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Clinical features and outcomes of paediatric moyamoya vasculopathy in Malaysia

[1]Wei Kang Lim *MPaeds*, [1]Lai Choo Ong *MRCP*, [2]Khian Aun Tan *MPaeds*, [1]Limin Li *MPaeds*, [2]Chee Ming Teh *MRCPCH*, [3]Hock Sin Heng *MRCPCH*, [4]Sumitha Murugesu *MRCPCH*, [1]Choong Yi Fong *FRCPCH*

[1]Division of Paediatric Neurology, Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur; [2]Paediatric Neurology Unit, Department of Paediatrics, Penang General Hospital, Penang; [3]Paediatric Neurology Unit, Department of Paediatrics, Sabah Women and Children's Hospital, Likas, Sabah; [4]Paediatric Neurology Unit, Department of Paediatrics, Tunku Azizah Hospital, Kuala Lumpur, Malaysia

Abstract

Background: Moyamoya vasculopathy (MMV) is a chronic progressive occlusive cerebrovascular disease causing recurrent strokes in children. We describe the clinical features, treatment and outcomes of childhood MMV in Malaysia; and compared their neurological outcome with the published literature. *Methods:* A retrospective study between 2005–2020 of Malaysian children with MMV seen at 4 tertiary Malaysian hospitals. Their post-stroke outcomes were assessed using the modified Rankin scale (mRS) and Pediatric Stroke Outcome Measure (PSOM). *Results:* Twenty one cases were included with a median age of presentation at 5.8 years and a median follow-up period of 4.6 years. The female-to-male-ratio was 2:1. All patients had acute ischaemic cerebrovascular accidents. The anterior cerebral circulation was affected in all cases with additional three having also posterior circulation involvement. Among 17 (81%) patients neuroimaging showed bilateral moyamoya. Eight (30%) had preceding febrile illness and the commonest presenting symptom was hemiparesis seen in 8 (38%). Seven (35%) had surgical revascularisation whilst the remainder opted for conservative management. Nineteen (90%) achieved a good stroke outcome but 2 had a poor PSOM outcome and 1 also had a poor mRS outcome. Both these patients declined surgical revascularisation.
Conclusion: Our cohort demonstrated the following MMV features: young age at the first presentation, female and Chinese preponderance; the main type of MMV was moyamoya disease; and ischaemic stroke as the commonest presentation. The overall neurological and functional outcomes were good despite the parental preference on medical therapy over surgical revascularization.

Keywords: Moyamoya, children, stroke, outcome

INTRODUCTION

Moyamoya vasculopathy (MMV) was first described by Takeuchi and Shimizu in 1957 as a case of "bilateral hypoplasia of the internal carotid arteries".[1] In 1969, Suzuki and Takaku named it as moyamoya (which means "a puff of smoke" in Japanese) disease due to its classical findings on cerebral angiography with abnormal net-like vessels in the base of the brain which resembles a puff of smoke.[2] At present, moyamoya disease (MMD) is defined as an idiopathic chronic, occlusive cerebrovascular disease characterized by steno-occlusive changes at the terminal portion of internal carotid artery and an abnormal vascular network at the base of the brain.[3] Moyamoya syndrome (MMS) is a term used when MMD is caused by another disease or associated with another medical conditions such as sickle cell anaemia, neurofibromatosis type 1 and Down syndrome.[4]

MMV, particularly MMD, is more common in East Asian countries, with the highest incidence in Japan[5], Korea[6] and China[7], and a lower incidence in Taiwan.[8] There is a female preponderance with the female-to-male ratio ranging from 1.7:1[5,8] to 1.8:1[6]; however, the gender ratio was 1:1 in China.[7] The disease appears to have a bimodal age of presentation with the first major peak in childhood at 5 to 9 years of age[5-8] and another at around forty years of age.[5,7,8] Outside Asia, MMV

Address correspondence to: Dr Choong Yi Fong, Division of Paediatric Neurology, Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Tel: +603-79492065, e-mail: cyfong@ummc.edu.my

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has also been reported in Europe[9] and USA[10] with a female preponderance but an older age of onset. The literature on childhood MMV/MMD is largely derived from case series from East Asia[11,12], UK[13] and the Indian subcontinent.[14,15] Given the paucity of data on paediatric MMV in South East Asia[16-19], our study aims to elucidate the clinical features, treatment modalities and outcomes of childhood MMV in Malaysia. We also compared the neurological outcome of our case series with the existing published literature.

METHODS

A retrospective case note review was conducted at four tertiary hospitals in Malaysia: University Malaya Medical Centre Kuala Lumpur and Tunku Azizah Hospital Kuala Lumpur from the central region, Penang General Hospital from the northern region, and Sabah Women and Children's Hospital Likas from East Malaysia. Children with MMD or MMS (age at diagnosis was up to 18 years old) who were seen in these hospitals from January 2005 to January 2020 were included in this study. Ethical approval of the study was given by the Medical Ethics Committee (Ref: MECID-20195297459) and the requirement for informed consent was waived by the ethics committee due to the retrospective design of the study. The diagnosis of MMV in our cohort was confirmed by neuroradiological imaging according to the International Pediatric Stroke Study (IPSS) Childhood Acute ischaemic stroke Standardised Classification and Diagnostic Evaluation (CASCADE) criteria[20] which encompass the following radiographic features: narrowing and/or occlusion of the distal part of one or both internal carotid arteries supplying the territory of infarct and associated collateral network of telangiectatic vessels distal to the occluded arteries.

A standardised data proforma was used to record the following information: patient demographic data, clinical features, radiographic findings, results, treatment modalities and outcomes. The demographic data of the patients encompassed their age, gender, ethnicity, comorbidities, and family history of MMV. Clinical features included age at presentation, presenting symptoms, types of cerebrovascular accidents (CVA) [transient ischaemic attack (TIA), arterial ischaemic stroke (AIS) or haemorrhagic stroke], recurrence of stroke and length of follow-up. Findings of the CT brain including CT angiography, MRI brain including MR angiography (MRA), and / or cerebral angiography were summarised with the following details: unilateral or bilateral cerebral hemispheres involvement, location of arterial involvement and angiographic staging of disease.

Classification and scoring of angiographic stages based on MRA findings corresponded well to the conventional Suzuki classification[3] (guidelines for diagnosis of MMD 2012) and was used in this study as most of our patients had MRA imaging. MRA stage I corresponded to stage I and II of the angiographic classification, MRA stage 2 corresponded to stage III, MRA stage 3 corresponded to Stage IV and MRA stage 4 corresponded to stage V and VI.[3] Treatment modalities (non-surgical, direct surgical revascularization, or indirect surgical revascularization) and their related complications were recorded.

Patients' post-CVA neurological outcome was assessed during their most recent outpatient clinic review using the modified Rankin Scale (mRS)[21] and Paediatric Stroke Outcome Measure (PSOM)[22] which are two widely used scales to evaluate childhood stroke outcome. PSOM rates the deficit severity from 0 (no deficit) to 2 (severe deficit) in five categories: right sensorimotor (including motor, visual, hearing, and somatosensory function), left sensorimotor, language production, language comprehension, and cognitive and behavioural performance. A score of ≥ 1 is considered as a poor outcome.[22] On the other hand, mRS is a scale with seven categories which range from 0 (asymptomatic) to 5 (severe disability requiring care for all daily needs) and 6 (death)[21] A mRS of > 2 indicates a poor outcome.

For continuous variables, median, first (Q1) and third (Q3) quartiles, and the interquartile range (IQR) were reported. Categorical data was reported as frequency in the form of percentage. Chi-square test was done to determine the significance of the differences observed between the categorical variables. A p-value < 0.05 was deemed to be statistically significant.

RESULTS

Patient demographics

Twenty one cases of paediatric MMV were identified and included in our case series. The median age at presentation was 5.4 years (Q1=3.2 years, Q3=8.0 years, IQR=4.8 years). The racial composition of our cohort was as follows: 9 (43%) Chinese, 7 (33%) Malays, 1 (5%) Indian

and 4 (19%) Malaysian indigenous people (3 were from Bajau ethnic group and 1 from Dusun ethnic group). Our cohort demonstrated female preponderance (14 females, 67%) with a female-to-male-ratio of 2:1. The female-to-male ratio for MMD patients was 1.6:1. The duration of follow-up ranged from 1.9 to 16.0 years (median 4.6 years, Q1=2.2 years, Q3=9.8 years, IQR=7.6 years) with 20 (95%) patients had follow-up of more than 2 years.

Disease characteristics

Table 1 showed the details of clinical and imaging characteristics, treatment, and outcome of our patients. The statistical data was summarised in Table 2. Fourteen children (67%) were diagnosed with MMD while seven (33%) had MMS which were associated with neurofibromatosis 1, Down syndrome, or PHACES syndrome. All of them presented with acute ischaemic CVA (18 AIS, 3 TIAs) with none having an acute haemorrhagic CVA. The commonest motor manifestation was hemiparesis (43%), followed by hemiparesis with focal seizure (33%) and focal seizure alone (24%). 6 patients (29%) had headache prior to the CVA while none of the subjects had preceding syncopal attack or experienced speech deficits. The commonest trigger of CVA in our cohort was febrile illnesses (38%) (3 cases of upper respiratory tract infection, 1 case of diarrhoea, and 4 cases of unspecified fever). Four patients (19%) had hyperventilation or prolonged crying prior to the CVA. Almost half of our patients (47.6%) had no apparent trigger which provoked their CVA.

All patients underwent MRI brain; 18 (86%) proceeded to MRA while the remaining 3 (14%) with MMD had cerebral angiography performed on them. Most cases (81%) had bilateral moyamoya while 4 (19%) patients had only unilateral hemispheric involvement. Anterior cerebral circulation was affected in all patients while 4 (19%) had both anterior and posterior cerebral circulation involvement. MRA / cerebral angiography demonstrated various stages of disease in 40 hemispheres, but most of the affected hemispheres were between MRA stage 1/Suzuki stage I and II (30.0%) and MRA stage 2/Suzuki stage III (57.5%).

None of our patients had family history of MMV. All patients were offered surgical revascularization but only 7 (33%) patients with total 10 cerebral hemispheres with MMV underwent surgery due to parental preference.

Surgical revascularization outcome

Six patients underwent the bypass surgeries in University Malaya Medical Centre while 1 patient from Sabah Women and Children Hospital had the surgical revascularization done in Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur. One patient underwent both direct (superficial temporal artery to middle cerebral artery (STA-MCA) bypass) and indirect revascularization surgeries (encephaloduroarteriosynangiosis (EDAS)) while the other six had indirect surgical revascularization (EDAS / encephalomyoarteriosynangiosis (EMAS) / multiple burr hole surgery / pial synangiosis). In the 10 cerebral hemispheres operated for the above patients, no surgical complications, stroke recurrence, and mortality were reported within 30 days and beyond 30 days postoperatively. One patient had the second stroke on another unoperated cerebral hemisphere 6 months after the first surgical revascularization (STA-MCA bypass). He underwent a left EDAS 6 months following his second stroke and remained clinically well postoperatively. All surgically treated children achieved good postoperative neurological outcome indicated by their most recent PSOM and mRS scores which were <1 and ≤ 2 respectively.

Conservative management outcome

The remaining 14 patients whose families refused surgery were managed conservatively with oral aspirin. Two had their second stroke following the first CVA at 6 months and 3 years interval respectively. No multiple (>2) stroke recurrences or mortality were reported in this cohort. 12 out of 14 patients (85.7%) achieved a good stroke outcome (PSOM<1 and mRS ≤ 2). 1 child had a PSOM score of 1 with unilateral motor deficit but achieved mRS score of 2. Another patient, who had MMS and DS, had a PSOM score of 5 (unilateral motor deficit, speech and cognitive impairment) and a mRS score of 4. Her high PSOM and mRS scores were due to her underlying intellectual disability related to DS. Sub-analysis of the MMD group did not show any significant differences from the MMS group.

DISCUSSION

We present the data of a Malaysian cohort of children with MMV which to our knowledge is the Southeast Asia's largest case series of childhood MMV to date. Fourteen of our patients

Table 1: Clinical and imaging characteristics, treatment, and outcome of Malaysian children with moyamoya vasculopathy (n=21)

Subject Number	Gender/ Race/Age (years)	Age at presentation/ Duration of follow up (years)	MMD/ MMS	Presenting symptoms	Possible triggers	Cerebral hemisphere involved	Surgical revascularization procedures	Outcome
UMMC								
1	Male/C/ 23.4	8.7/14.7	MMD	Headache, focal seizure	-	Bilateral	Right STA-MCA bypass at 15 years old (y.o.) Left EDAS at 16 y.o.	First stroke (right cerebral hemisphere) at 8.7 y.o. Second stroke (left cerebral hemisphere) at 15.5 y.o.
2	Female/M/11.6	0.8/10.8	MMD	Focal seizure	-	Bilateral	-	Mild left hemiparesis (PSOM=1)
3	Female/I/8.6	0.9/7.7	MMS (NF1)	Focal seizure, hemiparesis	Fever (URTI)	Unilateral	Left EDAS,EMAS at 3 y.o.	Well
4	Female/C/11.5	3.0/8.5	MMD	Hemiparesis	Fever and diarrhoea (unsure cause)	Bilateral	-	First stroke (right hemisphere) at 3 y.o. Second stroke (left hemisphere) at 6 y.o.
5	Male/C/9.6	3.8/5.8	MMD	Hemiparesis	HV (crying), URTI	Bilateral	-	Well
6	Female/M/11.2	0.7/10.5	MMD	Focal seizure, headache	HV (crying)	Bilateral	Left EMAS/EDAS at 6 y.o.	Well
7	Male/C/ 11.6	8.0/3.6	MMD	Headache, focal seizure	-	Bilateral	Right multiple burr hole at 9 y.o. Left multiple burr hole at 9.5 y.o.	Well

8	Female/M/9.6	6.0/3.6	MMD	Headache, hemiparesis	HV (crying)	Bilateral	Right pial synangiosis 7 y.o. Left pial synangiosis 8 y.o.	Well
9	Male/C/ 14.4	8.7/5.7	MMD	Hemiparesis	-	Bilateral	Left pial synangiosis at 13 y.o.	Well
HPP								
10	Female/M/12.5	8.6/3.9	MMS (DS)	Focal seizure, hemiparesis	-	Bilateral	-	Well
11	Female/M/4.9	0.3/4.6	MMD	Focal seizure, hemiparesis	-	Unilateral	-	Well
12	Female/C/18.9	9.7/9.2	MMD	Focal seizure, hemiparesis	Viral fever	Bilateral	-	Well
13	Female/C/21.4	5.4/16.0	MMD	Hemiparesis	HV	Bilateral	-	First stroke (right hemisphere) at 5.4 y.o. Second stroke (left hemisphere) at 6 y.o.
HTA								
14	Male/M/7.9	5.8/2.1	MMS (DS)	Hemiparesis	-	Unilateral	-	Well
15	Male/M/9.3	7.4/1.9	MMD	Focal seizure, Hemiparesis, headache	-	Bilateral	-	Well
16	Female/C/7.2	3.4/3.8	MMS (PHACES)	Focal seizure	Fever (non-specific)	Bilateral	-	Well
17	Female/C/5.6	3.4/2.2	MMS (NF1)	Hemiparesis	Fever (URTI)	Bilateral	-	Well
SWACH								
18	Female/B/8.9	6.6/2.3	MMD	Focal seizure, hemiparesis	Fever (non-specific)	Bilateral	-	Well

19	Male/D/10.0	7.9/2.1	MMS (NF1)	Hemiparesis, headache	Fever (non-specific)	Bilateral	-	Well
20	Female/B/5.9	3.8/2.1	MMS (DS)	Hemiparesis	-	Bilateral	-	Poor (PSOM=5, mRS=4) unilateral motor deficit, speech and cognitive impairment
21	Female/B/17.6	3.6/14.0	MMD	Focal seizure, hemiparesis	-	Unilateral	Right EDAS done in UKMMC, Kuala Lumpur.	Well

Abbreviations:
B=Bajau, C=Chinese, D=Dusun, DS=Down syndrome, EDAS= encephaloduroarteriosynangiosis, EMAS= encephalomyoarteriosynangiosis, HPP=Hospital Pulau Pinang, HTA=Hospital Tunku Azizah, HV=hyperventilation, I=Indian, M=Malay, MMD=moyamoya disease, MMS=moyamoya syndrome, NF1=neurofibromatosis type 1, PHACES=PHACE syndrome, PSOM=Pediatric Stroke Outcome Measure, STA-MCA= superficial temporal artery to middle cerebral artery, SWACH=Sabah Women and Children's Hospital, UKMMC=Universiti Kebangsaan Malaysia Medical Centre, UMMC=University of Malaya Medical Centre, URTI=upper respiratory tract infection

(67%) had MMD while seven (33%) had MMS. Other case series have reported 17-35% of their cohorts as having MMS.[13,14,22,23] The median age of first presentation of our patients was 5.4 years which was consistent with other paediatric case series[7,11-14,22] and nationwide population-based studies[5,6,8] which reported a peak between 5 and 9 years of age. Our cohort of MMD patients showed a female preponderance (female-to-male-ratio of 1.6:1) which is comparable to the female-to-male ratio ranging from 1.7:1 – 3.2:1) published in other studies from Asia[5,6,8,15], Europe[9] and USA.[10] The only East Asian country that did not report a female preponderance is China.[7,11,24]

All our patients presented with acute ischaemic but not haemorrhagic cerebrovascular accidents. These findings were similar to the data from other published paediatric MMV cohort studies which reported acute ischaemia as the commonest clinical presentation (73.9% to 92.7%) while cerebral haemorrhage was a rarer clinical manifestation (0% to 12.5%).[11-15,22-25] Nearly a quarter of our patient cohort presented with seizures (another 33% had seizures with hemiparesis) compared to a low rate of 2-5% reported by other case series.[5,11,13-15,23,24] Only 14% of our patients presented with TIA, compared to the 48-74% rate of other studies from East Asia.[11,12,24,25] Eight of our patients (38%) had preceding headache prior to the CVA, which was similar to the other paediatric case series that reported 11- 47% of their patients presented with headache.[5,11-13,22-24] This suggests the need for increased awareness of the milder (TIA) and atypical (seizures alone) presentation of MMV to improve the detection rate of MMV in Malaysia.

Malaysia is a multi-racial country with three major ethnicities: Malay (61.8%), Chinese (21.4%) and Indian (6.4%).[26] It is interesting to note that our cohort did not follow the racial distribution of our national population. The largest ethnic group in our cohort was Chinese (43%) followed by Malay (33%), the indigenous people (19%) and Indian (5%). The higher rate of MMV in Malaysian children of Chinese ethnicity is concordant with epidemiological evidence of MMD being most common among East Asians.[5-8] The higher proportion of indigenous people with MMV/MMD in our study may be due to selection bias, as one of our recruitment centres (Sabah Women and Children Hospital) is situated in east Malaysia which has a large indigenous population. However, a recent epidemiological study on MMD in the US also showed the incidence amongst Asian/Pacific Islanders was significantly higher

Table 2: Clinical and imaging characteristics, treatment and outcome of Malaysian children with moyamoya vasculopathy (n=21)

Characteristics	Central Malaysia (UMMC&HTA) N=13 (%)	Northern Malaysia (HPP) N=4 (%)	East Malaysia (SWACH) N=4 (%)	Total N=21 (%)
Gender				
Male	6 (46.2%)	0 (0.0%)	1 (25.0%)	7 (33.3%)
Female	7 (53.8%)	4 (100%)	3 (75.0%)	14 (66.7%)
Age (Years)				
0-3	0	0	0	0
4-8	4 (30.8%)	1 (25.0%)	2 (50.0%)	7 (33.3%)
9-12	7 (53.8%)	1 (25.0%)	1 (25.0%)	9 (42.9%)
≥13	2 (15.4%)	2 (50.0%)	1 (25.0%)	5 (23.8%)
Age at presentation (Years)				
0-3	7 (53.8%)	1 (25.0%)	2 (50.0%)	10 (47.6%)
4-8	6 (46.2%)	2 (50.0%)	2 (50.0%)	10 (47.6%)
9-12	0	1 (25.0%)	0	1 (4.8%)
13-17	0	0	0	0
Median follow-up duration (Years)	5.7	6.9	2.2	4.6
Types of moyamoya vasculopathy				
Moyamoya disease	9 (69.2%)	3 (75.0%)	2 (50.0%)	14 (66.7%)
Moyamoya syndrome	4 (30.8%)	1 (25.0%)	2 (50.0%)	7 (33.3%)
Types of stroke at presentation				
Arterial ischaemic stroke	11 (84.6%)	3 (75.0%)	4 (100%)	18 (85.7%)
Transient ischaemic attack	2 (15.4%)	1 (25.0%)	0	3 (14.3%)
Haemorrhagic	0	0	0	0 (0%)
Presenting symptoms				
Hemiparesis	5 (38.5%)	1 (25.0%)	2 (50.0%)	8 (38.1%)
Focal Seizure	5 (38.5%)	0	0	5 (23.8%)
Hemiparesis and focal seizure	3 (23.0%)	3 (75.0%)	2 (50.0%)	8 (38.1%)
Antecedent headache	5 (38.5%)	0	1 (25.0%)	6 (28.6%)
Triggers				
Febrile illness	4 (30.8%)	1 (25.0%)	2 (50.0%)	7 (33.3%)
Hyperventilation	3 (23.0%)	1 (25.0%)	0	4 (19.1%)
No apparent triggers	6 (46.2%)	2 (50.0%)	2 (50.0%)	10 (47.6%)
Cerebral hemisphere involvement				
Unilateral	2 (15.4%)	1 (25.0%)	1 (25.0%)	4 (19.1%)
Bilateral	11 (84.6%)	3 (75.0%)	3 (75.0%)	17 (80.9%)
Cerebral circulation involvement				
Anterior circulation	11 (84.6%)	4 (100%)	2 (50.0%)	17 (81.0%)
Posterior circulation	0	0	0	0 (0%)
Anterior and posterior circulation	2 (15.4%)	0	2 (50.0%)	4 (19.0%)
Angiographic stages (N=40 hemispheres)	N=25	N=7	N=8	N=40
MRA stage 1/ Suzuki I & II	9 (36.0%)	2 (28.6%)	1 (12.5%)	12 (30.0%)
MRA stage 2/Suzuki III	16 (64.0%)	2 (28.6%)	5 (62.5%)	23 (57.5%)
MRA stage 3/ Suzuki stage IV	0	2 (28.6%)	2 (25.0%)	4 (10.0%)
MRA stage 4/ Suzuki stage V&VI	0	1 (14.2%)	0	1 (2.5%)
Treatment (N=40 hemispheres)	N=25	N=7	N=8	N=40
Surgical revascularization	9 (36.0%)	0	1 (12.5%)	10 (25.0%)
Medical therapy	16 (64.0%)	7 (100%)	7 (87.5%)	30 (75.0%)

Outcome				
Stroke recurrence	2 (15.4%)	1 (25.0%)	0	3 (14.3%) *
mRS#				
0 – 2	13	4	3	20 (95.2%)
3 – 4	0	0	1	1 (4.8%)
5	0	0	0	0
PSOM#				
0 – 0.5	12 (92.3%)	4 (100%)	3 (75.0%)	19 (90.4%)
1 – 3.5	1 (7.7%)	0	0	1 (4.8%)
4 – 6.5	0	0	1 (25.0%)	1 (4.8%)
7 – 10	0	0	0	0

HPP=Hospital Pulau Pinang, HTA=Hospital Tunku Azizah, MRA: Magnetic resonance angiography, mRS: modified Rankin scale, PSOM: Paediatric Stroke Outcome Measure, SWACH=Sabah Women and Children's Hospital, UMMC=University of Malaya Medical Centre

*1 surgical patient (developed infarct on non-operated hemisphere), 2 on antiplatelet medication only.

#mRS ≤ 2 and PSOM ≤ 0.5 indicate good stroke outcome.

than all other ethnic groups.[10] Our study cohort, though small, had several distinct features: multi-ethnic population, sporadic nature (no positive family history), febrile illness as a trigger (one third of cases) and a less aggressive course (patients did not have multiple recurrent strokes and had relatively good outcome based on PSOM and mRS scores, even without revascularisation surgery). It was possible that other susceptibility genes and environmental triggers were implicated in the pathogenesis of moyamoya in the Malaysian population.

Table 3 summarises the treatment, neurological outcome and stroke recurrence rates in surgically versus conservatively treated paediatric MMV cases among our cohort compared with four published studies of paediatric patients from India, UK and, China.[11,13-15] These studies were selected as the data on treatment and outcome (mRS scores and /or stroke recurrence rate) in the paediatric age group could be extracted for direct comparison. The patients in these studies either had surgical or conservative treatment for their MMV. Three studies had higher surgical rates (63-76%)[11,13,14] compared to ours (35%) and another Indian case series (13%).[15] While different surgical procedures were performed, the majority were indirect bypass procedures.

The results of the individual studies showed a trend towards better long-term neurological outcomes in children who underwent surgery compared to those who were treated conservatively, except for the UK group which reported favourable neurological outcome in 44.2% of surgically treated children and 48.5% of the conservatively treated children respectively. When we pooled the studies which assessed patients' post-treatment neurological outcome using mRS[11,13,14] (Table 4), more patients who underwent surgery had good neurological outcome (77.1%) compared to patients who were managed conservatively (57.8%). The difference between these two groups was statistically significant ($p<0.001$).

Majority of the above studies also showed a trend towards a lower stroke recurrence rate (0-14.3%) among surgical patients compared to those who were treated conservatively (9.0-15.0%), although the differences were less obvious compared to the results for neurological outcome. Pooled analysis (Table 4) showed a statistically significant difference ($p<0.001$) in stroke recurrence between patients who underwent surgical revascularization (3.6%) and those who were managed conservatively (12.2%). A meta-analysis of symptomatic patients (mainly adults) from 16 studies showed that surgical intervention in MMD is associated with a decreased risk of stroke, but only for haemorrhagic MMD and not ischaemic MMD and direct bypass surgery may be more beneficial.[27] Paediatric MMD is largely ischemic in nature and direct bypass procedure is technically challenging in young children; furthermore issues about the ideal type of bypass procedure, access to expertise for surgery and postoperative care and effect on long term cognitive outcome have yet to be resolved. The reason for the low surgical rate in our cohort was attributed to parental preference for medical therapy over surgical intervention. Further studies are needed to explore possible factors influencing parental decisions such as parental educational and socioeconomic status, beliefs and understanding of the disease and access to surgical expertise.

There are several limitations of this study.

Table 3: Comparison of published neurological outcomes and stroke recurrence rates between pediatric moyamoya vasculopathy patients with surgery versus conservative treatment

Authors	Country	Number of patients	Recruitment period/ duration of follow-up	Treatment	Neurological Outcome	Stroke recurrence
Singhi *et al.* 2013[15]	India	23	16 years / mean 1.1 years	Conservative: 20 (87.0%) Surgery: 3 (13.0%)	Not available	Conservative: 2/15 (13.3%) Surgery: 0/3 (0%)
Patil *et al.* 2017[14]	India	41	14 years / median 2.2 years	Conservative: 13 (31.7%) Surgery: 28 (68.3%)	mRS: - Good : conservative 9/13 (70%), surgery 25/28 (89.3%) - Poor: conservative 4/13 (30%), surgery 3/28 (10.7%)	Conservative: 2/13 (15%) Surgery: 0/28 (0%)
Tho-Calvi *et al.* 2018[13]	UK	88	10 years / median 3.6 years	Conservative: 33 (37.5%) Surgery: 55 (62.5%)	mRS (3 patients from surgical group did not have mRS due to young age): - Good: conservative 16/33 (48.5%), surgery 23/52 (44.2%) - Poor: conservative 17/33 (51.5%), surgery 29/52 (55.8%)	Conservative: 3/33 (9%) Surgery: 4/55 (7.3%)
Zheng *et al.* 2019[11]	China	282	5 years / mean 3.4 years	Conservative: 68 (24.1%) Surgery: 214 (75.9%)	mRS: - Good: conservative 36/68 (52.9%), surgery 177/214 (82.7%) - Poor: conservative 32/68 (47.1%), surgery 37/214 (17.3%)	Conservative: 9/68 (13.2%) Surgery: 6/214 (2.8%)
Our cohort 2020	Malaysia	21	15 years / median 4.6 years	Conservative: 14 (66.7%) Surgery: 7 (33.3%)	mRS: - Good: conservative 13/14 (92.9%), surgery 7/7 (100%) - Poor: conservative 1/14 (7.1%), surgery 0 (0%)	Conservative: 2/14 (14.3%) Surgery: 1/7 (14.3%)

Table 4: Pooled data comparing post-treatment neurological outcome (measured by mRS) and stroke recurrence rate in pediatric moyamoya vasculopathy patients with surgery versus conservative treatment

Number of patients	Treatment received	Results	P-value
429	Conservative: 128 Surgery: 301 (48 direct, 228 patients indirect, 18 combined revascularization. Information of surgery was not available for 7 patients from the UK cohort)	Neurological outcome using mRS (n=429) Conservative (n=128) - Good outcome (mRS ≤ 2): 74/128 (57.8%) - Poor outcome (mRS > 2): 54/128 (42.2%) Surgery (n=301) - Good outcome (mRS ≤ 2): 232/301 (77.1%) - Poor outcome (mRS > 2): 69/301 (22.9%)	< 0.001*
455	Conservative: 148 Surgery: 307 (48 direct, 234 indirect, 18 combined revascularization. Information of surgery was not available for 7 patients from the UK cohort)	Stroke recurrence rate - Conservative (n=147): 18/147 (12.2%) - Surgical (n=307): 11/307 (3.6%)	< 0.001*

*P-value <0.05 was required for statistical significance

The results of this study may not be generalised to the whole Malaysian population as patients were recruited from four tertiary centres. The retrospective nature of the study limited access to important information such as milder symptoms and long-term neurocognitive outcome. The small sample size precluded conclusions about the efficacy of surgical intervention.

In conclusion, our case series identified the following demographic and clinical features associated with paediatric MMV cases in Malaysia: young age at the first presentation, female and Chinese preponderance; the main type of MMV was MMD; and ischaemic stroke as the commonest presentation of MMV. Surgical revascularization was less preferred by the parents of children with MMV in Malaysia compared to conservative medical treatment. Nonetheless, our cohort still had an overall good neurological (90.4%) and functional (95.2%) outcome despite the parental preference on medical therapy over surgical revascularization.

DISCLOSURE

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