Faculty of Medicine
University of Helsinki
Finland

MOYAMOYA ANGIOPATHY

A FINNISH PATIENT POPULATION

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DOCTORAL DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of
the University of Helsinki, in Lecture Hall 2,
Biomedicum, on 11 June 2021, at 12 o'clock.

Helsinki 2021

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ISBN 978-951-51-7264-8 (pbk.)
ISBN 978-951-51-7265-5 (PDF)

Unigrafia
Helsinki 2021

ABSTRACT

Moyamoya disease (MMD) and moyamoya syndrome (MMS), referred to as the moyamoya angiopathy (MMA), is a chronic progressive steno-occlusive angiopathy at the distal portions of internal carotid arteries (ICAs) and their proximal branches, with typical collateral artery formation, called the moyamoya vessels. MMS has similar vascular abnormalities as in MMD, but is associated with other conditions such as Down's syndrome or neurofibromatosis I (NFI). MMA is more common in East Asia (e.g. Korea and Japan) than in Western countries. Majority of the MMA studies are done in the Asian populations.

Typically the clinical presentation age of MMA has a bimodal distribution, and peaks both before the age of 14 and later, at the ages 21-59 years. Women are more affected than men, with a ratio varying from 1:1-3:2. Typical presenting symptoms are ischemic or hemorrhagic strokes, transient ischemic attacks, headaches, and epileptic seizures. In East Asian countries familial form of MMD is more common than in the Western countries and a *RNF213* gene has been identified as an important susceptibility gene in East Asian populations.

The underlying mechanisms of MMD are still unknown, despite extensive studies. Intimal hyperplasia, medial layer thinness, and the waving of internal elastic lamina are the representative histo-pathological features found in MMD-affected vessels.

Revascularization surgery is commonly used to treat MMA, although it does not cure the disease, but it can reduce the risk of an ischemic stroke. Antiplatelet therapy is also commonly used to treat the ischemic form of MMA.

For this thesis we collected an MMA database at the Helsinki University Hospital (HUH), including 61 Caucasian patients of Finnish origin treated in the HUH Neurology and Neurosurgery departments between January 1987 and December 2014.

The aim of the first study (I) was to investigate the prevalence of MMA in Finland, and the type of the disease, i.e. the clinical manifestations, and treatments used. The incidence of MMA in the HUH district was 0.14 per 100 000. The prevalence in the HUH district was 2.38 per 100 000 in year 2014. There was a female predominance found (ratio 4.5:1). At the time of the diagnosis, 10 patients were children. The most common clinical manifestations were ischemic stroke (51%), hemorrhagic stroke (13%), and headaches (11%). Twenty-six patients underwent revascularization surgery. Seventy percent of the patients were on antithrombotic medication.

In the second (II) study our aim was to study the long term prognosis of MMA in the Finnish patient population including all 61 patients of the HUH-MMA registry. The mean follow-up period was 9.5 years. Patient-years summed up to 581. Two-thirds of the patients had no new vascular events during the follow-up period. Eight patients had an ischemic and five patients had a hemorrhagic stroke during the follow-up. The average annual rate of a recurrent stroke from the first event for all the study subjects was 3.5%. Two patients died during the follow-up period. Cause of death was intracerebral hemorrhage in both cases. Patients reported significantly poorer physical and psychological health aspects of quality of life when compared to the general Finnish population.

In the third (III) study we performed a follow-up brain MRI and MRA to detect potential radiological changes over time. The mean follow-up time was 64 months between these two MRI/MRA imaging time points and we found new ischemic or hemorrhagic lesions only in one patient. All unilateral cases remained unilateral in the radiological follow-up study including 32 of our registry patients. Ivy sign was observed in 22%, cerebral microbleeds in 6% and white matter lesions in 9% of the patients.

The phenotype of MMD in Finland confirms occurrence of the Western phenotype of the disease, with a disease course rather benign in the Finnish patient population, despite the less common, hemorrhagic form, which has a higher mortality.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Saarela M, Mustanoja S, Pekkola J, Tyni T, Hernesniemi J, Kivipelto L, Tatlisumak T. **Moyamoya vasculopathy - Patient demographics and characteristics in the Finnish population.** Int J Stroke 2017; 12(1): 90-95.

II Savolainen M, Mustanoja S, Pekkola J, Tyni T, Uusitalo AM, Ruotsalainen S, Poutiainen E, Hernesniemi J, Kivipelto L, Tatlisumak T. **Moyamoya angiopathy: long-term follow-up study in a Finnish population.** J Neurol 2019; 266(3): 574-581.

III Savolainen M, Pekkola J, Mustanoja S, Tyni T, Hernesniemi J, Kivipelto L, Tatlisumak T. **Moyamoya angiopathy: radiological follow-up findings in Finnish patients.** J Neurol 2020; 267 (8): 2301-2306.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

ACA	anterior cerebral artery
BI	Barthel index
CT	computed tomography
CTA	computed tomography angiography
DM	diabetes mellitus
DSA	digital subtraction angiography
EC	external carotid
EDAMS	encephalo-duro-arterio-myo-synangiosis
EDAS	encephalo-duro-arterio-synangiosis
HUH	Helsinki University Hospital
IC	internal carotid
ICA	internal carotid artery
ICH	intracerebral hemorrhage
IVH	intraventricular hemorrhage
MCA	middle cerebral artery
MMA	moyamoya angiopathy
MMD	moyamoya disease
MMS	moyamoya syndrome
MMV	moyamoya vasculopathy
MRA	magnetic resonance angiography
mRS	modified Rankin Scale
MRI	magnetic resonance imaging
NF I	neurofibromatosis I
NIHSS	National Institutes of Health Stroke Scale
PCA	posterior cerebral artery
SAH	subarachnoid hemorrhage
STA-MCA	superficial temporal artery to middle cerebral artery
TIA	transient ischemic attack

1 INTRODUCTION

Moyamoya disease (MMD) is a cerebrovascular disease characterized by chronic progressive stenosis of the terminal portion of the internal carotid artery (ICA), or proximal portions of the anterior and/or middle cerebral artery (ACA, MCA) and abnormal vascular networks in the vicinity of the occlusive or stenotic arteries called moyamoya vessels. “Moyamoya” is the Japanese term for “puff of smoke”, which has been used to describe the appearance of these collateral vessels on cerebral angiograms. MMD was first described in Japan in 1957 (1) and was called “moyamoya disease” for the first time by Suzuki and Takaku in 1969 (2). Moyamoya syndrome (MMS) is a similarly appearing vascular abnormality associated with another underlying disease such as Down’s syndrome, neurofibromatosis I (NF I), autoimmune disease, meningitis, head injury or even after head radiation. The terms moyamoya angiopathy (MMA) or vasculopathy (MMV) are used when referred to both MMD and MMS. Previously the diagnostic criteria of definitive MMD required bilateral vascular findings but nowadays also unilateral findings can be diagnosed as MMD.

The clinical manifestations of MMA include ischemic and hemorrhagic strokes, transient ischemic attacks (TIAs), headaches, epilepsy and other symptoms, but the patients can also be asymptomatic. MMA may occur at any age from childhood to adulthood. By-pass surgery is often used for the treatment of MMA, although it is not a cure for the disease, but might reduce the risk of forthcoming ischemic strokes. MMA is more common in East Asian countries, such as Japan and Korea, than in other parts of the world. Majority of the publications concerning MMA are thus done in East Asian populations and the publications concerning western or Caucasian populations are scarse and there are no previous studies in the Finnish population. Many of the Asian studies are concentrated on operated patients. To provide data on MMA in Finland, we established a registry of MMA patients. The Helsinki University Hospital (HUH)-MMA registry consists of all 61 patients treated at the Departments of Neurology and Neurosurgery within the HUH region. In this thesis, the aim was to study prevalence/occurrence of MMA in Finland, clinical manifestations of MMA, treatment of MMA, the long term outcomes and follow-up of the disease, and cognitive function in the Finnish patient population. MMA has not been studied previously in Finland or in a Finnish patient population to this extent.

2 REVIEW OF THE LITERATURE

2.1 DEFINITIONS AND PATHOLOGY

MMD (spontaneous occlusion of the circle of Willis) is a chronic progressive stenosis/occlusion of distal portions of ICA and proximal portions of MCA and ACA, and rarely the posterior cerebral artery (PCA) (2,3). Reduced blood flow in the major vessels of the anterior brain circulation results in compensatory development of collateral vasculature. The collateral vessels near the apex of the carotid are basal collaterals i.e. moyamoya vessels (Figure 1) (2). Also cortical, leptomeningeal collaterals from the external carotid artery (ECA) supplying the dura are seen (4). Formation of moyamoya vessels is thought to be a secondary phenomenon that compensates cerebral ischemia due to primary distal ICA stenosis. Earlier the diagnostic criteria for definitive MMD required bilateral presentation (3) but according to the revised criteria by the Research Committee of MMD of the Japanese Ministry of Health, Labor, and Welfare in 2015 also unilateral presentation of the disease is included (5).

MMS (A.k.a. Quasi-moyamoya) refers to same-looking vascular changes in brain vasculature associated with an underlying disease. The diseases reported to be associated with moyamoya-like changes include intracranial atherosclerosis, autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome, periarteritis nodosa, and Sjögrens syndrome), meningitis, brain tumors, NF I, head radiation, Down's syndrome, head trauma, sickle cell disease, hyperthyroidism, stenocephaly, Turner's syndrome, Alagille syndrome, William's syndrome, Noonan's syndrome, Marfan's syndrome, tuberous sclerosis, Hirschprungs disease, glycogen storage disease type 1, Prader-Willi syndrome, Wilms tumor, primary oxalosis, Fanconi's anemia, spherocytosis, eosinophilic granuloma, type II plasminogen deficiency, leptospirosis, pyruvate kinase deficiency, protein C deficiency, fibromuscular hyperplasia, osteogenesis imperfecta, polycystic kidney, and illicit drug poisoning (cocaine)(3).

The mechanisms of MMD are still unknown despite extensive studies. Histopathological studies of affected ICA segments in MMD demonstrate eccentric fibrocellular thickening of the intima, increased number of smooth muscle cells (SMCs), prominently tortuous and often duplicated internal elastic lamina, and medial thinness with no inflammatory cell or macrophage invasion or atheromatous lipid pool (6,7). Vessel occlusion results from

excessive accumulation of SMCs and thrombosis in the lumen. The neuroimaging studies have also demonstrated a constrictive remodeling e.g. the narrowing of the arterial outer diameter in affected segments (8-11). The role of many cytokines including vascular endothelial growth factors has been studied but it is known that these cytokines fluctuate and it is not known if the cytokine abnormalities are just a result of ischemia and not the cause of MMD (12).

The moyamoya vessels are dilated perforating arteries displaying thinned media with fibrin deposition in the vessel walls, fragmented elastic laminae, and the formation of microaneurysms. It is hypothesized that arterial stenosis or occlusion causes hypoxia, which induces formation of collateral vessels (6,13). It is believed that these abnormal and fragile vessels are the cause of intracerebral hemorrhage (ICH) in MMA.

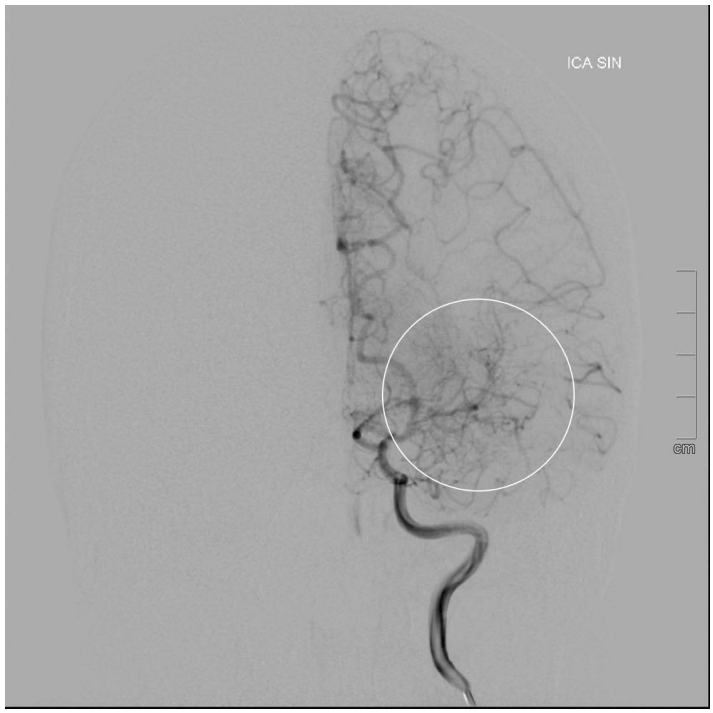

Figure 1. Left side ICA in DSA image showing the basal collaterals i.e. ”puff of smoke” circled.

2.1.1 GENETICS

Approximately 10% - 14.9% of MMD patients exhibit a familial occurrence in East Asian countries (14-16). Also racial differences in susceptibility to MMD suggest a role of genetic factors. In Asia the genetic factors may play even a bigger role than in Western countries. In European populations Germans have reported 5.7% and Italians 12% of familial occurrence (17,18). Several genetic loci have been identified in linkage studies in familial MMD. The strongest susceptibility gene associated to MMD is the Ring Finger 213 (*RNF213*) gene. The p.R4810K (c.14576G>A) variant of the *RNF213* gene was identified in 95% of patients with familial MMD, 73% with sporadic MMD, and 1.4% of control subjects in the Japanese population (19,20). Also other variants of the *RNF213* gene have been described (20,21) in Caucasian and East and South Asian patients, but in a small GWAS study done in Europeans (Germans and Czechs) no major founder variant was found nor the *RNF213* p.R4810K (c.14576G>A) variant (22). The mode of inheritance in Japanese families with familial MMD is autosomal dominant with incomplete penetrance (23). The exact biological function of *RNF213* is unknown.

MMS has been described in many chromosomal disorders and Mendelian diseases, with causative genes already identified such as NFI (17q11.2) gene in NF I, HBB (11p15.5) gene in sickle cell disease, and others e.g. Alagille syndrome and Noonan syndrome with many related genes identified, and Down's syndrome caused by the trisomy of chromosome 21 (24). Recently also new mutations causing MMS have been discovered, e.g. resessive X-linked syndrome due to loss of expression of BRCC3/MTCP1 genes resulting in bilateral MMS, short stature, hypergonadotropic hypogonadism, stereotyped facial dysmorphism, and heart involvement (25,26). Penetrance of MMA among these different inherited MMS is highly variable.

2.2 EPIDEMIOLOGY

2.2.1 ASIA

MMD has the highest prevalence in East Asian countries, such as Japan and Korea. The incidence and prevalence numbers are presented in Tables 1 and 2. MMD affects more often females than males, and there is variation in the female-to-male ratios between populations, see Tables 1 and 2. Also typical to the disease is a bimodal age distribution, one peak in childhood and the other in early middle-age, see Table 1.

Table 1. Incidences and prevalences of MMD in East Asian countries

Study	Country (n)	Incidence/ 100,000 person years	Prevalence/ 100,000 person years	F:M	Age peak 1	Age peak 2
Wakai 1997(14)	Japan (1176)	0.35	3.16	1.8:1	10-14	40-49
Baba 2007(27)	Japan (267)	0.94	10.5	2.2:1	5-9	45-49
Hoshino 2012(15)	Japan (941)	0.54	6.03	2.0:1	5-9	40
Ahn 2014(28)	Korea (8154)	2.3	16.1	1.8:1	5-14	45-54
Yim 2012(29)	Korea (4517)	1.0	9.1	1:9:1	10-19	40-49
Miao 2010(30)	China (202)	0.43	3.92	1.1:1	5-9	35-45
Chen 2014(31)	Taiwan (422)	0.15	1.16	1.7:1	5-14	40-44

F: female, M: male, n: number of patients

2.2.2 EUROPE AND WESTERN COUNTRIES

In the Western countries, mainly in Europe and the USA, the incidence and prevalence is much lower than in Asian countries. There are only three national studies published in Europe; one in Italy (17) and two recently published, from Denmark (32) and Ireland (33). Other studies concerning the prevalence and incidence in the USA and Germany are not nationwide. As in the Asian countries, a bimodal age distribution with peaks in the first and fourth decade of life is observed, with adults more commonly affected. Female predominance is reported to be higher in Europe than in the East Asian populations (Table 2). There are no previous studies of MMA incidence or prevalence in Finland, or other European countries besides Denmark (32) and Ireland (33).

Table 2 Incidences and prevalences of MMD in Western countries

Study	Country (number of patients)	Incidence/ 100,000 person years	Prevalence/ 100,000 person years	F:M	Age peak 1	Age peak 2
Uchino 2005(34)	USA† (298)	0.086	3.16	2.2:1	5-9	55-59
Starke 2012(35)	USA* (2280)	0.57	10.5	2.6:1	NA	NA
Acker 2015(36)	Germany (153)	NA	NA	2.9:1	11-18	40-49
Kraemer 2019(18)	Germany (185)	NA	NA	3.2:1	5-9	NA
Birkeland 2018(32)	Denmark (56)	0.047	1.16	2:1	4-14	40-44
Doherty 2020(33)	Ireland (16)	0.04	0.33	1.7:1	first decade	fifth decade

†Washington state and California

*49% white race, NA: not available

2.3 DIAGNOSIS

No international guidelines on MMA diagnostics have been published yet. There are two national guidelines concerning MMA; the Japanese guidelines and the French guidelines (3,37). The golden standard for diagnosing MMA is digital subtraction angiography (DSA), but because it is an invasive method, magnetic resonance angiography (MRA) is also used to diagnose MMA. Computed tomography angiography (CTA) may also reveal the moyamoya vessels and occlusions. Perfusion imaging is used to estimate hypoperfusion when bypass operation is being considered.

2.3.1 RADIOLOGICAL CLASSIFICATION OF THE DISEASE

Suzuki and Takauku described the staging system for MMD in 1969 and it is still largely utilized (2). The staging is based on DSA findings and includes six

stages. In stage I narrowed ICA bifurcation is seen. Stage II includes dilated ACA, MCA and narrowed ICA bifurcation and moyamoya vessels begin to develop in the base of the brain. In stage III moyamoya vessels become more prominent as ICA, ACA and MCA become severely stenotic or occluded. In stage IV the transdural collaterals from ECA develop. In stage V moyamoya vessels are diminishing with occlusion of ICA, ACA, and MCA, and ECA collaterals are more intense. In stage VI ICA is essentially disappeared with blood supply to the brain arriving from ECA. However, a stepwise progression from stage I through stage VI has been observed in only a limited number of patients (38) and this angiographic staging does not represent the severity of MMD, rather it indicates an intrinsic compensatory reorganization process (internal to external carotid conversion).

Houkin et al. established a MRA-grading system for MMD (39). In this grading system ICA and MCA are graded from 0 to 3 (0=normal, 3=invisible) and ACA and PCA from 0 to 2 (0=normal, 2=invisible). The MRA score is the total points from four main cerebral arteries (minimum=0 and highest=10). The MRA score is classified into four grades (MRA score 0-1, grade 1; 2-4, grade 2; 5-7 grade 3; and 8-10, grade 4).

2.3.2 DIAGNOSTIC CRITERIA

According to the Guidelines for Diagnosis and Treatment of Moyamoya Disease, the diagnosis requires stenosis or occlusion of the terminal portion of the ICA or proximal portions of the ACA and/or the MCA, and abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase on DSA (3).

DSA can be omitted if an MRA shows stenosis or occlusion of the terminal portion of the ICA or proximal portions of the ACA and/or the MCA, and abnormal vascular networks in the basal ganglia, and if the findings are bilateral (3,5). Previously only bilateral disease was considered as definitive MMD, but recently the Research Committee of MMD of the Japanese Ministry of Health, Labour, and Welfare (statement 2015) revised the diagnostic criteria to include both bilateral and unilateral presentation of terminal ICA stenosis with an abnormal vascular network at the base of the brain (38).

2.3.3 RADIOLOGICAL FINDINGS

Besides strokes, ivy sign, cerebral microbleeds (CMBs) and white matter lesions (WMLs) can be seen in the brain parenchyma of a MMA patient. Also intracranial aneurysms are reported approximately in 14% of the patients (40). Ivy sign refers to the appearance of the brain on post-contrast T1-weighted images or FLAIR images where prominent leptomeningeal collaterals with slow blood flow and profuse contrast enhancement appear as if the brain is covered with ivy (Figure 2.) (41). Occurrence of ivy sign has been reported to be quite common in Asian populations with MMD (42,43). It has been suggested that the ivy sign indicates decreased cerebral vascular reserve in MMD (44), although more recent studies showed no relationship between the collaterals on DSA and ivy sign (45). The pathophysiology of ivy sign and its clinical significance is so far unresolved.

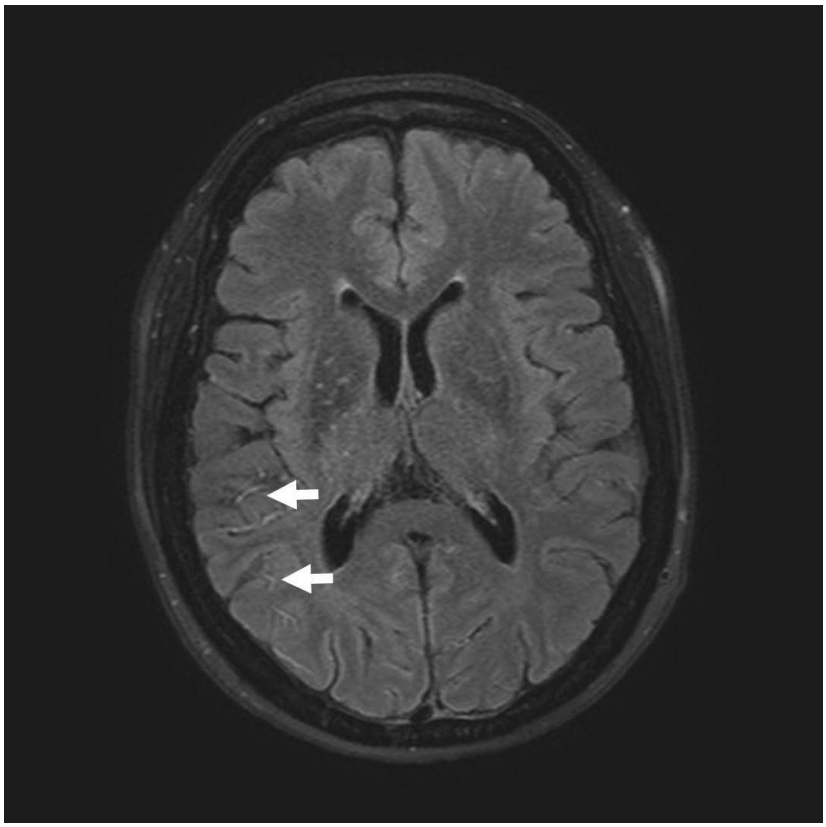

Figure 2. Ivy-sign (arrows) in a brain MRI-image.

Ishikawa described occurrence on CMBs in MMD (46). Incidence of CMBs is found to be high especially in the hemorrhagic onset-type MMD and a meta-analysis indicated that they may be an important factor for hemorrhagic stroke risk (47). CMBs can be detected using T2*-weighted imaging and/or susceptibility-weighted imaging. In Asian populations CMBs have been reported in 28.2-51.9% of the patients (47-49). In a German population CMBs were present in 12.9% of the patients (n=101) (50). Another German study found no CMBs after STA-MCA bypass surgery during a mean follow-up of 38.2 months (51).

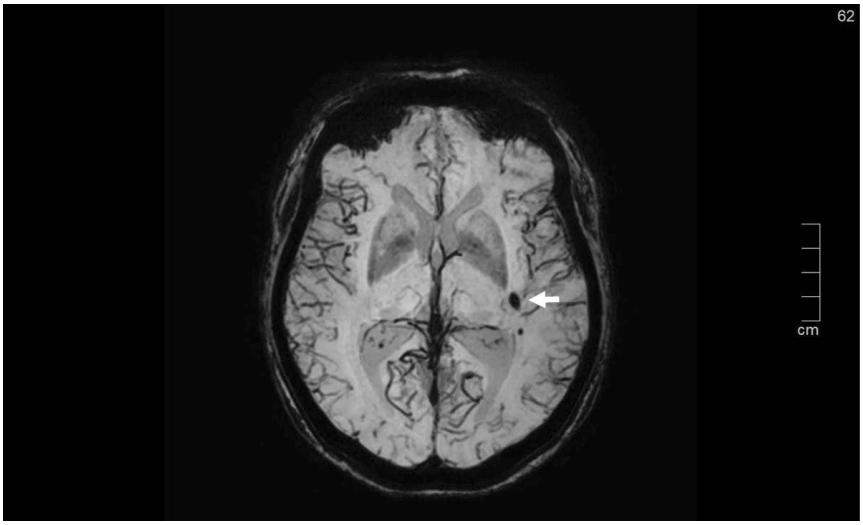

Figure 3. Cerebral microbleeds (largest marked with arrow) in a brain MRI-image (SWI).

WMLs are considered to be a consequence of small vessel disease and are located in subcortical structures of the brain (Figure 4). Ischemic injury due to chronic hypoperfusion causes axonal destruction and glial proliferation resulting to WMLs (52). MMD patients had more widespread WMLs than controls and the symptomatic side of the brain was more affected (53). In a small patient population (n=21) WML volume decreased after revascularization surgery (53). Japanese researchers have reported WMLs in 57/100 hemispheres in their patient population (54). Occurrence of WMLs in European populations has not been reported in detail.

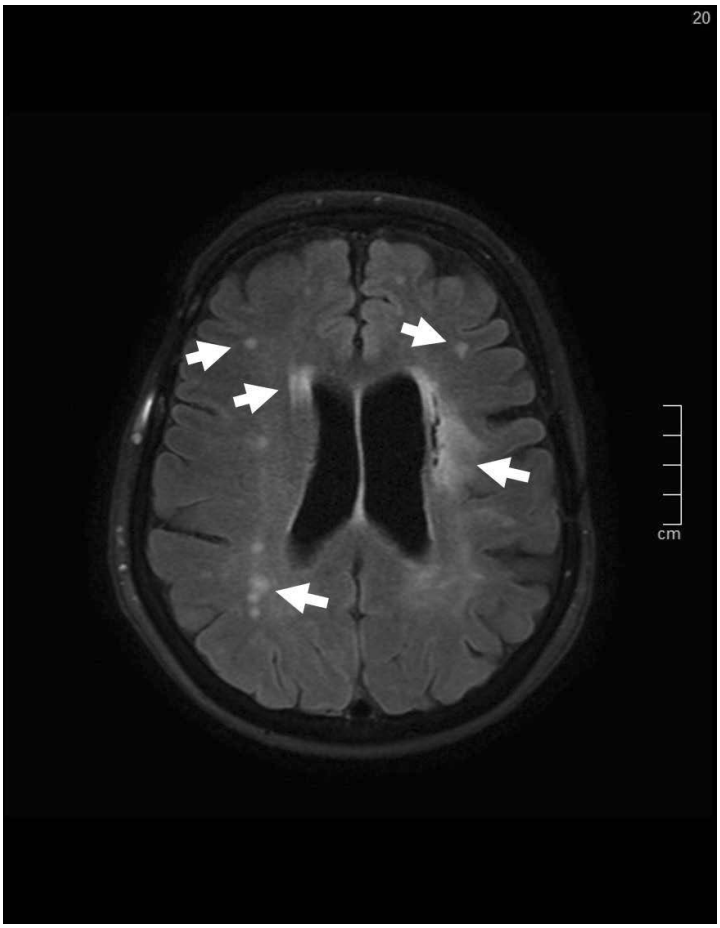

Figure 4. White matter lesions (some marked with arrow) in a brain MRI.

2.4 CLINICAL FEATURES

There are two major categories of symptoms in MMA; those due to a stroke and those due to compensatory mechanisms responding to the ischemia. Due to arterial stenosis and occlusion, MMA patients are prone to TIA and ischemic stroke. At the same time, the abnormal pathology of moyamoya vessels cause increased risk of intracranial bleeding. Symptoms also include epileptic seizures, movement disorders, cognitive decline, and headaches. Due to increased use of MRI, asymptomatic cases are also sporadically found.

Ischemic events are the most common clinical manifestation of MMA (3,16,36). Ischemic manifestations include TIA and repeated TIAs, and ischemic stroke. Stroke subtypes seen in MMA include hemodynamic infarct,

perforator infarct, and less often large-artery infarct (38). In children, the disease manifests most commonly/initially with cerebral ischemic symptoms (35,55,56). In Europe ischemic symptoms are more common than hemorrhagic symptoms in adults (17,36,57). Anterior circulation is more affected than posterior circulation (58). Ischemic events, especially TIA, can be triggered by hyperventilation due to physical or intellectual activity, dehydration, fever, and crying in babies (59,60). It is presumed that in this pathognomonic phenomenon the decrease in the partial pressure of carbon dioxide results in vasoconstriction in the already maximally dilated cortical vessels due to chronic ischemia and in reduced cerebral perfusion (61).

Intracranial hemorrhages seen in MMA include deep and lobar ICH, intraventricular hemorrhage (IVH), and subarachnoid hemorrhage (SAH). The hemorrhages usually occur in the anterior circulation (38) and IVH occurs more commonly than in hypertensive hemorrhage (62). Re-bleeding rates are higher in MMD patients with posterior hemorrhage (63). Primary IVH is associated with a prominent ipsilateral anterior choroidal artery (64). In pediatric patients intracranial bleeding is rarer than in adults (55,65). It is more common in Asian adult MMA patients that the disease manifests with intracranial hemorrhage than in Western populations (3,16-18,34-36,66-68).

Epileptic seizures are reported in 5% of patients, secondary to an ischemic lesion or hypoperfusion, usually starting in childhood (38). Movement disorders are uncommon symptoms of MMD and more commonly seen in children. Chorea, dystonia, and dyskinesias or a mix of these movement disorders have been described (69,70). Movement disorders might be precipitated by hyperventilation or emotional stress. In most patients the symptoms improved regardless of treatment (69).

Headache is a frequent presenting symptom in MMA patients, and it can either improve or develop after bypass surgery. It has been suggested that dilatation of meningeal and leptomeningeal collateral vessels may stimulate dural nociceptors, but the precise mechanism is not yet fully understood (71). The headache is typically migraine-like or a tension-type headache, and refractory to medical therapy.

Chronic hypoperfusion, white matter disease and strokes may cause cognitive impairment in MMA patients (72-75). The studies concerning adult MMA patients' cognition utilized varying methodologies, had small patient numbers, included few Caucasian patients, and lacked control groups (76-78). In a recent meta-analysis, including 17 studies (11 in children, 6 in adults), the median percentage with impaired cognition was around 30%, in children and adults (79). Majority of the studies in children are done in Asian cohorts. Information on specific domains of cognitive function is limited. In children, mostly modest impairments in memory and processing speed have been

observed. In adults, modest to large impairments across various cognitive domains have been observed (79). There are no prospective studies on the effect of surgical treatment on cognition.

2.5 TREATMENT

2.5.1 SURGICAL TREATMENT

MMD has an intrinsic nature to convert the blood supply for the brain from the internal carotid (IC) system to the external carotid (EC) system. The main objective of surgical revascularization is to reduce the risk of ischemic events by increasing cerebral blood flow within hypoperfused brain regions (3). This can be done by direct or indirect bypass operation or by a combination of the two operations (3,80). Direct revascularization procedures for MMA include superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis (81). Indirect procedures consist of laying a tissue vascularized by branches of ECA such as dura mater, galea, temporal muscle or ECA branches in contact with the brain in order to promote the development of neovascularization in hypoperfused areas (encephalosynangiogenesis)(82-85). Indirect procedures include pial synangiosis such as encephalo-myo-synangiosis, encephalo-duro-arterio-synangiosis, encephalo-duro-arterio-myo-synangiosis (EDAMS), encephalo-arterio-synangiosis, encephalo-duro-synangiosis, and multiple burr hole surgery (80). These techniques can be used separately or in combination. In STA-MCA operation only one hemisphere is allowed to be treated at a given time, having an immediate effect on cerebral blood flow. Indirect revascularization techniques are preferred in children because of the smaller size of STA. Indirect bypass begins to alter the cerebral blood flow only after angiogenesis has taken place, and it may take a few months to a year (85). Perioperative complications include infarction or cerebral hemorrhage with a frequency varying between 3-13% (56,86-88). Several imaging techniques are used to evaluate the patency of intracranial anastomosis including noninvasive (transcranial Doppler, MRA, and CTA) and invasive techniques (DSA). In a study including 132 MMD patients, three bypasses were occluded, resulting in an overall cumulative patency rate of 98%. All of the three occlusions occurred within one week of revascularization and were clinically asymptomatic (89). In another smaller study (n=10) only one MMD patient had a delayed occlusion of a STA-MCA bypass after 12 months (90).

According to the 2012 Japanese guidelines, surgical revascularization is effective for MMD manifesting as ischemic MMD, and can be considered for patients with hemorrhagic MMD, despite the fact that the adequate scientific evidence is still lacking for the latter group (3).

Japan Adult Moyamoya (JAM) trial is unique in being a randomized controlled trial. It was published in 2014 (n=80), and examined the efficacy of direct EC-IC bypass for hemorrhagic MMD. The patients were followed-up for 5 years. The primary end points were recurrent bleeding, stroke causing significant morbidity, significant morbidity or mortality from other medical cause, or requirement for bypass surgery due to progressive ischemic stroke or crescendo TIAs. The primary end point was observed in 14.3% in the surgical group and 34.2% in the nonsurgical group. The difference was significant using the Kaplan Meyer's cumulative curve analysis for the main criterion (p=0.048) but not when using the Cox regression model (91).

The French guidelines from 2018 conform the Japanese guidelines and underline that no randomized study has been published for the surgical treatment of ischemic forms of MMA and the non-randomized, mostly retrospective studies do not provide an answer about the superiority of surgical treatment over conservative treatment, although those studies demonstrate a significant reduction of ischemic cerebral events and thereby consider that indications for surgery are based more on consensus of experts rather than a high level of evidence (37). The French guidelines recommend that the indication of surgery should be discussed on a case-by-case basis, using a multidisciplinary approach and that revascularization should be discussed after a TIA or an ischemic stroke with impaired cerebral perfusion, in both children and adults. In a case with hemorrhage it is recommended to further look for a possible arterial aneurysm on DSA, and to go through all the possible treatment modalities, including considering revascularization in a second step (37).

The American Heart Association recommended in 2008 that surgical revascularization is recommended in case of persistent cerebral ischemia or alteration of cerebral hemodynamics in children with MMA and stroke (92).

In a meta-analysis of surgical outcomes of symptomatic MMD in adults, bypass surgery was found to significantly decrease future stroke events compared with conservative treatments (OR 0.301, $p< 0.001$). Direct bypass showed better future stroke prevention than indirect bypass (OR 0.494, p=0.028). There were no meaningful differences in perioperative complications between direct and indirect bypass (OR 0.665, p=0.176). Direct

bypass was associated with better angiographic outcomes than indirect bypass (OR 6.832, p<0.001) (93).

A meta-analysis of hemorrhagic MMD revealed that surgical revascularization was superior to conservative treatment in decreasing the rate of recurrent stroke (OR 0.39, 95% confidence interval (CI), 0.24-0.65) including ischemic stroke and hemorrhagic stroke, but not in reducing mortality (OR 0.53, 95% CI, 0.24-1.17) (94).

A meta-analysis on the efficacy of surgical treatment for the secondary prevention of stroke in symptomatic MMD surgical treatment significantly reduced the risk of stroke (OR 0.17, 95% CI, 0.12-0.26, p<0.01). A subgroup analysis revealed that it was more beneficial to hemorrhagic MMD (OR 0.23, 95% CI, 0.15-0.38, p<0.01) than for ischemic MMD (OR 0.45, 95% CI, 0.15-1.29, p=0.14) (95).

In a Chinese study with MMD patients at a late Suzuki stage no statistical difference was observed between conservatively and surgically treated patients in reducing the stroke risk (n=82, average follow-up 55 months) (96). In a Japanese study with 26 patients undergoing revascularization surgery and followed-up for 11 years there was an annual hemorrhagic rate of 1.14%. Re-bleeding was associated with posterior cerebral involvement, cerebral aneurysm, microbleeds, and post-operative periventricular anastomosis (97).

In a Japanese 10-year follow-up study, 261 patients underwent surgery and 83 patients were treated conservatively. All patients had TIA or cerebral infarction as an initial symptom, and the estimated recurrent rate of cerebral infarction was 1.8±0.9%/5 years in the surgery group and 3.8±2.2%/5 years in the non-surgery group. In contrast, the rate of cerebral hemorrhage, as well as that of total stroke (hemorrhage and infarction), was not reduced by surgery. The same study followed-up patients whose initial symptom was hemorrhage, including 42 operated patients and 59 conservatively treated patients. There was no statistically significant difference in the recurrence rate of cerebral hemorrhage between these two groups. The estimated rate of cerebral hemorrhage was 9.2±4.0%/ 5 years in the non surgery group and 13.0±5.5%/ 5 years in the surgery group (98).

2.5.2 MEDICAL TREATMENT

2.5.2.1 Acute phase

Intravenous tissue plasminogen activator therapy is not recommended for treatment of ischemic stroke caused by MMA or occurring in patients harboring MMA changes (3). Endovascular reperfusion therapy and intracranial stenting are, in addition, typically avoided mainly due to lack of evidence (99). Fever and blood pressure are treated as usual during the acute stroke. Oxygen supplementation and prophylactic administration of antiulcer agents are used when needed.

2.5.2.2 Preventive treatment in chronic phase

There is no consensus statement for the treatment with antithrombotic medication after a stroke, and there is insufficient evidence, but it is used rather universally (100). In French guidelines antiplatelet therapy (aspirin in first intention) is recommended after ischemic manifestations and in the absence of cerebral hemorrhage. Also, the Japanese guidelines recommend antithrombotic therapy for ischemic manifestations but not for asymptomatic MMD. In a ten-year follow-up study (n=735) done by the Research Committee on Moyamoya Disease in Japan, surgery and antiplatelet therapy were compared and the result showed that the rate of cerebral infarction was not significantly different between the antiplatelet subgroup and the non-antiplatelet subgroup, whereas the rate of cerebral hemorrhage was higher in the non-antiplatelet subgroup than in the antiplatelet subgroup (98). A Japanese nationwide survey on the trends of antiplatelet therapy for MMD in Japan showed that regarding ischemic stroke numerous departments (218/389) considered the use of antiplatelet drugs (APDs) “in principle” after surgery for a certain period (74 departments), and regarding asymptomatic MMD majority of departments (256) reported no use of APDs “in principle”. Aspirin was the most commonly used APD followed by cilostazol and clopidogrel (101). The usual vascular stroke risk factors are treated. If a patient has epileptic seizures, antiepileptic drugs are introduced. Headache is treated with analgesics with the exception of vasoconstrictor drugs. When oral contraception is considered, progesterone-only pills may be used according to the French guidelines (37).

2.5.3 FOLLOW-UP

The French guidelines recommend the follow-up imaging to be adapted on a case-by-case basis according to the clinical and radiological evolution of the patient (at least once a year during the first years) (37). The Japanese Guidelines do not give any specific recommendations of follow-up (3).

2.6 NATURAL COURSE AND PROGNOSIS

The natural course of MMA is not well known. It is known that the disease progression can be slow, with rare, intermittent events, or fulminant, with rapid neurologic deterioration. Limitations in the studies including non-operated cases are small sample sizes, not standardized clinical and imaging outcomes, and limited follow-up duration (102-107).

2.6.1 ASYMPTOMATIC INDIVIDUALS

A Japanese study analyzed 33 asymptomatic MMD individuals and found that four patients developed TIA and two died due to ICH in a 3.7 years average follow-up time (102). Another smaller Japanese study followed 10 asymptomatic patients with a mean period of 4.1 years and found that one patient developed an ischemic stroke (103). In a multi-center, nation-wide survey in Japan with 34 asymptomatic patients, 7 developed cerebrovascular events and the annual risk of any stroke was 3.2% during a mean follow-up period of 43.7 months, and 3 patients developed silent radiological changes including cerebral infarction, microbleed, and disease progression (107). In a Korean study including 42 asymptomatic adult MMD patients, with a mean follow-up period of 37.3 months, progression was found in 12 patients. Symptomatic progression was found in four patients and eight patients showed asymptomatic radiological progression. Of these eight, six had reduced cerebrovascular reserve capacity, detected with single photon emission computed tomography and one had a silent cerebral infarction and one had a focal microbleeding (104). In another Korean study, 40 asymptomatic adult individuals were followed clinically during a median of 32 months and three patients developed TIAs. In the same study during a median 24 month radiological follow-up, 3 patients displayed angiographic progression and 3 displayed new hemodynamic abnormalities, but none had ischemic or hemorrhagic stroke (105). In a third Korean study with 35 asymptomatic patients, the risk of hemorrhagic stroke was found to be higher

than the risk of ischemic stroke (2.5% vas. 0.8%) (106,108). In European populations there are no systemic studies or reports of asymptomatic individuals.

2.6.2 SYMPTOMATIC PATIENTS

In a Korean study (n=241, three groups: initial ischemic stroke, initial hemorrhagic stroke, and asymptomatic group) it was found that the annual risk of stroke was 4.5%/person year, and the 5- and 10-year cumulative risks of any stroke were 17% and 30%, respectively. Patients with hemorrhagic presentation tended to show a higher incidence of recurrent hemorrhage and patients with ischemic symptoms demonstrated a higher rate of recurrent ischemia than the hemorrhagic or asymptomatic groups. The 5- and 10-year risks of hemorrhagic stroke were 10% and 19%, respectively, and risks of ischemic stroke were 9% and 20%, respectively. By group, the 5- and 10-year risks of any stroke were 15% and 40% in the hemorrhagic group, 17% and 33% in the ischemic group, and 15% and 25% in the asymptomatic group, respectively (106,109).

In another Korean study with 59 adult MMD patients presenting with ischemic stroke or TIA the Kaplan-Meier estimate of ischemic stroke recurrence was 1.6% in the first year and equaled to 11.8% at the end of 5 years (108).

In a Korean study including 176 adult MMD patients presenting with hemorrhage, followed-up for a mean time of 83 months, the overall annual rate of recurrent hemorrhage was 3.4%/patient-year during 5 years after the initial episode of hemorrhage. The affected hemisphere showed a higher recurrent hemorrhagic rate. The presence of IVH and bilateral MMD had a marginal significance for recurrent hemorrhage. They also identified eight ischemic strokes including 4 postoperative infarctions, and all ischemic strokes were minor strokes (109).

In a French study, 90 MMA patients with no history of revascularization surgery were followed-up for a median time of 42.8 months. Ten strokes occured in 8 of these patients (9%) of which half were ischemic and half hemorrhagic. TIAs were reported by 14 patients (16%). Eighteen incident ischemic and hemorrhagic lesions were detected on MRI in 10 and 7 cases, respectively. At the end of the follow-up period 15 patients (17%) had a stroke, evidence of ischemic or hemorrhagic lesion on MRI, or had died due to ICH (3 patients), accounting to a total of 31 events (110). In this study 60% of the patients were of European ethnic origin, 13 % Asian, and 22% of African origin.

They found 3 predictors of clinical deterioration: Asian origin, history of TIA, and reduced cerebrovascular reserve (CVR) on SPECT imaging. Patients with none of these 3 predictors had an annual risk of stroke or cerebrovascular lesion of 0.5%. This risk was more than doubled for patients of Asian origin or those with history of TIAs, and was increased 10-fold when CVR was reduced. When all 3 predictors were present, the annual risk was greater than 20% per year (110).

A Japanese study included 1146 patients where the patients were divided according to disease type (ischemic or hemorrhagic) and duration (disease duration less than 10 years, and 10 years and more, recent and remote group, respectively). They found that in the cases in which the initial event was TIA or ischemic stroke, the stroke recurrence rate in 10 years was 3.8% in the recent group and 2.4% in the remote group. In cases in which the initial event was ICH, the stroke recurrence rate in 10 years was 25.7% in the recent group and 10.9% in the remote group. They concluded that patients with recent disease onset had a statistically higher risk of recurrent stroke. The mean follow-up time was 5.2 ±2.9 years in the recent group, and 8.1±2.1 in the remote onset group (65).

2.6.3 UNILATERAL TO BILATERAL

In a Japanese study, 17/64 of unilateral MMD progressed to bilateral disease during a period of 1-7 years after the diagnosis. In this study children or young adults tended to develop bilateral disease within 1-5 years (111). The reported progression from unilateral MMD to bilateral disease ranged from 11% to 39 % during a follow-up period ranging from one to 5 years in adults (112-114). In a Korean study, including 410 children with MMD, 24/53 (45%) of the unilateral cases progressed to bilateral within a mean of 23 months follow-up time (56). It seems that the progression to bilateral disease is more common in children, ranging from 18% to 59% (56,115,116), and it tends to happen within 1-3 years after the diagnosis in children under 10 years of age (111,116,117).

3 AIMS OF THE STUDY

To investigate the prevalence of MMA in Finland, the type of the disease, clinical manifestations, and treatments given (Study I).

To study long-term prognosis of MMA in the Finnish patient population (Study II).

To perform a follow-up brain MRI and MRA study to detect potential changes over time (Study III).

4 PATIENTS AND METHODS

4.1 DATA COLLECTION

The studies were performed at the Departments of Neurology and Neurosurgery, HUH, Helsinki, Finland. The studies included all the MMA patients treated in the HUH region between January 1987 and December 2014. HUH Neurosurgery is the only center in Finland where extracranial-intracranial bypass surgery is performed meaning we could include all the operated patients in Finland. Also most of the conservatively treated patients are referred to HUH Neurology for specialist-level consultation.

The local Ethics committee approved the studies (154/13/03/00/10). The patients who came for an outpatient clinical follow-up visit gave a written consent.

The patients 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. The diagnosis was done using methods and criteria recommended by the Japanese guidelines (3).

Each patient's diagnosis was first reviewed by a neurologist (MS), then discussed with a neuroradiologist (JP), a neurosurgeon (LK), and finally with a 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 year 2014 and in year 2015 at the neurological outpatient department and/or by reviewing the patients' hospital charts. A detailed family history was obtained for each patient.

A detailed database included the patients' medical history, family history of stroke and MMA, 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, mRS), 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 ICH, lesion sites, and vessel abnormalities. The baseline stroke risk factors including smoking, dyslipidemia, hypertension, diabetes, and family history of stroke, were documented. All data were inserted into an Excel-based electronic database.

4.1.1 STUDY I

Publication I included all patients included in the registry. A total of 61 Caucasian patients of Finnish origin were identified. Fifty-five of those participated in a dedicated face-to-face clinical evaluation. Two patients had died before being contacted and four patients did not wish to participate in the face-to-face clinical evaluation, and their data were collected by reviewing the patients' hospital charts.

4.1.2 STUDY II

Publication II included the same patients as in publication I. It was a cross-sectional clinical follow-up study including quality of life and profile of mood. The follow-up period started after the patient had visited the hospital for the first time due to the MMA-related symptoms and ended at the end of September 2015 when the hospital charts were last checked.

The clinical examination at the follow-up visit included the NIHSS score, mRS, and Barthel Index (BI). Working status was recorded. Any new stroke, any other new diagnosis after the MMA diagnosis, medication, surgical operations, and perioperational complications were recorded, based on the interview and the medical records.

We defined progression of the disease as a new ischemic or hemorrhagic stroke after the primary hospital admission or any worsening in a stenotic vessel according to visual examination of the angiography images and development of stenosis in a vessel that was normal-looking in the previous images. Favorable outcome was defined as mRS 0-2 and an excellent outcome as mRS 0-1.

Questionnaires concerning quality of life and the profile of mood were sent to the patients by mail. The patients returned the filled questionnaires at the beginning of the comprehensive neuropsychological examination. The questionnaires were checked after the enquiry and completed together with the patient if there were missing items. A psychologist, familiar with the neuropsychological assessment procedure, conducted all neuropsychological examinations and she was blinded to the current clinical neurological and neuroradiological data.

Quality of life was evaluated with WHOQOL-BREF (118). WHOQOL-BREF includes 26 items and four domains: physical health, psychological health, social relationships, and environment (119). The items are computed to four

separate domains and separately scaled from 0-100, where 0 is the worst possible score and 100 the best. The questionnaire also includes questions of perceived health in general (how satisfied are you with your health?) and quality of life in general (how would you rate your quality of life?). The questionnaire has a 5-point Likert-scale (1=very poor to 5=very good). Perceived quality of life in MMA patients was compared to a Finnish population based sample survey (120).

Mood state was evaluated by using the Modified Profile of Mood States (POMS) questionnaire (121,122). We used a total score of the modified version of the POMS that includes 38 adjectives rated on a 5-point Likert scale (0=not at all to 4=very much). Patients were asked to circle adjectives which describe feelings and emotions during their previous week. The characteristics of the controls of a previous Finnish study (123) were used to determine a cut-off point for elevated mood in our MMA patients. The elevated mood was determined as POMS score higher than 41.4 (i.e. 75 percentile of the control group, unpublished data).

4.1.3 STUDY III

Publication III included the patients from the registry living in the HUH catchment area (n=32). They were called for follow-up imaging. Imaging included brain MRI and head and cervical MRA imaging with a 3.0 Tesla scanner (Philips Achieva, Best, the Netherlands). The imaging sequences included T1-weighted and T2-weighted 3D-sequences with isotropic acquisition in sagittal plane, axial FLAIR sequence (slice thickness 4 mm), axial diffusion-weighted sequence (slice thickness 4 mm, spacing 5 mm), axial susceptibility-weighted sequence (thickness 1 mm, spacing 0.5 mm), time-of flight MRA of the cerebral arteries, and flow-based MRA of the cervical arteries. For the patients with extracranial-intracranial bypasses, the cerebral artery time of flight MRA was performed also with gadolinium contrast agent (Dotarem 279.3 mg/ml, Guerbet, France).

We used the MRA grading described by Houkin et al. to evaluate the progress of the disease (39). Both hemispheres were evaluated separately. In the grading systems ICA and MCA were graded from 0 to 3 (0=normal, 3=invisible) and ACA and PCA from 0 to 2 (0=normal, 2=invisible). The MRA score is the total points from four main cerebral arteries (minimum 0 and highest 10). The MRA score was classified into four grades (MRA score 0-1, grade 1; 2-4, grade 2; 5-7 grade 3; and 8-10, grade 4) (39). We also evaluated the presence of ivy sign, CMBs, pattern of ischemic lesions, presence of WMLs, and occurrence of new silent or overt ischemic or hemorrhagic lesions since previous imaging. Patients with revascularization operation done were

evaluated to see if the bypasses were still patent. The analysis of the radiological data was done by a neuroradiologist (JP) together with a neurologist (MS). Ischemic lesions were divided into small (<1.5 cm) and large anterior or posterior lesions. Extent of WMLs was classified according to the Fazekas classification (124). The sequences of the latest previous image used in the comparison to see the progression varied because they were done in normal clinical settings and not systemically using the same sequences as done in the imaging performed for this study.

4.2 STATISTICAL ANALYSES

A two-tailed value of $p<0.05$ was considered statistically significant. The analyses were performed with the commercially available, statistical software package SPSS for Windows (I and II: version 22.0, III: version 23.0).

4.2.1 STUDY I

Frequencies, means and medians were analyzed using SPSS. The incidence was calculated by dividing the number of diagnosed MMD patients with the total population at the HUH district per year.

4.2.2 STUDY II

We compared two groups: those treated with a revascularization bypass operation to those treated conservatively by using Crosstabs function and Kaplan-Meier. Actual annual stroke risk with 95% confidence intervals (CI) was calculated with the Life tables function using the formula $1-[(1-Ic)^{1/n}]$, with Ic as cumulative incidence rate and n as the number of years. Quality of life and mood symptoms were compared between bypass operated and conservatively treated patient groups using an independent sample T-test with 95% confidence. One sample T-test was used to compare MMA patients QOL with a Finnish population-based sample survey (120).

4.2.3 STUDY III

Frequencies, means and medians were calculated using SPSS. Crosstabs and chi-squared test were used to compare the groups.

5 RESULTS

5.1 STUDY I

5.1.1 DEMOGRAPHIC DATA AND DISEASE TYPE

Our study included 61 Caucasian patients with Finnish origin. Most patients (n=45, 74 %) were diagnosed with a definite MMD, 13 (21%) with unilateral MMD, and only 3 (5%) with MMS (Table 3). There was a female predominance found (n=50; 82%) with only 11 (18%) males (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 old and the oldest patient was 77 years old. Forty patients were from the Helsinki University Central Hospital (HUCH) district and the rest from other parts of Finland (Turku University Hospital 3, Oulu University Hospital 7, Kuopio University Hospital 4, Tampere University Hospital 5, Helsinki University Hospital Erva-region 2). The incidence of MMA in the HUCH district was thus 0.14 per 100 000. The prevalence in the HUCH district was 2.38 per 100 000 in year 2014.

Table 3. Characteristics of patients

	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)

5.1.2 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%).

5.1.3 DIAGNOSTIC FEATURES

For diagnostic purposes, 75% of the patients underwent MRA, 69% DSA, and in one case only CTA was performed.

5.1.4 CLINICAL MANIFESTATIONS AND CO-MORBIDITIES

The most common clinical manifestations were ischemic stroke (51%), hemorrhagic stroke (13%), and headaches (11%), while TIA and epileptic seizures were rare as the first presenting symptoms (Table 4). The proportion of hemorrhage was higher in men than in women (27% vs 10%). Mean NIHSS at admission to hospital was 4 (range 0-32) and the median was 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 MMA patients.

5.1.5 BASELINE 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 percent of patients with ischemic lesions had cortical infarcts and 77% had subcortical lesions. Fifteen per cent were border zone infarcts. Thirty-seven percent had bilateral infarcts. Most (67%) of the hemorrhages were deep ICHs and the rest of the patients had SAH. Of the deep ICHs 33% were IVHs 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.

Table 4. Presenting symptoms and associated syndromes/diseases

	All n=61(%)	Children n=10(%)	Adults n=51(%)
Presenting symptoms			
Ischemic stroke	31 (51)	7 (70)	24 (47)
men	5	2	3
Hemorrhagic stroke	8 (13)	0	8 (16)
ICH	6 (9.8)	0	6 (12)
men	2	0	2
SAH	2 (3.3)	0	2 (3.9)
men	2	0	2
TIA only	4 (6.6)	1 (10)	3 (5.9)
men	0	0	0
Seizure only	3 (4.9)	0	3 (5.9)
men	1	0	1
Headache only	7 (11)	0	7 (13)
men	0	0	0
Asymptomatic	7 (11)	2 (20)	5 (9.8)
men	2	0	2
Other	1 (1.6)	0	1 (2.0)
men	0	0	0
Associated syndromes/diseases			
Neurofibromatosis type 1	1	0	1
men	0	0	0
Down's syndrome	2	2	0
men	0	0	0

ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack

5.1.6 TREATMENT

Twenty-six patients underwent revascularization surgery. Direct bypass operation was more common than indirect operation (16 vs. 10). 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, and some had clopidogrel alone. One patient used warfarin due to atrial fibrillation (Table 5).

Table 5. Summary of surgical and antithrombotic treatments

	Total (%)	Adults	Children
Surgical treatment	26 (43)	16	10
Direct bypass			
STA-MCA	16	16	0
Indirect bypass			
EDAMS	11	1*	10
Antithrombotic treatment			
ASA	27 (46)	22(43)	5 (50)
ASA + 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)

ASA, acetyl salicylic acid; STA-MCA, superficial temporal artery-middle cerebral artery; EDAMS, encephaloduroarteriomyosynangiosis, *one adult, who has had STA-MCA+EDAMS

5.2 STUDY II

In the follow- up study all of the 61 patients were followed-up. Fifty-five patients came to the face-to face follow-up visit. The rest of the patients were followed-up by viewing their medical records. The mean age at the start of the follow-up was 35 (SD 17; range 3-77). The mean follow-up period was 9.5 years (SD 6.7 years; range 1.3-35.4 years). Patient-years summed up to 581.

5.2.1 MORTALITY

Two female patients died during the follow-up period. Neither of them were using antiplatelet therapy. One of them was diagnosed with MMD at the age of 50 years after an IVH. A year later she underwent bilateral revascularization surgery (STA-MCA+EDAMS). She died four years later after a new ICH. The second patient was diagnosed at the age of 19 after a TIA. On DSA bilateral ICA occlusion and moyamoya collateral network were detected. At the age of 47 and 48 she had vertigo and balance problems and imaging showed microhemorrhages as well as typical bilateral MMD vessel abnormalities. She died at the age of 53 due to ICH.

5.2.2 NEW VASCULAR EVENTS

Two-thirds (n=40, 65.6%) of the patients had no new vascular events. Eight patients (13.1%) had an ischemic and five patients (8.2%) had a hemorrhagic stroke during the follow-up. The average annual rate of a recurrent stroke from the first event for all study subjects was 3.5%. There were no differences between the operated and the conservatively-treated patients in the stroke recurrence risk. In 7 patients (11.5%) we detected asymptomatic progression in their vascular stenosis. During the follow-up period one of the unilateral MMS patients progressed to bilateral MMS. Three out of 8 (37.5%) patients initially presenting with a hemorrhagic stroke had a new hemorrhagic event during the follow-up, and 6 out of 31 patients (19.4%) initially presenting with an ischemic stroke had a new ischemic stroke during the follow-up.

5.2.3 NEUROLOGICAL OUTCOMES

The mean NIHSS at follow-up was 1 and the median was 0. The mean/median mRS at follow-up was one. The follow-up examination was done 0.2-11.7 years after recurrent strokes, in 12 patients. Functional outcome was favorable (80%) or excellent (71%) in most of the patients. There was no difference in the outcome between the operated (n=26) and the conservatively-treated (n=35) patients, when measured with mRS or BI. The mean BI at follow up was 97 (SD 12) and the median was 100 (min. 25). Only 10% of the patients required assistance in activities of daily living.

5.2.4 QUALITY OF LIFE AND PSYCHOSOCIAL FACTORS

More than half (59%) of the patients were working, while 32% were on permanent disability pension due to MMA, 5% had retired due to age, and 3% were on sick leave at the follow-up visit.

The WHOQOL-BREF questionnaire was available for 48 MMV patients. The patients reported significantly poorer physical health and psychological health aspects of QOL and a trend for poorer environmental aspects of the QOL when compared to the Finnish population based sample survey.

The surgically-treated patients reported better social relationship aspects of QOL compared to conservatively-treated patients (mean ± SD 81.0±17.2 vs.

69.7±19.2; p=0.04). There were no significant differences in the other three subdomains (physical, psychological, and environmental domains) of QOL, however, the working MMA patients estimated their physical, psychological, and social aspects of QOL to be better than patients on sick leave or pension.

POMS was obtained from 48 MMA patients. Mean POMS total score was 45.4±24.5. Symptoms of low mood were found in 27 (56%) patients, using a cut-off point of 41.4 points derived from the scores of the previous Finnish study (123). Surgically- and conservatively-treated patients did not differ significantly in POMS total score (39.3±25.4 vs. 50.1±23.2; p=0.13). Working status (i.e. work, sick leave, and pension) was not associated with patients' mood symptoms.

5.3 STUDY III

The follow-up imaging was done 103 (range 6-380) months after the initial diagnosis of MMA and 64 (range 6-270) months after previous (baseline) imaging for 32 patients (7 male, 22%). Two of these patients had MMS; one with Down's syndrome with bilateral disease and one with NF type 1 with unilateral disease. Seventy-three percent (22/30) of the MMD patients had bilateral disease. Ten (31%) patients had had revascularization surgery.

Ivy sign was observed in 7 (22%) patients and 2 of these had had revascularization operation done. Interestingly, in two patients ivy sign was present in the previous image but not in the follow-up image. Neither the amount of ischemic strokes (p=0.36), multiple ischemic strokes (p=0.42), nor the location of ischemic strokes (P=0.67) differed between ivy sign-positive and ivy sign-negative patients. Only 2 (6%) patients had CMBs, one of them being asymptomatic and the other one having had ischemic stroke as the presenting pathology at the time of diagnosis. None had CMBs in the previous image, but only 11 had had susceptibility-weighted imaging/T2* sequence done in the baseline image. 91% of the patients had no WML (Fazekas 0) and the rest (three patients) had only mild WML (Fazekas 1) and one of those had had revascularization operation. Only one had WML in the previous imaging but again only 26 had had FLAIR-sequence and thus could be evaluated.

Five (16%) patients were asymptomatic at the time of diagnosis. One of those patients had CMBs, one had ivy sign and none had WMLs in the follow-up image. All of these patients remained asymptomatic during the follow-up time (Table 6). One, the only MMS patient with Down's syndrome, had progression of stenosis in the arteries.

Table 6. Follow-up imaging time and MRA grade of the asymptomatic patients

Age at the time of diagnosis and sex	*Date of diagnosis*	*Date of control imaging*	*MRA grade* right*	*MRA grade left*
51 female	**12.9.2005**	**12.10.2014**	**3**	**3**
17 female (MMS)	**1.10.2005**	**12.10.2014**	**3**	**3**
35 male	**27.12.2006**	**7.9.2014**	**2**	**1**
22 female	**6.11.2003**	**5.10.2014**	**2**	**2**
51 male	**14.12.2013**	**14.12.2014**	**1**	**2**

MMS= moyamoya syndrome, MRA= magnetic resonance angiography

*According to Houkin et al. 1 to 4. (39)

None had acute ischemic or hemorrhagic stroke in the follow-up image. None had new silent ischemic strokes compared to previous imaging. None of the 8 patients with unilateral MMD had progressed to bilateral MMD during the mean follow-up period of 71 (range 12-161) months. Twelve (38%) patients had completely normal brain parenchyma in the follow-up image.

Only one patient had a new vascular event in the follow-up image since the last imaging. Initially this patient sought medical help because of tinnitus at the age of 39. The first brain MRI was normal, although the MRA disclosed a bilateral MMD. In the follow-up MRI performed 9 years later there were signs of old subcortical parenchymal hemorrhage on the right. However, she had not experienced neurological symptoms.

Ten of these patients had had revascularization operations, 3 (1 bilateral, 2 unilateral) of them had had EDAMS operation and the rest (5 bilateral, 2 unilateral) STA-MCA bypass. We evaluated 10 hemispheres of those who had had STA-MCA operation and only 1 of 10 of the bypasses was not patent.

Median MRA grade was 3 and 2.5 (right and left, respectively), median scores were 6 and 4.5 points (right and left, respectively, mean 4.9 ± 2.5, 4.3 ± 2.7) in 28 patients with evaluable MRA data.

6 DISCUSSION

6.1 STUDY

We found in our study that the incidence and prevalence of MMA in Finland is close to the incidence reported in Taiwan and USA, but lower compared to Japan and Korea as expected (Table 7). In our study the female predominance (4.5:1), seen in both the adults and children, was higher than previously reported in Asian (14,15,27,30,31), North American (34,68), or German (36) populations but close to that reported in another German population (4.25:1) (57). The recently published Danish and Irish (32,33) studies also disclosed a higher female predominance, although lower than in our study. The greater female predominance is postulated to be typical of the Western phenotype, which our results confirm.

Table 7. Incidences and prevalences of MMD in Western countries

Study	Country (number of patients)	Incidence/ 100000 person years	Prevalence/ 100000	F:M	Age peak 1	Age peak 2
Uchino 2005	USA (298)	0.086	3.16	2.2:1	5-9	55-59
Starke 2012*	USA (2280)	0.57	10.5	2.6:1	NA	NA
Acker 2015	Germany (153)	NA	NA	2.9:1	11-18	40-49
Kraemer 2019	Germany (185)	NA	NA	3.2:1	5-9	NA
Birkeland 2018	Denmark (56)	0.047	1.16	2:1	4-14	40-44
Doherty 2020	Ireland (16)	0.04	0.33	1.7:1	first decade	fifth decade
Saarela 2017	Finland (61)	0.14*	2.38*	4.5:1	first decade	NA

*HUCH district (n=40); NA=not available

In our study the mean age at the time of the first MMA symptoms was quite the same (37.1 vs. 40.5) in our adult population as in German population (125), but lower in children (5.7 vs. 11.4) than previously reported. In our population, as in German population (125), in most of the patients the first manifestations

of MMA were seen in adulthood, which is in line with the observations of the later manifestation of the disease in European Caucasians.

Also the incidence of unilateral disease in our patient population (23%) was close to that reported by the Germans (17%) but twice as high than that reported in Japan (10.6%) (126). Interestingly, most of the patients with unilateral disease were men (57%). Unfortunately, others have not reported gender distribution information on unilaterality and the small number of our patients with unilateral disease allows the possibility of a chance finding.

In our patient population there was no familial MMD found. In the German population, only two patients (1.3%) had a family history of MMD (125), whereas in the Japanese population, 15% had a family history of MMD (27). Finnish population is known to be genetically distinct from other European populations due to founder effect which may explain the lack of familial cases in our study.

The frequencies of ischemic and hemorrhagic strokes in adult MMA patients in our study were closer to the Japanese population than to the German population with the largest ever published European study (125). In our pediatric patients no ICH was observed, but ICH occurred in adults more often than in the German population (15.7% vs. 7.8%). Also 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) (27) than those reported by the Germans (82.8% and 7.8%) (125) or Americans (80% and 12%) (68). However, in our population men had more hemorrhages than women which is the opposite compared to Japan (men 19.5%, women 22.2%) (27) though the number of men in our study was quite small.

Involvement of the posterior circulation was rarely seen in our patients (13%) compared to the Germans (32%) (125), and the difference was even stronger in pediatric patients (10 vs 60%). The distributions of ICH, IVH and SAH were the same as in the German population. 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-American series. These differences may be merely due to small numbers and do not allow firm conclusions.

Antithrombotic medication was commonly used in our patients, which might be due to predominance of ischemic events in our patient population. Antithrombotic therapy was commonly used also in Germany, while its use is not common in Asian countries (57,100). Less than half of the patients underwent neurosurgical revascularization procedures and the most common methods were STA-MCA bypass and EDAMS which are the most frequently

employed techniques universally. The proportion of surgically treated patients was lower than reported in the German studies (57,125).

6.2 STUDY II

During a total of 581 patient-years follow-up study, two patients died (due to ICH), 13.1% (*n*=8) had an ischemic and 8.2% (*n*=5) a hemorrhagic stroke, while two-thirds (65.6%) had no new vascular events. The major studies reporting long-term outcomes of MMA patients have included 1146 (65), 104 (108), and 101 (127) patients with 5.2-9 years, 29-46 months, and 26.5 months of follow-up time reported.

Our 3 % mortality during a 9.5-year period (mean follow-up) is quite close, or even less, to that reported in a German study (9.5% during 3.7 years) (57) or in a study from the United States (2.3% during 4.9 years) (128). In a Korean study with a mean follow-up of 82.5 months the mortality rate was 6.5% (106). Interestingly, ICH appears to be the main cause of death in all published series as was in our population.

In our study the average annual rate of a recurrent stroke from the first event for all study subjects was 3.5%. In the Korean population, the reported annual risk of stroke was 4.5%/person-year, with 5- and 10-year cumulative risks of any stroke being 17% and 30%, respectively (106). Furthermore, patients presenting with a hemorrhagic event tended to show a higher incidence for a recurrent hemorrhage, and patients with ischemic symptoms had a higher rate of recurrent ischemia (106), which is in line with our results. Another Korean study found that 86% of adult MMD with conservative treatment did not develop a recurrent ischemic stroke after an ischemic stroke when 90% of the patients used antiplatelet medication (108). Our results are in line with this Korean study. In a small German study (*n*=21) the 5-year-Kaplan-Meier risk for recurrent stroke was 80.95% (57).

Less than half of the patients underwent neurosurgical revascularization procedures. Those of our patients who did not receive revascularization operation were either severely handicapped due to a stroke, or were nearly symptom-free, and thus, not willing to take the potential risk of surgery. One-third of our patients had not been referred to neurosurgical consultation at all, as some physicians have doubts on efficacy and safety of surgical treatment because of the lack of published randomized studies. This results in a significant selection bias, making the surgery and conservative treatment groups even less comparable.

Concerning long term disability (mRS) our results are in line with German (57), American (128), and Korean (106) studies. It appears that MMA affects

the patients mildly in Western populations including the Finnish population. There may be differences between different Asian populations.

Vocational outcomes in MMA patients have not been published earlier. In our study only 59% of the patients could return to work, and even one-third (32%) became disability-pensioned despite good mRS and BI scores. Cognitive decline occurring over several years often attributed to chronic hypoperfusion is often suggested in MMA patients, but has not yet been adequately investigated.

Chronic diseases (i.e. stroke and other neurologic diseases) are known to diminish QOL, which was shown also in our study. MMA patients estimated their QOL as less satisfying in physical and psychological domains when compared to the Finnish population-based study (129). Awareness of MMD has been suggested to develop severe disturbances in performance and could be the main reason for psychological symptoms caused by MMD (78). In patients who were currently not working, QOL was perceived lower compared to those who were in work life. Our findings are in line with the study where better QOL and fewer signs of low mood were associated with return to work after a mild stroke (130).

6.3 STUDY III

In study III with a mean follow-up of 64 months between the two MRI/MRA imaging time points we found new ischemic or hemorrhagic lesions only in one patient. All unilateral cases remained unilateral in this radiological follow-up study including 32 of our registry patients. Ivy sign was observed in 22%, CMBs in 6% and WMLs in 9% of the patients. The French guidelines suggest that MRI and MRA imaging should be done on a case by case basis according to clinical and radiological evolution of the patient, but at least once a year during the first years (37). The Japanese guidelines do not give a clear follow-up approach. There is a lack of studies on regular clinical and imaging follow-up of MMA patients in the white patient populations, describing disease progress over long time. These kind of studies could help to understand the disease progress speed as well as look into various subgroups, whether the disease progress differs in certain subpopulations.

In a Japanese patient population with asymptomatic MMD 3/34 non-surgically treated patients experienced silent radiological changes, including cerebral infarction, CMB, and one progression of the disease stage on follow-up MRA in the 43.7 months follow-up period (107). In another Japanese study silent CMBs were found in 2 out of 20 asymptomatic patients during the 48.8 months follow-up time (131). In our study the number of asymptomatic

patients was small (n=5) and their radiological findings were few, one CMB and one ivy sign.

Occurrence of CMBs in MMD was described by Ishikawa (46). Especially in the hemorrhagic onset type MMD incidence of CMBs is found to be high, and a meta-analysis indicated that they may be an important factor for hemorrhagic stroke risk (47). In Asian populations CMBs have been reported in 28.2-51.9% of the patients (47-49). In a German population-based study CMBs were found in 12.9% of their patient population (n=101) (50), which is close to our 6% result and it seems that the incidence of CMBs is lower in European populations. Another German population-based study found no CMBs after STA-MCA bypass surgery during a mean follow-up of 38.2 months (51). Unfortunately blood-sensitive MRI imaging have not been widely used in earlier MRI imaging sessions and therefore long-time follow-up data are not extensively available on this aspect.

Ivy sign, seen on post contrast T1-weighted images or FLAIR images, has been reported in 67%-100% of Asian patients (42,43). In our population ivy sign was present in only 22% of patients. It has been suggested that the degree of the ivy sign indicates decreased cerebral vascular reserve in MMD (44), but a more recent study found no relationship with ivy sign and the presence or absence of collaterals on DSA (45). Our ivy-positive patients did not differ from our ivy sign-negative patients in terms of other imaging parameters or clinical characteristics. The pathophysiology of ivy sign is still unresolved, but it seems that presence of ivy sign is far less usual in white patients compared to Asian MMD patients.

WMLs are seen more often in MMD patients than in controls and the symptomatic side of the brain being more affected suggesting that WMLs might precede TIAs (53). The same study showed that WML volume decreased after revascularization surgery. In our patient population only 3 patients (9%) had WMLs and only one of them had had revascularization surgery. In the previous imaging only one had WMLs, but unfortunately only 26/32 of the patients had FLAIR-sequence done. A Japanese study found WMLs in 57/100 hemispheres (54). Since our patients were slightly older than the patients in these two studies, the differences in the presence and extent of WMLs are not explained by a younger population in our study and it seems that the Finnish MMA patients have substantially less WMLs than Asian patients.

In our patient population none of the unilateral cases progressed to bilateral during a mean follow up of 71 months. The frequency of progression from unilateral to bilateral varies between 12-39% over 1-15 years of follow-up in previous studies (43,111-114,116). It seems that the progression from unilateral to bilateral disease might be an extremely slow process or that unilateral disease remains mainly unilateral in most cases.

6.4 STRENGTHS AND LIMITATIONS

All the patients in our study (HUH-MMA database) were thoroughly investigated and they represent genetically a rather homogeneous population (Finnish origin and living in Finland), which can be considered as strengths of these studies (I, II, III). We included all the patients within our catchment area and also from other university hospital catchment areas (KUH, OUH, TAUH, TUH), closely approaching to the population-based setting and including most of the Finnish MMA patients at the beginning of the study. Almost all the patients were examined by a neurologist (I, II, III) and by a neuropsychologist (II). The limitation is the small number of patients as there is less MMA in Finland than for instance in Asia, which was expected. The lack of large series of European patients makes comparisons difficult since the large German study included mainly surgical patients (125) and no patients under conservative follow-up. Although our patient number was small compared to Asian studies it was the second largest in the European populations after the German studies. Also in our patient population over half of the patients were treated conservatively compared to many studies where most of the patients have been operated giving important information on conservatively treated patients in European populations.

Even though our data was quite comprehensive, we might still not catch all MMA patients in Finland, especially in other university hospital catchment areas (KUH, OUH, TAUH, TUH), which might lead to some selection bias supposed that maybe those send to HUS had a more severe disease and this might have an impact on results in all studies. Also because of the same reason the incidence and prevalence in Finland and other regions besides HUH might be slightly different than in HUH region.

Patients were investigated in detail, both retrospectively (I) and prospectively (II, III). We had a rather long follow-up time (II, III), which can further be considered as a strength of the study.

In study III we could not include all our HUH-MMA database patients because of long distances in our country and logistical difficulties of arranging radiological standardized follow-up imaging leaving us with a smaller number of patients living near HUCH. Also the imaging sequences done previously were not always comparable because of the variation of imaging sequences used for clinical routine practice, and thus comparing the findings of previous images with the latest images taken for this study could not be done in all cases. All the images taken for this study were evaluated by neuroradiologist and also the previously taken images for clinical practice were re-evaluated by the same neuroradiologist. Nevertheless, existing data on follow-up imaging changes in MMA is limited and our study adds new data to the field.

7 CONCLUSIONS

The occurrence and prevalence of MMA and MMD are low in Finland compared to the Asian countries and are similar to those in other Western countries (I). In the Finnish population the most common phenotype of MMA is the ischemic type of disease including ischemic stroke and TIA, as described in the other Western patient populations. There is a bimodal age distribution as in other populations all over the world, but the onset of the disease appears more often in adulthood than in childhood in the Finnish patient population (I). Among children the hemorrhagic type of the disease is rare. The female predominance of the disease was more common than in Asian countries and highest in European populations (I).

Over time it seems that the course of the disease is relatively benign and there is no clear difference between operated patients and conservatively treated patients, concerning new clinical events or new radiological findings on a rather long follow-up time (II, III). In our study population, as in other populations, the hemorrhagic type of the disease seemed to have higher mortality rate.

Most of the patients could return to work, but one-third became disability-pensioned despite good mRS and BI scores. MMA patients estimated their QOL as less satisfying when compared to the Finnish population-based study. Among the patients, who were currently not working, QOL was perceived lower compared to those who were working (II).

Antithrombotic medication is commonly used in Finland in the ischemic type of the disease, as seems to be the international expert opinion consensus, even though there is no clear clinical evidence to support this. Revascularization treatment in children seems to be common practice in Finland, but among adult patients the operative treatment is not as common as in Asia and in some European countries such as Germany.

There are no national guidelines for treatment or follow-up of MMA in Finland. Such guidelines may improve patient care and increase awareness. Further, a clear pathway for management of these patients should be agreed upon nation-wide. A multiprofessional team evaluation is necessary. At the beginning, a standard evaluation may include clinical evaluation by a neurologist, a neurosurgeon, and a neuropsychologist together with rehabilitation personnel, in the presence of neurological deficits coupled with adequate imaging studies including brain MRI, cervical and intracranial vasculature imaging by an angiographic study, possibly positron emission tomography, and probably ancillary tests selected according to individual

considerations. The HUH Neurosurgery department is responsible for organizing the specialist-level MMA revascularization operations for the whole country of Finland, with no major complications among the patients operated in Finland. The follow-up of the patients should be concentrated to a tertiary hospital level, as this is a rare disease with little evidence-based data, and after the diagnosis, a yearly follow-up visit with a neurologist and at least once in a life time a neurosurgeon consultation should be organized. This approach enables us to include all patients into a national registry, conduct research studies and increase knowledge and skills within the team. According to current knowledge aspirin can be used in the secondary prevention of the ischemic type of the disease.

The use of MRI techniques in medical diagnostics is becoming more common every day which means that more of the symptomatic and asymptomatic MMA patients will be diagnosed. There is still a major deficiency in understanding MMA and therefore we are still not able to accurately predict the prognosis for an individual patient.

Our study confirms the postulation of a Western phenotype of MMA, including a later onset of the disease and a greater female predominance. It seems that the MMA patient demographics and characteristics of the Finnish patient population somewhat differ from those of Germany and North America, and in some aspects resembles more the Japanese population. This is one of the largest studies describing a European subpopulation, and the first study to describe MMA in Finland. In the future there is a need for a larger European registry of patients and follow-up studies including more conservatively treated patients, and another follow-up study for Finnish patients after 10 years or so. Future genetic studies of MMA require multinational efforts.

8 ACKNOWLEDGMENTS

I express my sincere gratitude to my supervisor Professor Turgut Tatlisumak, who has been patient and encouraging during these ten years. I could have not hoped for a better supervisor in research as well as in clinic. I am really thankful for your valuable time to help me improve my scientific writing. Thank you for organizing the facilities to do research so that I could concentrate to research work itself. Thank you for your belief in me to do this thesis and thank you for carrying on with me even though you moved to Sweden.

I am very thankful for my second supervisor, « work life big sister », docent Satu Mustanoja for being on call all the time for me, and for all the tea moments shared and patience and support over the years in clinical and research life. Thank you for your expertise in language problems, in English and Swedish. Thank you for being there for the tough moments.

I want to thank the former and current heads of the Department of Neurology, Markus Färkkilä, Nina Forss, and Professor Emeritus Timo Erkinjuntti and Professor Perttu Lindsberg for providing excellent research facilities.

I want to thank the co-author Anna Uusitalo who was crazy enough to go on a « moyamoya tour » through Finland, we had great time! Thank you also for your work concerning the neuropsychological part of the work. I thank colleague and co-author Johanna Pekkola for your time spend with me analyzing the images and all the radiological expertise you provided to this project. Also colleague and co-author Professor Leena Kivipelto, thank you for your neurosurgical expertise and help in this thesis, and neurosurgeon Ville Nurminen for your help during this work.

I want to express gratitude to my other co-authors Docent Erja Poutiainen, Professor Juha Hernesniemi, colleague Tiina Tyni and Sanni Ruotsalainen. I am grateful for Judith Klecki for the language revision of my work.

I want to thank research nurses Jaana Koski, Marja Metso, Saija Eirola for their help with organizing the meetings with patients, laboratory assistance and all the practical support. I also thank Anu Eräkanto for all the help in paper work.

I also want to thank friend and colleagues Kaisa Kotisaari, Jukka Putaala, Karoliina Aarnio for their support and help.

I thank the reviewers Professor Juhana Frösen and Professor Marc Fisher for critically reading the manuscript and their constructive comments. I am also thankful to thesis committee group Docent Minna Riekkinen and Docent Heikki Numminen.

I am thankful to The Finnish Medical Foundation, Helsinki University Central hospital Research Funds, Etelä-Karjalan lääkäriseura and Duodecim-seuran Viipurin alueen paikallisosasto for supporting my work financially. I also want to thank the Doctoral Programme in Clinical Research in Helsinki University.

I also want to thank all my friends who have had the patience to hear all my worries concerning this project during these ten years.

I am thankful to my mother who has encouraged me to study more when I decided to go to medical school after two other degrees. Without that I would not be a doctor, a neurologist or at this point with my thesis.

The most special thanks goes to my beloved husband Mika for the mental and technical support during the last years of this thesis. Without your support I would have not finished this thesis. I love you!

Lappeenranta, April 2021
Marika Savolainen

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