population.

Limitations

This study's limitations include its small sample size, inherent to the disease's rarity. It underscores the need for larger, multicentric studies in the Iran and Middle East region to explore the genetic and clinical aspects of Moyamoya disease more comprehensively. Such research could elucidate whether the genetic patterns of MMD in the Mid-

dle East differ from East Asian, European, and American populations, contributing to the global understanding of this complex disease.

Conclusions

This study reveals MMD as a significant contributor to stroke in Iran, characterized by a high incidence of ischemic strokes and bilateral occlusions. Notably, right and left ICA occlusions were prevalent in 66.6% and 60% of cases, respectively. While medical therapy was effective for milder cases, revascularization surgery showed promise in managing more severe forms. These findings underline the need for tailored treatment approaches in MMD and advocate for further research to understand its unique characteristics in the Iran, potentially influencing global diagnostic and therapeutic strategies.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval

The paper is exempt from ethical committee approval because it is a retrospective study and does not involve human beings. Written informed consent was obtained from all the patients for publication of the clinical data.

Contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity and the accuracy of the data and analysis.

Data availability

All data analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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