Coronary Heart Disease in Moyamoya Disease: Are They Concomitant or Coincidence?

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Received: 8 July 2014
Accepted: 3 December 2014

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INTRODUCTION

Moyamoya disease (MMD) is known as a progressive steno-occlusive intracranial angiopathy with small, fragile, and multiple collateral formation (1). The prevalence of MMD was found to be 16.1 per 100,000 in the Republic of Korea, when calculated with the 2011 population (2). The MMD is usually known to involve intracranial arteries, but systemic involvement of endothelial hyperplasia was raised in an autopsy study (3). Also, the renal artery is often involved with this disease in around 8% of the cases (4). It has been reported that the systemic arterial involvement in MMD can be a manifestation of certain genetic mutation such as ACTA 2 (5). Up to date, coronary artery disease in MMD has been described sporadically in several case reports, and the association between MMD and coronary heart disease (CHD) has been constantly suggested in the literature (6-14). However, to the best of our knowledge, there have been no reports determining the prevalence of symptomatic CHD in MMD. In this study, we retrospectively reviewed the adult patients in MMD registry to determine the prevalence of CHD. Also, we explored the potential risk factors and analyzed the characteristics of CHD in MMD.

MATERIALS AND METHODS

Patients

From January 1995 to December 2012, 456 consecutive adult patients (≥ 20 yr of age) with MMD visited our hospital and were registered as adult MMD patients. The diagnosis of MMD was made based on idiopathic steno-occlusion at the terminal portion of internal carotid artery with concomitant abnormal vascular networks in the vicinity of the steno-occlusive lesions, which was confirmed by conventional angiography and/or magnetic resonance imaging.

All clinical data including coronary evaluation and medical history from our adult MMD registry were reviewed by two neurosurgeons. To obtain possible missing data from manual analyses, data collection of CHD was also performed using computerized queries, retrieving all coronary angiographic details and discharge summaries in the registry. The CHD patients were identified by searching with the keywords “coronary artery”, “angina”, or “myocardiac infarction”. CHD was defined as typical chest pain with corresponding coronary artery lesion on imaging study.

The following explanatory variables were assessed: age, gender, type of MMD, and clinical risk factors that were known for causes of atherosclerosis and CHD, such as hypertension, diabetes mellitus (DM), smoking and dyslipidemia (15). Framingham Score at MMD diagnosis was also assessed in the patients with CHD. The different types of MMD were categorized according to clinical symptoms at the initial diagnosis with MMD as follows: ischemic, hemorrhagic, asymptomatic, and atypical symptoms, such as headache and dizziness.

The purpose of this study was to determine the prevalence and characteristics of symptomatic coronary heart disease (CHD) in patients with moyamoya disease (MMD). This retrospective study evaluated 456 patients who received examination for MMD between 1995 and 2012. We reviewed the patients’ medical history and coronary imaging, including conventional coronary angiography and coronary computed tomography angiogram (CTA). Among 456 patients with MMD, 21 (4.6%) patients were found to have symptomatic CHD. Ten patients were treated with coronary artery bypass graft or percutaneous coronary intervention for unstable angina or myocardial infarction. Eleven were treated with medication for stable angina (n = 6) and variant angina with mild degree of stenosis (n = 5). The median age of these patients was 44 yr (range, 27-59). The median Framingham score at diagnosing MMD was < 1% (range, < 1%–16%). The old age was associated with CHD in uni- and multivariate analyses \( (P = 0.021, \text{OR, } 1.053; 95\% \text{ CI, } 1.008-1.110) \). Considering low age of onset and low stroke risk factor, CHD might be a systemic manifestation that is clinically relevant to MMD.

Keywords: Moyamoya Disease; Coronary Disease; Prevalence; Characteristics
Statistical analysis
To explore the potential risk factors of CHD in MMD, statistical analyses were performed. The frequency comparisons were performed with Fisher’s exact test. For continuous variables, Mann-whitney U-test was performed, and multiple logistic regression test was performed for multivariate analysis. Statistical analysis was performed using SPSS 20.0 software (SPSS, Chicago, IL, USA).

Ethics statement
This study was approved by the institutional review board of the Samsung Medical Center (IRB No. 2014-07-077-001). Informed consent was waived by the board.

RESULTS
The baseline characteristics of the patients are described in Table 1. Twenty one (4.6%) out of 456 patients were diagnosed as symptomatic CHD. The detailed information on these patients with CHD are described in Table 2. The median follow-up period was 32 months (range, 1-192). During the follow-up period, one patient was admitted to emergency room and dead upon arrival. The sudden death could have been caused by coronary heart disease, but there was no definite evidence associated with it as a cause of death, because medical examination could not be performed. Thus, we excluded the patient from CHD

Table 1. Baseline characteristics of the patients

| Characteristics        | No. of without CHD (n = 435) | Patients with CHD (n = 21) | P value by univariate analysis |
|------------------------|-------------------------------|-----------------------------|-------------------------------|
| Age, median years (range)* | 39 (20-76)                  | 46 (20-63)                 | 0.003                         |
| Gender (Male/Female)*  | 126/309                      | 7/14                       | 0.631                         |
| Diabetes†              | 35 (8.8%)                    | 5 (23.8%)                  | 0.031                         |
| Hypertension†          | 130 (30.7%)                  | 10 (47.6%)                 | 0.145                         |
| Dyslipidemia†          | 52 (12.6%)                   | 3 (14.2%)                  | 0.743                         |
| Smoking†               | 43 (10.3%)                   | 4 (19.0%)                  | 0.177                         |
| Presenting Symptom†    |                              |                            | 0.876                         |
| Hemorrhagic            | 93 (20.4%)                   | 3 (14.2%)                  |                               |
| Ischemic               | 272 (59.6%)                  | 13 (61.9%)                 |                               |
| Atypical               | 77 (16.9%)                   | 4 (19.0%)                  |                               |
| Asymptomatic           | 14 (3.7%)                    | 2 (9.5%)                   |                               |

*Estimated by Mann-whitney U-test; †Estimated by Fisher’s exact test. CHD, coronary heart disease.

Table 2. Detailed characteristics of the moyamoya disease patients with coronary heart disease

| Patient No. | Sex | Age† (yr) | Type of CAD      | DM | HTN | Dyslipidemia | Smoking | Framingham score* | Time from MMD to CAD (yr) | Premature CAD | Treatment for CAD |
|-------------|-----|-----------|------------------|----|-----|--------------|---------|-------------------|--------------------------|---------------|------------------|
| 1           | F   | 39        | Unstable angina  | Yes| Yes| Yes          | No      | < 1%              | 8                        | Yes           | CABG             |
| 2           | M   | 45        | Unstable angina  | Yes| Yes| Yes          | Yes     | 10%               | 8                        | Yes           | PCI              |
| 3           | F   | 41        | Unstable angina  | No | Yes| No           | No      | < 1%              | 3                        | Yes           | PCI              |
| 4           | M   | 53        | Stable angina    | No | No | No           | No      | < 1%              | 2                        | Yes           | Medication       |
| 5           | M   | 49        | Stable angina    | No | No | No           | No      | 3%                | 5                        | Yes           | Medication       |
| 6           | F   | 45        | Unstable angina  | Yes| Yes| Yes          | No      | < 1%              | 1                        | Yes           | PCI              |
| 7           | F   | 52        | Unstable angina  | No | Yes| No           | No      | 1%                | 1                        | Yes           | CABG             |
| 8           | M   | 36        | Myocardial infarction | No | Yes| No           | No      | < 1%              | 5                        | Yes           | PCI              |
| 9           | F   | 32        | Stable angina    | No | No | No           | No      | < 1%              | 3                        | Yes           | Medication       |
| 10          | M   | 57        | Stable angina    | No | Yes| No           | Yes     | 16%               | 2                        | Yes           | Medication       |
| 11          | M   | 38        | Stable angina    | No | No | No           | No      | < 1%              | 3                        | Yes           | Medication       |
| 12          | F   | 52        | Stable angina    | No | No | No           | No      | 2%                | 2                        | Yes           | Medication       |
| 13          | F   | 44        | Unstable angina  | No | Yes| No           | No      | 3%                | -12                      | Yes           | CABG             |
| 14          | F   | 38        | Myocardial infarction | Yes| No| No           | No      | < 1%              | -1                      | Yes           | CABG             |
| 15          | F   | 41        | Unstable angina  | No | No | No           | No      | < 1%              | 2                        | Yes           | PCI              |
| 16          | M   | 41        | Unstable angina  | No | No | No           | Yes     | 4%                | 1                        | Yes           | PCI              |
| 17          | F   | 41        | Variant angina   | No | Yes| No           | No      | < 1%              | 1                        | Yes           | Medication       |
| 18          | F   | 20        | Variant angina   | No | No | No           | NA      | 7%                | 7                        | Yes           | Medication       |
| 19          | F   | 45        | Variant angina   | No | Yes| No           | No      | < 1%              | 5                        | Yes           | Medication       |
| 20          | M   | 58        | Variant angina   | No | No | No           | No      | 6%                | 1                        | Yes           | Medication       |
| 21          | F   | 55        | Variant angina   | No | No | No           | No      | 1%                | 0                        | Yes           | Medication       |

*At the time of MMD Diagnosis; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.
The median age at CHD diagnosis was 44 yr (range, 27-59). Three (Patient No. 7, 13, and 14) of them were unilateral disease and 4 (Patient No. 2, 3, 15, and 16) were hemorrhagic subtype of MMD.

The treatment for CHD were as follows: 11 medical treatments (5 variant angina with mild degree of stenosis, 6 stable angina), 4 coronary artery bypass graft (CABG), and 6 percutaneous coronary intervention (PCI). One patient (Patient No. 7) who underwent CABG surgery had a postoperative ischemic stroke.

The patients with CHD were older in age (median, 46; range, 20-63) when diagnosed with MMD than the patients who were diagnosed as MMD without CHD (median age, 39; range, 20-76; \( P = 0.003 \), Mann-Whitney U-test). The patients with MMD and CHD had higher percentage of DM than the MMD patients without the CHD (23.8% vs. 8.2%, \( P = 0.031 \) Fisher’s exact test). Multivariate analyses using multiple logistic regression test showed that only the age factor was associated in those with both CHD and MMD (\( P = 0.021 \), OR, 1.053; 95% CI, 1.008-1.110).

**Fig. 1.** Angiographic findings of coronary heart disease in moyamoya disease. (A) and (B) show coronary stenosis (arrows) without calcification. (C) shows calcified plaque (arrow) on a non-contrast coronary computed tomography, and (D) shows aneurysmal dilatation and focal stenosis (arrow). Nitroglycerin (NG) was administered to the patient.
Other variables, such as gender, hyperlipidemia, hypertension, smoking, and subtype of MMD (hemorrhagic vs. ischemic vs. atypical vs. asymptomatic) were not statistically different between those with and without CHD (Table 3).

Coronary computed tomography angiography (CTA) was available for 7 patients, and 4 patients showed no calcification of affected coronary artery (Fig. 1), and one patient showed aneurysmal dilatation.

**DISCUSSION**

Several of the previous reported articles demonstrated CHD in MMD, and most of them were reported from East Asian countries (7-14, 16). Ikeda demonstrated that MMD is involved with the extra-cranial vessels as well as the intracranial vessels, and there are systemic etiologic factors, which cause intimal thickening in the systemic vessels (3). Histopathologic studies of the involved internal carotid arteries in MMD showed fibrocellular thickening of the intima and proliferated smooth muscle cells (SMC) as the cause of the arterial occlusion (17, 18). Also, the SMC proliferation is part of the mechanism of atherosclerosis in CHD, which is similar to the histopathology of MMD (19, 20). Several mutant genes which can cause stenosis in both MMD and CHD have already been reported (5, 17).

Both MMD and CHD can cause life-threatening events. If these two diseases had significant association, screening test should be performed to reduce the morbidity and mortality. In our adult MMD registry, 4.6% showed CHD. However, this percentage could be underestimated because only the symptomatic patients who underwent diagnostic study at our hospital were retrospectively included. The prevalence of CHD in the Asian population is known to be less than 1% person per year in the population of 65 or less years of age (21), which could be significant.

In this study, all of the CHD were developed at relatively young age (< 65 yr), and Framingham scores were low at the initial diagnosis of MMD. Also, half of the patients showed no calcification on CTA, which reflects the atherosclerotic burden of the coronary artery. These findings support the idea that MMD is a causative factor of CHD rather than pure atherosclerosis (16, 22).

Previous case reports about CHD in MMD described the minimal atherosclerotic burden on the affected coronary artery (10, 16), and half of our data supported this except the coronary artery lesions were heterogeneous in this study. The prevalence was not high enough to designate MMD as the main culprit. Also, in this study the classic risk factors for atherosclerosis, such as old age and diabetes, were associated with CHD in MMD. Therefore, we hypothesized that the underlying endothelial hyperplasia in the coronary artery is not so significant in the most cases of MMD, but smaller atherosclerotic burden seemed to be causing the symptomatic CHD in MMD patients at younger age than normal population. In our study, 5 (23.8%) of 21 CHD patients were diagnosed as variant angina, and this proportion was high compared with general CHD patients. In 1998, Ikeda et al., reported variant angina associated with MMD, and 2 (22.2%) out of 9 MMD patient were diagnosed as variant angina (23). There seems to be an association between MMD and variant angina. However, there has been no evidence that supports this idea, considering the mechanism of variant angina and MMD.

Several limitations must be noted in this study. First, this was an uncontrolled, retrospective study. Therefore, the data cannot provide the exact prevalence of CHD in MMD. Also, not all of the patients underwent coronary CTA, which could have provided more information about atherosclerotic components, such as calcium score or plaque content. The MMD is a rare disease and there is no adequate evidence regarding the association between CHD and MMD, which makes it difficult to perform a prospective, controlled study. This study also reflects mainly the patients who were treated in our hospital. Since we have considered those with CHD treated in other hospitals, there are some loss of data from outside medical records. Therefore, the prevalence suggested in this study might be underestimated.

In conclusion, MMD does not seem to be the main culprit of CHD, but it can lead to CHD with small atherosclerosis probably due to the underlying endothelial proliferation. The screening test for CHD in the MMD patients with older age is in need, and DM might have a role for this matter. The future study with a larger sample size is warranted to reveal the general characteristics of CHD in MMD and to determine the usefulness of coronary screening test in MMD.

**DISCLOSURE**

Relevant conflicts of interest/financial disclosure: Nothing to report.

**AUTHOR CONTRIBUTION**

Study design: Nam TM, Jo KI, Kim JS. Data collection and analysis: Nam TM, Jo KI. Writing manuscript: Nam TM, Jo KI. Kim JS. Discussion and manuscript revision: Nam TM, Jo KI. Yeon JY, Hong SC, Kim JS. Manuscript artpoval: Kim JS.

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