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Differential Arterial Stiffness in Upper Limbs and Descending Aorta in a Young Patient with Moyamoya Disease and Hypertension in Singapore –A Rare Finding in a Rare Case

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Manifestations of moyamoya disease; Middle cerebral artery; Femoral

1. Introduction

Extra cranial Manifestations of Moyamoya Disease (MMD) involving systemic vessels has been explored scarcely in literature. We describe a 22-year-old male who initially presented with headaches and neck ache and was found to have young-onset hypertension contributed by intracranial disease and possible Reno vascular hypertension. After extensive investigations, he was eventually diagnosed with an MMD variant involving bilateral Middle Cerebral Artery (MCA) stenosis and was surgically managed through bypass. He was found to have differential arterial stiffness in upper limb vessels and renal vessels which is very rare and not described in literature.

2. Case

JCW, a 22 year-old Singaporean male of Chinese descent with no previous medical history, presented in May 2019 with headaches and neck aches lasting 3 weeks. His systolic blood pressure 150/100 mmHg, with no background history of hypertension.

His family history includes hypertension in his father (diagnosed at age 56 years), and his grandfather had a history of hypertension, myocardial infarction and stroke in his 50 years.

Clinical examination revealed normal systemic examination with no bruit in carotids, femoral or renal vessels

He was subsequently seen by a cardiologist and underwent extensive work up in July 2019, which included undergoing an echocardiogram, electrocardiogram and blood tests including potassium, UFEME and ESR which were all within normal limits. In August 2019, JCW was admitted for atypical chest pain and was diagnosed with musculoskeletal chest pain after undergoing an equivocal cardiac stress test and a 24-hour ambulatory blood pressure monitoring which revealed hypertension. He was treated with amlodipine 5 mg once a day for hypertension.

JCW underwent further investigations between September and October 2019 including 24hr urine catecholamine's and metanephrine's which were within normal limits. He also underwent aortograms in November 2019 which revealed no coarctation, renal mass or adrenal nodularity.

He was seen by Neurologists in December 2019 and was subsequently diagnosed with a Moya-Moya variant involving bilateral middle cerebral artery (MCA) stenosis, and was commenced on regular aspirin and omeprazole. He then underwent bypass surgeries involving the left MCA in early 2020 and right MCA in March 2021, with target systolic blood pressure set below 150mmHg.

JCW was followed up in the General Medicine clinic in April 2020. This involved evaluation for secondary causes of hypertension, including Reno vascular disease and renal artery stenosis through renal Doppler scans and SphygmoCor. He was followed up in clinic with last follow up in June 2022. His basic investigations done in June 2022 is as shown in Table 1. The SphygmoCor done in April 2020 showed no increase in Augmentation index, normal aortic systolic and pulse pressure. Operator index was 95%. There was no evidence of any arterial stiffness on SphygmoCor done on

radial artery. This renal Doppler was done in January 2022 which showed increased peak systolic velocity (PSV) in both renal arteries and descending aorta (Table 2). There was no renal artery stenosis but increased PSV in both renal vessels and aorta showed that there was generalised process of arterial stiffness in descending aorta and renal vessels.

Table 1: Basic Investigation

	Jun-22	Reference range
Serum Urea	6.5	2.8 – 7.6 mmol/L
Plasma Creatinine	97	60-105 micromol/L
eGFR (CKD-EPI)	95	>90 ml/min/1.73m^2
Serum Bicarbonate	23	22-29 mmol/L
Serum Potassium	3.8	3.5-4.5 mmol/L
Serum Chloride	107	101-110 mmol/L
Anion Gap	12.5	8.0-16 mmol/L
Full Blood Count		
Haemoglobin	14.7	13.1-17.2 g/dL
External haematocrit	46.3	39.8-50.4%
Red Blood Cells	7.38*	4.46-5.90 x 10^{12}L
MCV	62.7*	78.3 – 96.0 fL
MCH	19.9*	25.5 – 33.2
MCHC	31.7	31.7-35.6 g/dL
RDW	17.8*	11.0 – 14.4%
Platelets	318	172 – 379 x10^9/L
Neutrophils	7.51*	1.13 – 6.86 x10^9/L
Lipid profile		
Fasting serum glucose	4.5	3.0 – 6.0 mmol/L
Total Cholesterol	3.4	Mmol/L
Triglycerides	0.6	Mmol/L
HDL Cholesterol	1.3	Mmol/L
LDL	1.8	Mmol/L

Table 2: Renal Vascular Doppler Scan January 2022

AORTA:	Normal diameter		
Juxtarenal aorta cm/s:	153 cm/s		
RIGHT:		**LEFT:**	
Bipolar length (cm)	9.94	Bipolar length (cm)	11.2
Renal vein	Patent	Renal vein	Patent
Peak systolic velocity (cm/s)		Peak systolic velocity (cm/s)	
Origin:	124	Origin:	160
Proximal:	163	Proximal:	137
Mid:	141	Mid:	124
Distal:	155	Distal:	86
Renal aortic ratio (RAR)	1.07	Renal aortic ratio	1.05
Acceleration Time (ms)	44	Acceleration Time (ms)	44

3. Discussion

MMD is a unique vascular phenomenon with an unknown aetiology, characterised by progressive narrowing and occlusion of carotid artery terminus, and the secondary development of small-vessel collaterals. On angiography, these collateral vessels produce a characteristic ‘smoky appearance’. The Japanese term ‘moyamoya’, meaning puffy, hazy or obscure was hence used to describe this phenomenon [1]. The term moyamoya disease is used to describe a primary condition, while moyamoya syndrome refers to secondary moyamoya. Moyamoya syndrome can be caused by Down’s syndrome, cranial radiation, Alagille syndrome, trisomy 21, sickle cell disease, Williams syndrome and neurofibromatosis type I [2].

3.1. Clinical Characteristics

Japanese and Chinese epidemiological studies have found a bimodal distribution in the age of onset of MMD, with the first peak around 10 years old and the second around 35-40 years-old [3,4]. In Singapore, Peh et al. found most cases to present in adulthood, however, the age of our patient does not conform to this [5].

Hypertension is often seen in patients with MMD, and is often described with renal artery stenosis, especially in paediatric MMD. Korematsu et al. were the first to highlight severe hypertension in a 1 year-old girl, later diagnosed with mid-aortic syndrome [6]. The higher prevalence in paediatric MMD may be attributed to the retrospective study design and more severe course of childhood-onset MMD than that of adult-onset MMD [7,8]. Implications of MMD on systemic arteries have been scarcely explored since. Nevertheless, given our patient's presentation, we believe MMD has possible implications on systemic vessels, from the pathological consequences of sheer stress and endothelial damage of arterial wall, and may be further complicated by the underlying pathophysiology of MMD.

There is a familial history of the condition in 10.0-15.4% of patients. While our patient had a familial history of stroke, there was no history of MMD in his family. Stroke recurrences are common in MMD, and is known to be the most common presentation of MMD. The International Paediatric Stroke Study (IPSS) showed that children mostly presented with ischemic stroke (about 90%) and transient ischemic attacks (about 7.5%) [9]. Other clinical presentations of MMD seen include intracerebral haemorrhages, headaches and seizures [1,10]. More uncommonly, MMD can also present with other neurological symptoms such as dystonia, chorea or dyskinesia [1,11,12].

3.2. Classification

MMD is classified to six stages according to Suzuki staging, based on its stage of progression in vessel stenosis (Table 3).

Our patient had evidence of bilateral MCA stenosis, with concomitant involvement of extra cranial arteries, in particular increased flow velocity in his aorta and renal arteries shown on Doppler ultrasound. While the Suzuki staging does not include extra cranial artery involvement, tools to stage MMD with consideration of extra cranial involvement do not exist, but should be considered if seen more often.

Table 3: Suzuki staging of moyamoya disease

Stage 1	'Narrowing of the carotid fork only'
	Bilateral ICA stenosis
Stage 2	'Initiation of basal moyamoya with dilatation of all main cerebral arteries'
	Collateral vessels begin to form
Stage 3	'Intensification of moyamoya with reduction of the flow in the anterior and the middlecerebral artery'
	Prominence of collateral vessels
Stage 4	'Minimization of moyamoya vessels with involvement of the proximal posterior cerebral artery'
	Severe stenosis/complete occlusion of circle of Willis, moyamoya vessels narrow, extracranial collaterals begin to form
Stage 5	'Reduction of moyamoya and absence of all main cerebral arteries'
	Prominence of extracranial collaterals
Stage 6	'Disappearance of moyamoya vessels. The cerebral circulation is supplied by the external carotid arteries'
	Complete carotid occlusion

The description in inverted commas is that of Suzuki in the original paper. The one below is a more concise description from Smith and Scott [30].

3.3. Pathophysiology

Fibro cellular thickening of the intima (through hyper-proliferation of vessel wall components, active angiogenesis and matrix accumulation) and internal elastic laminae, attenuation of the media, and a decrease in the outer diameter of the stenotic segments in MMD are the main pathological changes seen in MMD [13]. Recent Magnetic Resonance Imaging (MRI) studies have also demonstrated constrictive remodelling (narrowing outer diameter) and concentric enhancement of affected segments occurring in MMD [14,15]. MMD may also affect extra cranial vessels, including cervical carotids, coronary, pulmonary and renal arteries, although these have been scarcely explored in literature [16]. One study done on 13 autopsy cases with MMD revealed extra cranial arties exhibited intimal fibrous thickening similar to that seen by intracranial arteries [17].

Recent studies have found intrinsic immune reactions including autoimmune responses involved in the tissue remodelling and angiogenesis seen in MMD [18]. M2-polarized macrophages heavily influence tissue remodelling and angiogenesis. In the serum of a cohort of patients with MMD, the active marker of M2-polarized macrophages - soluble (s)CD163, was found to be significantly than in healthy controls. Given that sCD163 has also been correlated with the severity of autoimmune diseases, Fujimura et al. concluded that patients with MMD may have increased autoimmune activity, and has been supported by other studies [19-21]. Studies have also measured other unusual circulating angiogene-

tic factors such as growth factors, vascular progenitor cells and inflammatory factors [18,20,22-24]. These were found to be increased in patients with MMD, and could be involved in promoting intimal hyperplasia in vessels and excessive collateral formation through endothelial hyperplasia, smooth muscle migration, and atypical neovascularization [21].

3.4. Genetics

While the aetiology of MMD remains unknown, several genetic associations have been identified. In particular, the RING finger protein 213 (RNF213) predominantly found in blood cells and the spleen, is known to be an important risk gene involved in MMD, although its exact function is unknown [19,22]. One of its variants, RNF213 p.R4810K, was found to be Asian-specific and may contribute to a higher incidence of MMD seen in East Asia [25]. Interestingly, Jee et al. found higher prevalence of extra cranial arteriopathy in the presence of a different variant - RNF213 p.Arg4810Lys. This was most commonly coronary artery stenosis in their cohort [26]. Other studies have also found a positive association of MMD with Human Leukocyte Antigen (HLA) DQB1*0502 and ACTA2 [27,28]. While the mode of inheritance of MMD remains unclear, Mineharu et al. suggests it is an autosomal dominant condition with incomplete penetrance [29]. These studies suggest that MMD does have an underlying genetic pathophysiology, and should be further evaluated in patients with MMD. Although our patient did not undergo genetic studies, we recognise that this would prove interesting in our academic pursuit.

4. Conclusion

We present an interesting case of MMD in a 22-year-old patient, with differential arterial stiffness in upper limb vessels and descending aorta based on sphygmoCor and renal Doppler results. We have highlighted studies exploring the genetic and histopathological processes underlying MMD. MMD is a complex condition with unknown aetiology requiring further research. In particular, research on its implication on systemic vessels should be further explored, to strategize on ways to prevent further vascular damage.

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