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Hyperhomocysteinemia Independently Associated with Adult Moyamoya Disease: Hospital Based Study of 237 Patients

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ABSTRACT

AIM: To clarify the risk factors for adult moyamoya disease (MMD) in patients from South China.

MATERIAL and METHODS: We prospectively studied adult patients who were diagnosed angiographically with MMD. The demographic profiles, medical history and clinical characteristics were compared between adult MMD and non-MMD stroke patients. Logistic regression analysis was used to determine the risk factors associated with adult MMD.

RESULTS: A total of 35 adult MMD patients and 202 adults patients with non-MMD stroke were included. Of the 35 MMD patients, bilateral MMD occurred in 48.6% and bypass surgery was performed in 28.6%; these figures were significantly lower than those reported in patients from Korea and the United States ($p<0.05$). After adjusting for baseline demographics and potential confounders, multivariate logistic regression analysis was conducted, which showed that the plasma homocysteine level (odds ratio [OR]: 1.10; 95% confidence interval [CI]: 1.06–1.14) and occupation as a technological worker (OR: 4.23; 95% CI: 1.65–10.89) were independently associated with adult MMD.

CONCLUSION: Hyperhomocysteinemia and type of occupation were found to be independent risk factors for adult MMD in patients from South China. However, there is still a need for further research to clarify the pathogenesis of MMD. Given the lack of understanding about the risk factors and prevention measures for MMD, we suggest bypass surgery be used for MMD treatment in clinical practice in China to achieve more desirable effects in the management of the disease.

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KEYWORDS: Moyamoya disease, Angiography, Digital subtraction, Hyperhomocysteinemia, Adult

ABBREVIATIONS: MMD: Moyamoya disease, **DSA:** Digital subtraction angiography, **HDL:** High-density lipoprotein, **LDL:** Low-density lipoprotein, **ApoA1:** Apolipoprotein-A1, **ApoB:** Apolipoprotein-B, **MTFHR:** Methylenetetrahydrofolate reductase

INTRODUCTION

MMD is characterised by compensatory irregular perforating vessels (i.e., 'moyamoya vessels') that are generated in parallel with bilateral angiopathy of intracranial vascular networks and are located near the occluded or stenotic regions, corresponding to the lenticulostriate and thalamoperforating arteries (28). The outgrowth of small vessels produces a hazy image described as a 'puff of smoke' on the radiograph, hence the disease's name *moyamoya* in Japanese (28). The intrinsic nature of MMD is to convert the brain's vascular supply from the internal carotid system to the external carotid system. MMD is a rare disease in most parts of the world, except for Japan and other

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areas in Asia (31). It has recently been revealed that the age of onset of MMD has two peaks (10). The first peak is observed around 10 years of age, and the second peak occurs between 30 and 45 years of age.

Numerous studies have been conducted to characterise MMD in patient populations from East Asia (7,11,12,15), and Western countries (14,18), but the pathogenesis of MMD remains largely unknown. Inflammation and immune dysfunction have been implicated in its pathogenesis (27-29); however, the history of such events is often subjective and unreliable. Tuberculous meningitis, atherosclerosis, neurofibromatosis and irradiation have all been reported to be causes of MMD (3), and a congenital cause has also been suggested (13,17). Recent studies have shown that concentrations of certain growth factors or cytokines are increased in the cerebrospinal fluid of patients with MMD. However, there is no internationally accepted aetiology of MMD. Therefore, in this study, we aimed to clarify the risk factors and potential pathogenesis of MMD in adult patients from South China.

MATERIAL and METHODS

Patient and Public Involvement

This research was conducted without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Study Population

We prospectively studied 35 consecutive patients with adult MMD (age of MMD onset >18 years) admitted to the stroke unit at our hospital (serving a population of more than 10,000,000 in Guangzhou, China). All patients were diagnosed with MMD by digital subtraction angiography (DSA) from January 2014 to August 2018. According to the modified Suzuki scoring (mSS), there 3 MMD patients were classified as mSSI, 17 as mSSII, 13 as mSSIII and 2 as mSSIV.

Inclusion criteria included patients with angiographically identified unilateral or bilateral severe stenosis or occlusion in the distal internal carotid artery or proximal middle and anterior cerebral arteries with eminent lenticulostriate arteries known as 'moyamoya collaterals'.

Exclusion criteria were patients with systemic vasculitis, neurofibromatosis, meningitis, sickle-cell disease, Down syndrome, prior radiotherapy on the skull base, or any other diseases that might be responsible for the observed vasculopathy. Consecutive patients with stroke subtype-matched non-MMD stroke admitted during the same period were selected as controls.

Baseline information on demographics and medical history were obtained predominantly by face-to-face interviews and medical records. Detailed data forms on clinical features were completed on admission by stroke physicians. Written informed consent for study participation was obtained from patients or an appropriate family member of the patient (in the case that the patient was disabled). The study was approved by the Ethics Committees of the second affiliated hospital of Guangzhou Medical University (Guangzhou).

In addition to bypass surgery in some MMD patients, other treatments were similar between the two groups. Cerebral perfusion pressure was guaranteed while avoiding hypovolaemia. Regulation of blood pressure, blood sugar, lipid and dehydration was performed as necessary. Acute management was mainly supportive, with a focus on reducing intracerebral pressure and managing seizures. Medical treatments included vasodilators, antiplatelet agents, antifibrolytic agents and fibrinolytic agents. Epileptic patients were treated with anticonvulsants.

DSA and Biochemical Tests

All examinations were performed using a Politron 1000 VR unit (Siemens, Nürnberg, Germany). After selective common carotid artery catheterisation through right transfemoral artery puncture, iohexol (Omnigraf; Juste, Madrid, Spain) was injected at a rate of 10 mL/s, and three different projections (posteroanterior, lateral and 45° oblique views) were taken. The diagnosis of MMD was confirmed according to previously described criteria. Peripheral venous blood samples were collected in the morning. A Beckman CX5 Automated Analyzer was used to determine the levels of fasting blood glucose, total cholesterol, triglycerides, HDL, LDL, ApoA1, ApoB, prothrombin time and high-sensitivity C-reactive protein. Plasma homocysteine level was determined by fluorescence ratio biochemical assay kit.

Statistical Analysis

To determine the statistical differences in baseline characteristics, continuous variables were compared using *t* tests or Wilcoxon tests, and categorical variables were compared using c^2 tests. Analysis of variance was used to study the homocysteine levels in subgroups of patients with adult MMD divided by the mSS. Logistic regression analysis was used to determine the risk factors associated with adult MMD. Univariate analyses were conducted first, followed by multivariate logistic regression analyses after adjusting for age, sex, medical history (hypertension, coronary heart disease and diabetes) and present history of smoking and alcohol use. Results from the univariate analyses showed that the variables were significantly associated with MMD, indicating statistical significance ($p<0.05$). All analyses were conducted using PASW statistics 18.0 (SPSS Inc., Chicago, Ill, USA).

RESULTS

Study Population

A total of 35 patients with adult MMD and 202 patients with non-MMD stroke (180 patients with ischaemic stroke and 22 patients with haemorrhagic stroke) were included in this study. All analyses herein were based on data from these 237 patients.

Among the 35 patients with adult MMD, the average age was 48.2 ± 13.5 years, and the female-to-male ratio was

1.7. Eighteen patients (51.4%) had ischaemic stroke, and 17 (48.6%) had haemorrhagic stroke. The percentage of patients with unilateral MMD was 51.4% (18/35), and bypass surgery was performed 28.6% (10/35) of the patients, both of which are lower than in Korea (84.4%, 37.7%) and the United States (60.7%, 100%; p<0.05).

As shown in Table I, stroke patients with adult MMD were younger than non-MMD stroke patients. The proportion of patients who were technological workers was higher in those with MMD stroke. Similarly, the mean serum homocysteine level was significantly higher in patients with adult MMD than in non-MMD stroke patients. In contrast, hypertension was a more common comorbidity in non-MMD patients. There was no difference between homocysteine levels in the subgroups of MMD patients divided by the mSS, as shown in Table II.

Multiple logistic regression analysis was performed to further evaluate the independent risk factors for MMD (versus non-MMD stroke). As shown in Table II, after adjusting for baseline demographics, risk factors for stroke, significant variables from univariate analyses, homocysteine level and being a technological worker were still shown to be significantly associated with MMD.

DISCUSSION

Moyamoya disease is a rare cerebrovascular disorder. Worldwide, the incidence of MMD is higher in Japan and in other East Asian countries. However, the incidence of MMD is estimated to be less than 11 per 100,000, even in Japan. In patients from South China, the detection rate of MMD is 3.2% in patients undergoing cerebral angiography, yet we do not know the exact incidence of adult MMD. In terms of age and sex distributions, the Chinese patient population has similarities to patient populations from other East Asian countries [such as Japan (20), and Korea (25)] as well as Western countries [such as the United States (30)]. Our experiences indicated several clinical differences between Chinese patients and patients from the above-mentioned countries. Among East Asian populations, ischaemic stroke

Table I: Baseline Demographics and Clinical Characteristics in Patients with Adult MMD and non-MMD Stroke*

Variable	MMD stroke (n=35)	Non-MMD stroke (n=202)	p
Age, years	48.2 ± 13.5	55.6 ± 12.3	**0.003**
Male	22 (62.9)	140 (69.3)	0.45
Technological worker	18 (51.4)	31 (15.3)	**<0.001**
Current smoker	10 (28.6)	65 (32.2)	0.67
Current alcohol user	6 (17.1)	37 (18.3)	0.87
With family history	4 (11.4)	18 (8.9)	0.64
Medical history			
Hypertension	11 (31.4)	127 (62.9)	**<0.001**
Coronary heart disease	1 (2.9)	23 (11.4)	0.123
Diabetes mellitus	5 (14.3)	26 (12.9)	0.82
Pathology results			
Fasting glucose (mmol/L)	5.6 (4.8, 6.5)	5.4 (4.6, 7.0)	0.31
Triglyceride (mmol/L)	1.7 (1.0, 2.7)	1.7 (1.2, 2.3)	0.81
Total cholesterol (mmol/L)	4.8 (4.4, 5.8)	4.9 (4.2, 5.7)	0.78
HDL (mmol/L)	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)	0.83
LDL (mmol/L)	3.0 (2.7, 3.8)	3.0 (2.5, 3.7)	0.34
ApoA1 (g/L)	1.2 (1.0, 1.3)	1.2 (1.1, 1.4)	0.24
ApoB (g/L)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	0.58
Homocysteine (g/L)	21.0 (16.2, 33.0)	11.6 (9.5, 14.7)	**<0.001**
HsCRP (mg/L)	3.8 (0.9, 11.3)	3.2 (1.1, 10.8)	0.75
Prothrombin time (seconds)	14.3 (13.0, 15.4)	14.3 (13.1, 15.2)	0.78

Values are reported as mean ± SD, number of subjects, or median (IQR);* ***Abbreviations: HDL:* *high-density lipoprotein,* ***LDL:*** *low-density lipoprotein,* ***ApoA1:*** *apolipoprotein-A1,* ***ApoB:*** *apolipoprotein-B,* ***HsCRP:*** *high sensitivity C-reactive protein.*

Table II: Logistic Regression Analysis of Independent Risk Factors for Adult MMD

Variable	Crude, n=237		Adjusted, n=237†	
	OR (95% CI)	p	OR (95% CI)	p
Sociodemographic				
Age, years	0.96 (0.93, 0.98)	0.002	-	-
Male	1.33 (0.63, 2.82)	0.45	-	-
Technological worker	5.84 (2.72, 12.56)	<0.001	4.233 (1.65,10.89)	**0.003**
Current smoker	0.84 (0.38, 1.86)	0.67	-	-
Current alcohol user	0.92 (0.37, 2.38)	0.87	-	-
With family history	1.32 (0.42, 4.16)	0.64	-	-
Medical history			-	-
Hypertension	0.27 (0.13, 0.58)	0.001	0.26 (0.10, 0.71)	**0.009**
Coronary heart disease	0.23 (0.03, 1.75)	0.16	-	-
Diabetes mellitus	1.13 (0.40, 3.17)	0.82	-	-
Pathology results			-	-
Fasting glucose (mmol/L)	1.04 (0.93, 1.17)	0.50	-	-
Triglyceride (mmol/L)	1.11 (0.97, 1.27)	0.14	-	-
Total cholesterol (mmol/L)	1.04 (0.77, 1.40)	0.79	-	-
HDL (mmol/L)	1.56 (0.40, 6.14)	0.53	-	-
LDL (mmol/L)	0.97 (0.73, 1.28)	0.81	-	-
ApoA1 (g/L)	0.25 (0.05, 1.24)	0.09	-	-
ApoB (g/L)	1.57 (0.31, 7.98)	0.59	-	-
Homocysteine (g/L)	1.08 (1.04, 1.11)	<0.001	1.100 (1.06, 1.14)	**<0.001**
HsCRP (mg/L)	0.99 (0.97, 1.01)	0.36	-	-
Prothrombin time (seconds)	1.01 (0.84, 1.22)	0.91	-	-

†Adjusted for Sociodemographic, medical history, and significant (p<0.05) variables from the univariate analyses: homocysteine.

is the primary clinical symptom. Interestingly, bilateral MMD was observed more frequently in patients with adult MMD in Japan (82.5%), Korea (84.4%) and the United States (60.7%), whereas a higher frequency of unilateral MMD was observed in Chinese patients. In addition, we found that the frequency of bypass surgery was significantly lower in China in comparison with other East Asian countries (such as Japan [63.5%] and Korea [(37.7%]) and Western countries (such as the United States [100.0%]). Because bypass surgery is a proven effective therapy for MMD (19,32), this finding suggests room for improvement in the clinical management of MMD patients in China.

We found that hyperhomocysteinemia was an independent risk factor for MMD. Serum homocysteine level was significantly higher in patients with adult MMD than that in patients with non-MMD stroke, even after adjusting for extraneous variables. This finding is consistent with previous findings from case reports of MMD (bilateral or unilateral), in which homocysteine level was also noted to be a risk factor for MMD (5,23). Many retrospective and prospective studies have confirmed that hyperhomocysteinemia is a potential independent risk factor for atherosclerosis (22), and an increased homocysteine level has been reported to be an independent risk factor for cerebral atherosclerosis (2). Hyperhomocysteinemia is a risk factor for middle cerebral artery stenosis (16), and is recognised to be associated with the presence and severity of systemic atherosclerosis (6). The potential mechanisms of action of homocysteine have been summarised as follows (1,26): damage to endothelial cells; reduction in NO generation; stimulation of smooth muscle cell proliferation; increasing foam cell formation; promotion of platelet aggregation, which in turn promotes thrombus formation; and reduction in the flexibility of vessels. Homocysteine can also enhance the negative impacts from risk factors such as smoking and abnormal lipid metabolism, resulting in the development of inflammation

(4). These results suggest that homocysteine may have the same effects on adult MMD as it has on atherosclerosis. As a result, atherosclerosis secondary to increased homocysteine was the likely cause of moyamoya (5). Our hypothesis is supported by the presence of peripheral atherosclerotic disease, ischaemic heart disease, the relevant risk factors for atherosclerosis and the absence of other predisposing conditions of MMD in the patient samples in our study. On the other hand, one case report of homocystinuria with moyamoya was also described (9), and the possible role of the enzyme activity of methylenetetrahydrofolate reductase (MTFHR), which is associated with hyperhomocysteinemia, in MMD was discussed in the literature (24). A recent study indicated an association between two novel single-nucleotide polymorphisms in the gene regulating homocysteine metabolism (rs9651118 in MTHFR and rs117353193 in TCN2), resulting in increased homocysteine levels in patients with MMD (7,8). We believe that the genetic metabolic factor for homocysteinemia in the release of nitric oxide is the proposed mechanism (21), resulting in the development of moyamoya vessels and stroke (23).

Interestingly, we also found that the patient's occupation (ie, technological worker) plays a significant role in the development adult MMD. Previous studies have shown that radiation is one cause of MMD. Results from our study may implicate the role of radiation in adult MMD. However, we excluded patients with a history of radiotherapy on the skull base. In addition, we did not divide technological workers into subgroups (eg, exposure vs. nonexposure to radiation) because of insufficient data. Therefore, it is difficult to confirm the exact effects of radiation on adult MMD in this study.

There are several limitations of our study that are worth attention and further discussion. First, this study was a single-city hospital-based study in China, and as such, concerns about its external validity in other regions of China are raised. Moreover, only MMD patients with stroke were assessed, and the risk factors for MMD patients who have not yet experienced end-organ diseases may be different from those reported herein. Second, several important potential risk factors for MMD, such as concentrations of certain growth factors or cytokines, were not studied because they were out of scope for this study. Nonetheless, the definite similarity of results from this study to those from previous case reports reassures us of the validity of our data.

CONCLUSION

In conclusion, results from our study indicate an independent association between elevated homocysteine levels and MMD and also suggest that environmental factors such as type of occupation may play an important role in the development of MMD in China. Furthermore, given the practical blank of application and proven efficacy, bypass surgery should be more widely promoted in clinical practice.

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