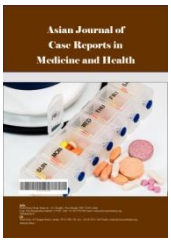

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Increased Arterial Stiffness in Moyamoya Disease Presenting with Hypertension and Stroke: A Novel Finding in a Very Rare Condition in Singapore

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Authors' contributions

All authors contributed equally to the conception and writing of the manuscript. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

We present a rare case of a 42 year old lady who presented initially with hypertensive emergency and episodes of transient ischemic attacks who was later diagnosed to have Moyamoya disease (MMD). She continued to have hypertension after left external carotid-internal carotid bypass. We followed her case for evaluation of hypertension. She was found to have increased arterial stiffness on SphygmoCor. The prevalence of hypertension MMD is high, but most notably associated with renal artery stenosis (RAS). Case studies of hypertension in patients with MMD without RAS are rare. We did a literature search on the histopathology and genes involved in MMD. RNF213 and ACTA2 gene mutations are identified to be related to MMD. Interestingly, ACTA2 gene mutation carriers are seen to have a variety of vascular diseases. We postulate that the genes involved in causing intimal thickening and media attenuation of the intracranial vasculature seen in MMD exerts systemic implications. We think this could possibly present with increased arterial stiffness and hypertension. In summary, we would like to highlight increased arterial stiffness as a cause of hypertension in patients with MMD. We postulate that the underlying histopathological changes affecting Moyamoya vessels might also affect systemic blood vessels presenting as increased arterial stiffness.

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Keywords: Moyamoya disease; hypertension; arterial stiffness; vascular medicine.

1. INTRODUCTION

Arterial stiffness in Moyamoya disease (MMD) has not been described before in literature. We describe a young 42 year-old lady who initially presented as hypertensive urgency and was later diagnosed with MMD. We would like to highlight increased arterial stiffness as a cause of hypertension in patients with MMD.

2. PRESENTATION OF CASE

ML, a 42-year-old Singaporean female, first presented to our hospital in June 2015 with headaches. Her systolic blood pressure (BP) was 200mmHg, on a background of known hypertension diagnosed since 28 years old.

Her chronic medication included telmisartan 40mg once daily. She had a significant family history of hypertension, present in all 9 siblings. Her father and two brothers had ischemic heart disease. Both parents had history of strokes. Two of her brothers had chronic kidney disease.

Clinical examination revealed a well-looking patient with a body mass index of 22.2kg/m^2. Her cardiovascular, respiratory and neurological examinations were unremarkable. There was no radio-radial or radio-femoral delay. She had no features of Cushing's syndrome or acromegaly, and was clinically euthyroid. Abdominal examination did not reveal renal bruits or ballotable kidneys. Fundoscopy did not reveal hypertensive retinopathy.

Computed tomography (CT) scan of the head was unremarkable. Electrocardiogram (ECG) revealed sinus rhythm, without evidence of left ventricular hypertrophy. Her blood pressure (BP) while on the ward ranged from 120-130/60-80 mmHg, on telmisartan.

She was followed up in the General Medicine (GM) clinic from 2015. An evaluation for secondary causes of hypertension – inclusive of renovascular disease, renal artery stenosis, phaeochromocytoma and hyperthyroidism – returned negative. ML was treated for presumptive essential hypertension. There were no signs of end-organ damage from hypertension. Total urine protein was in the normal range. Over time, her BP remained stable on candesartan 16mg and bisoprolol 2.5mg once daily. She continued to have intermittent headaches.

In retrospect, she was noted to have persistent mild hypokalemia (serum K 3.0- 3.5mmol/L) from mid-2016 onwards. Investigations in June 2017 revealed renal potassium loss (urine K/Cr ratio 2.64 when serum K 3.1 mmol/L), and simultaneously serum aldosterone 526 pmol/L with PRA <0.6 ng/mL/h. The patient was on losartan 25mg daily at the time. While these results were suggestive of a diagnosis of primary aldosteronism (PA), ML discontinued her follow-up with Endocrinology; hence confirmatory testing was not performed.

2.1 Recurrent Ischemic Strokes and Diagnosis of Moyamoya Disease

ML presented with intermittent right-sided facial numbness in February 2017. Magnetic resonance imaging (MRI) of the brain did not show acute infarct or hemorrhage, but demonstrated moderately severe narrowing of the left terminal internal carotid artery (ICA), associated with poor flow signals in both the A1 segment of the left anterior cerebral artery (ACA) and the M1 segment of the left middle cerebral artery (MCA). There was decreased arborization of the left MCA's cortical branches. She was diagnosed with a transient ischemic attack, and started on clopidogrel 75mg and atorvastatin 40mg daily. The thrombophilia screen was negative.

The second stroke occurred in March 2019, when ML presented with acute right upper and lower limb weakness, and right facial, upper and lower limb numbness. Her BP was 189/85mmHg. MRI brain revealed an acute left-sided posterior temporal-parietal infarct, in the left posterior MCA territory. Another small acute infarct was noted in the left pre-central gyrus. The magnetic resonance angiography (MRA) demonstrated severe stenosis at the left terminal ICA, also involving the left M1 and A1 segments; collateral flow was observed. Trans-thoracic echocardiogram and telemetry ruled out potential cardio-embolism. Tests done to rule out autoimmune causes and vasculitis were unremarkable.

The third stroke happened in April 2019, presenting with acute right-sided facial and upper limb weakness, with BP of 201/86mmHg. MRI and MRA of the brain revealed new acute infarcts scattered in the territories of the left MCA and ACA. A CT angiogram again showed severe

steno-occlusive disease involving the left ICA T-junction and left M1 and A1 segments, with extensive basal collaterals (Fig. 1). In light of these findings, MMD was diagnosed.

ML was referred to Neurosurgery, and underwent a left external carotid-internal carotid bypass in June 2019.

2.2 Further Outpatient Progress

Spironolactone was introduced from June 2020 onwards for a presumptive diagnosis of primary aldosteronism. Her BP was kept in stable range of 130-150/80-95mmHg. An arterial stiffness study by SphygmoCor in June 2020 showed markedly increased arterial stiffness with markedly increased augmentation index, aortic augmentation pressure, aortic systolic pressure and aortic pulse pressure for the patient's age (Fig. 2).

3. DISCUSSION

MMD is a unique cerebrovascular disease characterised by progressive stenosis of distal internal carotid artery and the resulting hazy network of basal collateral vessels. The diagnosis is largely based on characteristic angiographic findings [1]. Suzuki's angiographic grading is used to help in the staging of collateralization of MMD [2].

3.1 Pathophysiology

Pathological changes found in stenotic segments in MMD are characterized by fibrocellular thickening of the intima, irregular undulation of internal elastic laminae, medial thinness and a decrease in the outer diameter. Recent neuroimaging techniques like 3D constructive interference in steady state (CIISS) MRI demonstrate constrictive remodeling in symptomatic segments and concentric enhancement of symptomatic segments [1].

Moyamoya vessels have various histopathological changes – fibrin deposits in the wall, fragmented elastic laminae, attenuated media and the formation of microaneurysms [2]. Cortical microvascularization is suggested as a specific finding in MMD. These basal and cortical neovascularizations may represent a compensatory mechanism for reduced blood flow. However, there is also a suggestion that cortical neovascularization occurs before significant hemodynamic impairment in a large cohort of pediatric patients with MMD [3].

3.2 Clinical Characteristics

Japanese and Chinese epidemiological studies show a bimodal distribution in the age of onset of MMD. The first peak happens around 10 years old and the second peak happens around 35 – 40 years old [4-5]. In Singapore, an epidemiological study by Peh et al found that most cases presenting in Singapore are adult cases, which was slightly different from the Japanese population [6]. The age in which our patient presented correlates with this study.

The most common presentation of MMD is stroke. The International Pediatric Stroke Study (IPSS) showed that children mostly presented with ischemic stroke (about 90%) and transient ischemic attacks (about 7.5%) [7]. In contrast, higher incidences of intracranial hemorrhage occur in the adult population, with initial presentation as high as 50% in the Asian population and 10 – 20% in the non-Asian population [8]. Multiple studies have shown that stroke recurrences are common and are usually ischemic [9]. The IPSS study showed that 20% of children had recurrent symptoms in the median 13-month follow-up interval [7]. We see this reflected in our patient, who had 3 symptomatic ischemic events prior to surgical intervention in June 2019.

3.3 Genetics

There is a higher incidence of MMD among the Japanese and Asian population, with familial occurrence in approximately 10 – 15% of cases. The mean age of onset drops from 30 years in sporadic cases to 11.8 years in familial cases [10]. Although the mode of inheritance is not established, one study suggested that familial Moyamoya is an autosomal dominant disease with incomplete penetrance [11]. Herve et al also presented a case study which suggested a possible hereditary Moyamoya multisystem disorder with an X-linked recessive pattern of inheritance in an Algerian family [12].

RNF213 gene in 17q25-ter region has been identified as the strongest susceptibility gene for MMD in an East Asian population, although the exact function of RNF213 is unknown. Research has shown that carriers of RNF213 variant may be susceptible to cerebral hypoxia because of insufficient angiogenesis if inflammation and

hypoxia occur simultaneously [13]. Pro-inflammatory cytokines are also shown to activate RNF213 transcription, and RNF213 functions as a common downstream effector of the PI3 kinase-AKT pathway in endothelial angiogenesis, which suggests inflammation may play a part in MMD development although MMD itself is not an inflammatory disease [14].

ACTA2 is another gene identified to be related to MMD. Heterozygous ACTA2 gene mutations cause familial thoracic aortic aneurysms and dissections by affecting the vascular smooth muscle cell. In a study accumulating data from families harboring heterozygous ACTA2 mutations, it was shown that ACTA2 mutations predispose individuals to occlusive vascular diseases, specifically premature CAD, strokes and MMD, in addition to the established predisposition to thoracic aortic aneurysm and dissection [15].

Although there are suggestions of genetic components involved in the pathophysiology of MMD, there was no suggestion of family history of stroke in our patient. We did not carry out any genetic testing in our patient. We acknowledge that genetic testing in this patient would prove interesting to our academic pursuit.

Hypertension is often seen in patients with MMD and this is often described with renal artery stenosis. We were only able to identify one case study during our literature search on hypertension in MMD patients without renal artery stenosis, which was highlighted by Limaye et al in a 13 year old Indian boy [16]. Korematsu et al were the first to highlight a case of MMD and severe hypertension in a 1 year old girl, who was later diagnosed with mid-aortic syndrome [17]. This suggests possible implications of MMD on other systemic blood vessels such as the aorta. A high prevalence of systemic hypertension in pediatric patients with MMD after surgical treatment was demonstrated in another study by Lee et al. [18]. Information on whether there is increased arterial stiffness in this group of patients is scarce.

P.R4810K, a polymorphism of RNF213, the susceptibility gene for MMD, is associated with increased blood pressure [19] particularly an increase in systolic blood pressure. Similarly, it is not known if this polymorphism causes increased arterial stiffness in MMD.

It is established that there is a coexistence of proliferation and shrinkage in stenotic segments in cerebral arteries, as well aberrant and compensatory processes in neovascularization in patients with MMD. However, data is limited regarding whether this aberrant process affects predominantly cerebral vasculature or exerts further systemic effects, such as increased arterial stiffness as demonstrated in our patient.

4. CONCLUSION

In conclusion, we present an interesting and rare case of hypertension in a young patient with MMD associated with increased arterial stiffness, with no renovascular disease. This is one of the first cases reported in MMD with increased arterial stiffness. We also highlighted genetic studies and case reports that have suggested that the histopathological process underlying Moyamoya vessels may also affect systemic vessels. We hope that this article will inspire more research on the relationship between MMD and hypertension, particularly in terms of how systemic vasculature is affected.

CONSENT AND ETHICAL APPROVAL

All authors declare that ‘written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal. As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

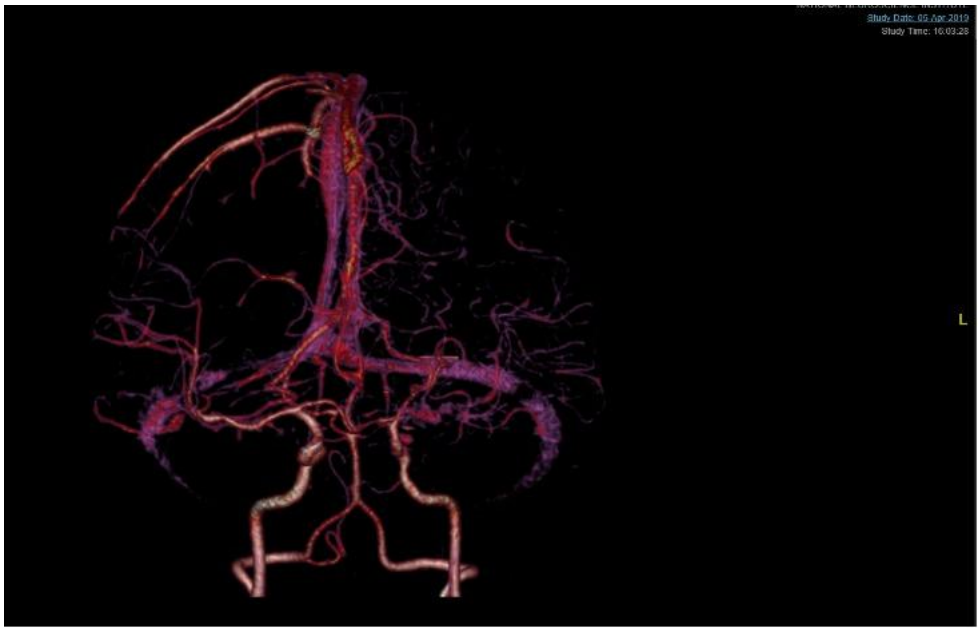

Fig. 1. CT Angiogram showed severe steno-occlusive disease involving the left ICA T-junction, left M1 and A1 with extensive basal collaterals, in keeping with a Moyamoya pattern of disease

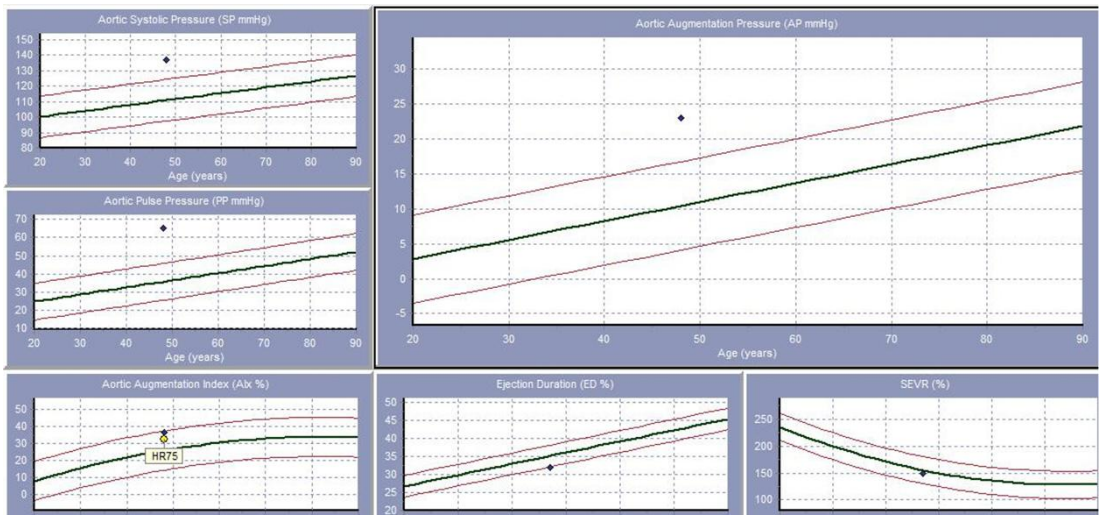

Fig. 2. Arterial stiffness using SphygmoCor showing markedly increased arterial stiffness parameters like augmentation index, aortic systolic and pulse pressure

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