Moyamoya vasculopathy - Patient demographics and characteristics in the Finnish population

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ABSTRACT

Background and Purpose: Moyamoya vasculopathy (MMV), a rare steno-occlusive progressive cerebrovascular disorder, has not been thoroughly studied in Caucasian populations. We established a registry of Finnish patients treated at the Helsinki University Hospital (HUH), to collect and report demographic and clinical data.

Methods: We collected data both retrospectively and prospectively from all the patients with a MMV referred to our hospital between January 1987 and December 2014. All patients underwent a neurological outpatient clinic visit.

Results: We diagnosed 61 patients (50 females, 10 children) with MMV. The mean age at the disease-onset was 31.5 ± 17.9 years. The two most common presenting symptoms were ischemic stroke (n=31) and hemorrhage (n=8). Forty-four per cent underwent revascularization surgery, and 70 % were prescribed antithrombotic treatment.

Conclusions: The results support in part the Western phenotype of the disease considering the later presentation and larger female predominance compared to the Asian MMV reports. However, the proportion of ischemic strokes and hemorrhagic strokes is closer to Japanese population than German population. The absence of familial cases points to a different genetic profile in the Finnish patients.

Key words: moyamoya, ischemic stroke, hemorrhagic stroke, epidemiology, clinical characteristics, vasculopathy

INTRODUCTION

Moyamoya vasculopathy (MMV) is a rare steno-occlusive progressive cerebrovascular disorder. It usually affects the anterior circulation, more specifically the distal portion of the internal carotid artery and its distal branches, and only rarely the posterior cerebral arteries. Occlusion of the anterior circulation cerebral arteries leads to formation of collateral vessels, i.e. moyamoya vessels.(1) The term moyamoya in Japanese means a “puff of smoke” referring to the collateral network seen on digital subtraction angiography. (2) When the disorder is idiopathic, it is referred to as the moyamoya disease (MMD). The moyamoya syndrome (MMS), on the other hand, has the same kind of vascular findings, but is associated with certain other conditions such as Down syndrome, neurofibromatosis, sickle cell anemia, or head injury. (1) MMV usually peaks before the age of 14 years and again at 31-59 years. Women are affected more often than men with a ratio varying from 1.1-2.8:1. (3) The most common presenting symptoms are ischemic or hemorrhagic strokes, transient ischemic attacks (TIA), headaches, and epileptic seizures. (1)

MMD is more common in Asia than in the western countries, (3) and most studies have been done on Asian populations. Only few studies concerning the European populations have been published. (4-9) The incidence and prevalence of MMD in Finland is not known. Furthermore, it is not known whether the age of onset, clinical features, and many other aspects of MMV are similar to those of the Asian populations or non-Finnish European populations. Therefore, we searched for all the diagnosed MMD and MMS patients referred to our hospital to collect the patient data into a detailed database, to report the patient demographics, clinical features, and treatment modalities.

MATERIALS AND METHODS

This study was performed at the Departments of Neurology and Neurosurgery, Helsinki University Hospital (HUH), Helsinki, Finland. The local Ethics committee approved the study (154/13/03/00/10). The patients who came for an outpatient clinical follow-up visit gave a written consent. For registry-based data collection, Finnish legislation does not require patient consent.

HUH is one of the five university hospitals in Finland. The population of HUH district in year 2014 was 1 599 390 as the population of Finland was 5 471 753. The Departments of Neurology and Neurosurgery at HUH are together responsible for organizing the specialist-level care of all neurological and neurosurgical patients in the whole HUH district. HUH Neurosurgery is the only center in Finland where extracranial-intracranial bypass surgery is performed. All the MMV patients in the HUH region are referred to or diagnosed at the HUH neurology department and all the MMV patients in Finland requiring surgery are referred to the HUH neurosurgery department.

A detailed database included the patients' medical history, family history of stroke and MMV, medication on admission and preventive medication at discharge, hospital admission data, clinical manifestation and time course, treatment and procedures, discharge details, outcome (modified Rankin Scale at discharge), laboratory tests on admission, and radiological data. The radiological data included a list of all the radiological studies done and the patterns of the ischemic lesions and intracerebral hemorrhages (ICH), lesion sites, and vessel abnormalities. The baseline stroke risk factors including smoking, dyslipidemia, hypertension, diabetes, and family history of stroke, were documented.

All patients treated between January 1987 and December 2014 were retrospectively identified from our hospital's electronic patient records using the diagnosis numbers 4375A, 4331A, 4331X, 4339A, 4339X, 4349A, 4349X until 1994 and the ICD 10 diagnosis number I67.5 after 1994. All the patients diagnosed after that date were added to the database prospectively. Because our neurological team runs the stroke center at HUH and the neurosurgical co-author (LK) is in charge of MMV surgery in Finland, most of the patients have been seen, diagnosed, and treated by ourselves. The diagnosis was done using methods and criteria recommended by the Japanese guidelines(1). For this study, each patient's diagnosis was first reviewed by MS, then discussed with neuroradiologist JP, neurosurgeon LK, and finally with stroke neurologist TT to confirm a consensual diagnosis. All these patients were included in our registry. Medical histories were collected either by interviewing the patients in 2014 and 2015 at the neurological outpatient department and/or by reviewing the patients' hospital charts. A detailed family history was obtained for each patient. Additionally, blood samples were collected for various future biomarker and genetic studies. All data were inserted into an Excel-based electronic database. The incidence was calculated by dividing the number of diagnosed MMD patients with the total population at the HUS district per year.

Statistical analyses

Frequencies, means, and medians were analyzed using the SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

RESULTS

Demographic data and disease type

We identified 61 Caucasian patients of Finnish origin. Fifty-five of the 61 patients were re-evaluated as part of this research project during years 2014 or 2015 by a neurologist (MS). Two patients had died before being contacted and four patients did not wish to participate in the dedicated clinical evaluation and additional tests. Most patients, (n=45, 74 %) were diagnosed with a definite MMD, 13 (21%) with unilateral MMD, and only 3 (5%) with a MMS (Table 1). There was a female predominance found (n=50; 82%) with only 11 (18%) male (ratio 4.5:1). At the time of the diagnosis, 10 were children. None of the patients had family members with either MMD or MMS. The time from the first symptoms to the diagnosis ranged from zero to 324 months. The youngest child diagnosed was 3 years and the oldest patient was 77 years old.

Forty patients were from the HUH hospital district. The incidence of MMV in HUH district was thus 0.14 per 100 000. The prevalence in HUCH district was 2.38 per 100 000 in year 2014.

Baseline stroke risk factors

Over one third (36%) of the patients had no cerebrovascular risk factors: almost one third (28%) had only one single risk factor and the rest had two or more stroke risk factors. The most common risk factor was smoking (36%), followed by hypertension (33%) and dyslipidemia (30%).

Diagnostic features

For diagnostic purposes, 75% of the patients underwent magnetic resonance angiography (MRA), 69% digital subtraction angiography (DSA), and in one case computed tomography angiography (CTA) was performed.

Clinical manifestations and co-morbidities

The most common clinical manifestations were ischemic stroke (51%), hemorrhage (13%), and headaches (11%), while TIA and epileptic seizures were rare as the first presenting symptoms (Table 1). The proportion of hemorrhage was higher in men than in women (27% vs 10%). Mean National Institutes of Health Stroke Scale (NIHSS) at admission to hospital was 4 (range 0-32) and median 0. Most common findings at arrival to hospital were motor and/or sensory hemiparesis and aphasia. Single cases of diabetes insipidus, Gilbert's syndrome, essential thrombocythemia, Crohn's disease, atrial septal defect, and pituitary adenoma were observed in MMV patients.

Radiological characteristics

All patients showed typical anterior circulation vasculature changes. Posterior circulation vasculature was involved in 13% of the patients depicting various degrees of arterial changes. The majority of the ischemic lesions (61%) were located in the anterior circulation area. Fifty-eight per cent of patients with ischemic lesions had cortical infarcts and 77% had subcortical lesions. Fifteen per cent were border zone infarcts. Thirty-seven per cent had bilateral infarcts. Most (67%) of the hemorrhages were deep ICHs and the rest of the patients had subarachnoid hemorrhage. Of the deep ICHs 33% were intraventricular hemorrhages without an intraparenchymal component. Of all the hemorrhages, 78% had an intraventricular extension. Ten per cent of the patients carried cerebral arterial aneurysms, 4.9% had posterior circulation aneurysms.

Treatment

Twenty-seven patients underwent revascularization surgery. Direct bypass operation was more common than indirect operation (16 vs. 11). Seventy percent of the patients were on antithrombotic

medication. Most of the patients used acetyl salicylic acid (ASA) only, while some had a combination of ASA and dipyridamole, some clopidogrel alone. One patient used warfarin due to atrial fibrillation (Table 2).

DISCUSSION

This study is the first to report on MMV in the Finnish population. There was a higher female predominance found than in the previously reported populations. The diagnosis was done using methods and criteria recommended by the Japanese guidelines and according to internationally accepted clinical practice. The later onset of disease as well as the greater female predominance, postulated to be typical of the Western phenotype, are in line with our results (10).

The incidence and prevalence of MMV in Finland was lower compared to Japan and Korea as expected, and close to the incidence reported in Taiwan and USA (US reports include patients with Asian origin). The female predominance seen in both the adults and children (4.5:1) was higher than previously reported in the Asian (11-15), North American (16,17) or German population (3:1) (9) but close to that reported in another German population (4.25:1) (7). Mean age at the time of the first MMV symptoms was quite the same (37.1 vs. 40.5) in our adult population as in a German population (9), but lower in children (5.7 vs. 11.4) than previously reported. In our population, MMV symptoms were first seen in adulthood, being equal to the German population (9), and in line with the observations of a later manifestation of the disease in European Caucasians. The incidence of unilateral disease in our patient population (23%) was close to that reported by the German group (17%) (9) but twice higher than that of the Japanese (10.6%) (18). Interestingly, most of the patients with unilateral disease were men (57%). Unfortunately, others have not reported gender distribution information on this topic and the small number of our patients with unilateral disease allow the possibility of a chance finding.

There was no familial MMD found in our study population. In the German population only two patients (1.3%) had a family history of MMD (9) whereas in the Japanese population 15% had a

family history of MMD (12). The Finnish population is genetically distinct from other European populations due to founder effect which may explain the lack of familial cases in our study.

Smoking, hypertension, and dyslipidemia were the most common stroke risk factors in our population. Only one-third of the patients had no risk factors which is less than the number reported previously (7). Other co-existing diseases observed in single cases were essential thrombocythemia, Gilbert syndrome, and Crohn's disease. One patient had an atrial septal defect and one had a pituitary adenoma. Essential thrombocythemia has been previously reported in two case reports (19,20), but we could not find previous reports on Gilbert syndrome and Crohn's disease appearing simultaneously with MMV.

The frequencies of ischemic and hemorrhagic strokes in adult MMV patients of our study were closer to the Japanese population than to the German population which is the largest ever-published European study (9). We did not observe ICH in pediatric patients, but ICH occurred in adults more often compared to the German population (15.7% vs. 7.8%). Interestingly, the frequencies of ischemic strokes (47.1%) and hemorrhages (15.7%) in adults were closer to the numbers previously reported in Japan (57.4% and 21%, respectively) (12) than those reported by Germans (82.8% and 7.8%) (9) or Americans (80% and 12%) (16). However, in our population men had more hemorrhages than women which is the opposite compared to Japan (men 19.5%, women 22.2%) (12) though the number of men in our study was quite small. We also report more patients with headaches as the only symptom, compared to the German study.

MMV changes in the posterior circulation were seen rarely in our patient population (13%), far less frequently than in the German population (32%) (9). The difference was particularly great among the pediatric patients (10 vs. 60%). The distributions of ICH, intraventricular hemorrhage, and subarachnoid hemorrhage were the same as in the German population. We observed no arterio-venous malformations. Cerebral aneurysms were observed in 10% of the patients, more frequently than the 3 % reported in the German population and equal to the 10% in the North-Americans. These differences may be merely due to small numbers.

Most of our patients received antithrombotic medication. This may be due to predominance of ischemic events in our patient population. Antiplatelet therapy is commonly applied in Germany as well, while its use is not common in the Asian countries (7,21). Less than half of the patients underwent neurosurgical revascularization procedures which is a lower number than that reported in the German study (7). The most common revascularization methods were superficial temporal artery-middle cerebral artery (STA-MCA) bypass and encephaloduroarteriomyosynangiosis (EDAMS) which are the most frequently employed techniques universally.

All the patients in our study were thoroughly investigated. They represent genetically a rather homogenous population. These aspects can be considered as strengths of this study. The limitation is the small number of patients as there is less MMV in Finland than for instance in Asia. The lack of large series of European patients makes comparisons difficult since the large German study included mainly surgical patients (9) and not at all patients under conservative follow-up.

Our study confirms the postulation of a Western phenotype of MMV, including a later onset of the disease and a greater female predominance. However, it seems that the MMV patient demographics and characteristics of the Finnish population somewhat differ from those of Germany and North America and, in some aspects resemble more the Japanese population.

This is the second relatively large study describing a European subpopulation. In the future, a larger, international survey with substantially more patients would be useful to gain a better overview of the MMV in Europe, especially if the study include detailed information on family members and preferably coupled with genetical data.

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Table 1. Demographic data, disease type, presenting symptoms, and associated diseases.

	All n=61(%)	Children n=10(%)	Adults n=51(%)
Female	50 (82)	8 (80)	42 (82)
Female:male ratio	4.5:1	4:1	4.6:1
Age, time of first symptoms			
Mean	31.5 ± 17.9	5.7 ± 2.1	37.1 ± 14.5
Median	33	5	38
Age, time of diagnosis			
Mean	34.9 ± 17.3	7.9 ± 3.9	40.2 ± 13.5
Median	38	8	41
Type of disease			
MMD	45 (74)	7 (70)	38 (75)
MMD (unilateral)	13 (21)	1 (10)	12 (23)
MMS	3 (4.9)	2 (20)	1 (2.0)
Presenting symptoms			
Ischemic	31 (51)	7 (70)	24 (47)
Hemorrhagic	8 (13)	0	8 (16)
ICH	6 (9.8)	0	6 (12)
SAH	2 (3.3)	0	2 (3.9)
TIA only	4 (6.6)	1 (10)	3 (5.9)
Seizure only	3 (4.9)	0	3 (5.9)
Headache only	7 (11)	0	7 (13)
Asymptomatic	7 (11)	2 (20)	5 (9.8)
Other	1 (1.6)	0	1 (2.0)
Associated syndromes/diseases			
Neurofibromatosis type 1	1	0	1
Down's syndrome	2	2	0

MMD, moyamoya disease; MMS, moyamoya syndrome; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack

Table 2. Summary of the surgical and antithrombotic treatment.

	Total (%)	**Adults**	**Children**
Surgical treatment	27 (44)	17	10
Direct bypass			
STA-MCA	16	16	0
Indirect bypass			
EDAMS	11	1	10
Antithrombotic treatment			
Aspirin	27 (46)	22(43)	5 (50)
Aspirin + Dipyridamole	6 (10)	6 (12)	0
Clopidogrel	7 (12)	5 (10)	2 (20)
Warfarin	1 (2.0)	1 (2.0)	0
None	18 (30)	15(29)	3 (30)

STA-MCA, superficial temporal artery-middle cerebral artery; EDAMS, encephaloduroarteriomyosynangiosis