Review Article

MOYAMOYA DISEASE - A REVIEW

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ABSTRACT

Moyamoya syndrome is a specific chronic cerebrovascular occlusive disease first reported by Japanese surgeons in 1957. The disease moyamoya, which is a Japanese mimetic word, gets its characteristic name due to the appearance of puff of smoke on relevant angiographs resultant from the tangle of tiny vessels in response to stenosis. This makes the blood to leak out of the arteries, causing pressure to the brain. It may cause ischemic attacks or cerebral infarction, which is more frequent in children than in adults. The highest peak is in childhood at <10 years of age. The disease causes constrictions primarily in the internal carotid artery (ICA), and often extends to the middle and anterior cerebral arteries, branches of the ICA inside the skull. When the ICA becomes completely blocked, the fine collateral circulation that it supplies is obliterated. The clinical features are strokes, recurrent transient ischemic attacks, sensorimotor paralysis (numbness and paralysis of the extremities), convulsions, and/or migraine-like headaches. Moreover, following a stroke, secondary bleeding may occur. Such bleeding called hemorrhagic strokes. Treatment with perivascular sympathectomy and superior cervical ganglionectomy. Etiology of the disease is still unknown; however, multifactorial inheritance is considered possible because of a higher incidence of the disease in Japanese and Koreans and approximately 10% of familial occurrence among the Japanese. Recent genetic studies suggest some responsible genetic foci in chromosomes 3, 6 and 17.
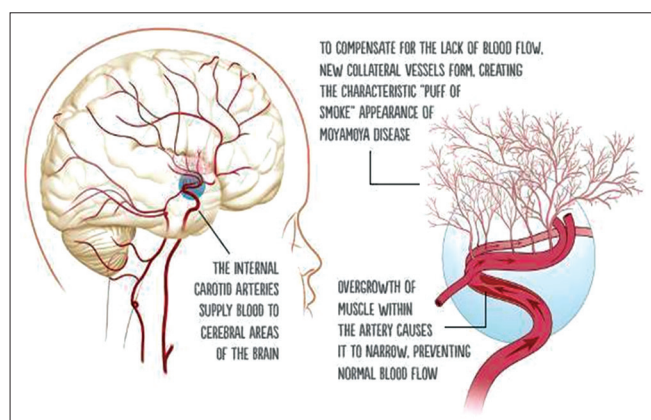
Keywords: Moyamoya disease, Intracranial hemorrhage, Proteomics, Stenosis.

INTRODUCTION

Moyamoya disease is a rare, progressive cerebrovascular disorder caused by blocked arteries at the base of the brain in an area called the basal ganglia. The name "moyamoya" means "puff of smoke" in Japanese and describes the look of the tangle of tiny vessels formed to compensate for the blockage. High incidence of the disease is noted mainly in Asia (in Korea and Japan predominantly), with 3 cases per 100,000 of pediatric population [1]. In non-Asian countries, the incidence is much lower - in Europe, it is 10 times lower than in Japan [2,3]. In Poland, there were only single reports, and this topic has rarely been discussed in the Polish medical literature [4,5].

TO COMPENSATE FOR THE LACK OF BLOOD FLOW, NEW COLLATERAL VESSELS FORM, CREATING THE CHARACTERISTIC "PUFF OF SMOKE" APPEARANCE OF MOYAMOYA DISEASE

THE INTERNAL CAROTID ARTERIES SUPPLY BLOOD TO CEREBRAL AREAS OF THE BRAIN

OVERGROWTH OF MUSCLE WITHIN THE ARTERY CAUSES IT TO NARROW, PREVENTING NORMAL BLOOD FLOW

The highest known prevalence of moyamoya disease (MMD) is in Japan. A survey from 2003 reports 7700 Japanese treated for the disease, an almost 100% increase over the 3900 reported in 1994. This prevalence corresponds to a rate of newly diagnosed cases in Japan of 0.54/100,000 people in 2003. A study from 2002 to 2006 states the incidence rate is now up to 0.94 patients per 100,000 people, with a prevalence of 10.5 patients per 100,000 [6].

According to the classification of the Japanese Health Ministry, there are 4 clinical forms of the moyamoya disease: Ischemic, hemorrhagic, epileptic, and "other" [7]. The ischemic form is the most common in children, while the hemorrhagic form is more popular in adults. In children, the MMD has a form of transient ischemic attacks (TIAs) or lacunar strokes, leading to mental retardation [8]. In adults, there may appear intracranial hemorrhages, including subarachnoid hemorrhages [9,10]. There were also reports on strokes of "the last meadow" type in adults [10]. Rarely reported clinical symptoms include also alien limb syndrome [11]. In the European population, the disease symptoms appear mostly at a later age than in Asian countries, and the hemorrhagic lesions are less frequent [7,5].

MMD in this survey was more prevalent in women than men, with a female to male ratio of 1.8:1. The survey showed the highest prevalence for males at ages 10-14 and smaller peaks at 35-39 and 55-59. For females, the biggest peak was at ages 20-24 and a smaller peak at 50-54. In one-third of these reported cases, onset of the disease was more than 10 years before the survey and in another third was within the 5 years prior. These data correspond to a prevalence of 6.03 per 100,000 people in 2003, up from 0.35 in 1993. However, the surveyors of the data, Kuriyama *et al.*, do acknowledge that improved diagnostic measures, as well as improved prognosis for these patients, may have contributed to the increase in the incidence and prevalence of the disease. In a recent study by Baba *et al.* from 2002 to 2006, the female to male ratio was up to 2.18:1, with similar bimodal age distributions.

The strong prevalence of MMD in Japan suggests a genetic trait associated with the disease. There was a family history of MMD in 12.4% and 11.9% of cases for men and women, respectively, from the 2003 survey. In a recent study by Mineharu *et al.*, MMD was noted to follow an autosomal dominant inheritance pattern with the gene found in the telomeric region of 17q25. Although this study was limited to 15 extended Japanese families, other researches have found associations between MMD and chromosome 17q25.

Recent studies in the US have highlighted a difference between MMD presentation in Japanese and American cases. In these studies, MMD cases in the US have shown a lack of bimodal age of onset, a prevalence of the ischemic type at all ages, more benign symptoms at presentation, and better response to surgical treatment. However, still evident in all the studies is a higher prevalence among women. Studies in which the MMD profile more closely matches that in Japan are found in the states of Hawaii, California, and Washington. These studies attribute their aberrations from the other US studies to high Japanese immigrant populations, while also noting that the disease continues after Japanese move to the US. The incidence of MMD in California was only 0.087 per 100,000 from 1987 to 1998, even with a higher Asian population. The adjusted incidence rates by ethnicity were Caucasian 0.06, Asian American 0.28, African American 0.13, and Hispanic 0.03. Although the data suggest a higher incidence, predominantly genetic, in Asian subpopulations, the incidence of MMD in the US may change with improved imaging technology and increased awareness of the disease in the differential diagnosis of patients with intracranial cerebrovascular disease.

PRESENTATION AND NATURAL HISTORY

MMD cases typically present acutely with various cerebrovascular events including intracranial hemorrhage, TIAs, brain infarction, and sometimes epileptic seizures. The Ministry of Health and Welfare of Japan has defined 4 types of MMD with the following presentation percentages: Ischemic 63.4%, hemorrhagic 21.6%, epileptic 7.6%, and "other" 7.5% [12]. There are also asymptomatic cases in which MMD is found incidentally on angiography [13]. As stated before, the ischemic type of MMD predominates in childhood, making up 69% of cases in patients under 10 years old. Some cases involve ≥1 one symptom, including 40% of patients with TIAs and 29% with infarction resulting in motor paresis and disturbances of consciousness, speech, and sensation [12,14]. Ischemic symptoms are often instigated by hyperventilation. The symptoms may present repetitively and can result in motor aphasia, cortical blindness, or, within several years of onset, even a vegetative state. The course of the disease often leads to mental retardation and low IQ over the long term, especially in children [15].

Furthermore, as stated before, the hemorrhagic type of MMD is more characteristic of adult-onset. 66% of adult cases exhibit hemorrhages with a higher occurrence in females. Symptoms often include disturbance of consciousness, motor paresis, and headache. Hemorrhages are often recurrent with intervals of days to 10 years. Large hemorrhages are often fatal. The epileptic type is noted more often in children younger than 10 years of age.

Progression of occlusion is more common in children than adults. In a study of 120 Japanese adult cases, progression over a 15-year period (1990-2004) was noted in 15 of 120 patients [16]. Even though a low percentage of cases progressed, this contradicts the previous notion that the disease was progressive in childhood but stable in adults. Three of these cases showed occlusion of the PCA [13]. Four of 11 unilateral cases showed the progression of the contralateral carotid fork leading to a bilateral case. Progression of MMD started, on average, more than 1.5 years from onset for all types, although significantly sooner in bilateral cases. From the Kuroda *et al.* [13] study, none of the following were considered to be predictors for progression: Age of onset, disease type, symptoms at onset, or previous bypass surgery. However, 13 (32.5%) of 40 female cases and 2 (8.7%) of 23 males exhibited disease progression, which was statistically significant. Overall, about 20% of all adult MMD cases progressed [17].

At diagnosis, adults are usually at a more advanced stage than children [14,15]. Pediatric cases appear to progress into adult cases although the process is still unclear. Children progress much more rapidly than adults. This is especially true in patients younger than 2 years of age, accounting for their poor prognosis. According to the study by Ishii *et al.*, childhood patients with MMD progressed with in 5-10 years to more severe stages angiographically, while some of the cases progressed after adolescence. Some of the pediatric patients

exhibited slow progression, proving to be adult cases with pediatric onset. All of these cases had an MMD onset after the patient was 5 years old. Although most adult cases were stable, some showed progression even after long periods of angiographic stability [18].

Recent research into asymptomatic cases of MMD has shown that its classification is likely a misnomer. Patients are usually considered asymptomatic if they have MMD angiographically but have not suffered ischemic or hemorrhagic episodes [13]. In one study, about 20% of "asymptomatic" MMD hemispheres had a silent cerebral infarction and 40% showed disturbed cerebral hemodynamics during an average 43.7-month follow-up period [13]. This disturbed hemodynamics included increased O_2 extraction and decreased performance with acetazolamide challenge. Seven of 34 patients who did not undergo surgery suffered a TIA, stroke, or intracranial hemorrhage during follow-up, projecting to a 3.2% annual risk of infarction in asymptomatic MMD. Furthermore, 5 cases (20%) showed disease progression, 4 of which involved an ischemic event or silent infarction. Interestingly, in other case series, none of the patients who underwent surgical revascularization showed any MMD symptoms on follow-up [13,19]. Recent research on asymptomatic MMD suggests that it is not truly asymptomatic but rather an early stage or less severe form of MMD. The prevalence of asymptomatic MMD favors females in a ratio of 2:1, about the same as in symptomatic cases [13].

Further investigation into progression of unilateral to bilateral MMD has shown that neither unilateral cases nor their progression to bilateral cases is rare. Three separate studies reviewed a total of 512 patients with MMD, 14% of whom had unilateral disease at diagnosis. 32 (44%) of the original 72 unilateral cases progressed to bilateral cases. The 3 studies all showed an average time of progression between 1.5 and 2.2 years [13,16,18]. The researchers suggest predictors of progression as follows: Abnormalities on the initial angiogram of the contralateral ACA, internal carotid artery (ICA), or MCA; previous history of cardiac anomalies; cranial irradiation; Asian heritage; or a family history of MMD. A younger age of onset (younger than 7 years old) corresponded to faster progression in the study by Smith and Scott [18]. The only factor noted to predict no progression was a normal angiogram of the contralateral side at diagnosis.

PATHOPHYSIOLOGY: HISTOLOGY TO PROTEOMICS

Progressive bilateral stenosis or occlusion of the ICA with frequent involvement of the proximal anterior and middle cerebral arteries is characteristic of moyamoya disease. Histopathological studies of affected ICA segments in MMD demonstrate eccentric fibrocellular thickening of the intima, proliferated smooth muscle cells (SMCs), prominently tortuous and often duplicated internal elastic lamina, with no inflammatory or atheromatous involvement. Vessel occlusion results from excessive accumulation of SMCs and thrombosis within the lumen. It is hypothesized that in the setting of arterial stenosis or occlusion, hypoxic regions of the brain induce collateralization through the formation of dilated and tortuous perforating arteries. Histopathologically, the moyamoya collateral vessels display thinned media with fibrin deposition in the vessel walls, fragmented elastic laminae, and microaneurysm formation. This native revascularization strategy is orchestrated by the expression of various growth factors involved in angiogenic signaling cascades, including hypoxia-inducible factor-1 (HIF-1), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor-β_1, hepatocyte growth factor, and matrix metalloproteinase (MMPs) [20,21]. Taken together these studies indicate the existence of a proangiogenic intracranial milieu in patients with moyamoya disease. Future investigations are needed that focus on high throughput proteome-wide approaches that go beyond individual molecules to provide a better insight into global pathways and interactions at play in MMD and that correlate expression levels to extent of disease on neuroimaging (for example, correlation of angiogenic factors in cerebral spinal fluid (CSF), serum, and urine to extent of collateralization seen on cerebral angiography and measurements of cerebral blood flow (CBF)

and blood volume on perfusion magnetic resonance imaging (MRI/ single-photon emission computed tomography [SPECT]/positron emission tomography [PET]). Future studies will also aim to develop genetic and serum biomarkers that can be used as predictors of outcomes after initial presentation. Biomarkers reflective of changes in the proangiogenic intracranial milieu after direct and indirect revascularization procedures will help clinicians monitor disease evolution in patients with moyamoya disease.

ACCUMULATION OF SMCS IN VASCULAR LESIONS

The excessive accumulation of SMCs and abnormal production of extracellular matrix components seen in MMD are also characteristic pathological entities in a number of other vascular diseases. Previously, it was assumed that pathological SMC accumulation derives from the adjacent medial SMC layer of the vascular wall, which regulates vascular tone and blood flow. However, neointimal SMCs differ from medial SMCs in phenotype and gene expression pattern. Migration of SMCs from the media across the internal elastic lamina is not commonly observed and neointima can be formed in the absence of medial cells, suggesting neointimal SMCs differed in origin from medial SMCs. Recent evidence now suggests that bone marrow-derived vascular progenitor cells have the potential to home in on diseased vessels and differentiate into neointimal SMCs and endothelial cells in models of postangioplasty restenosis, transplant-associated graft vasculopathy, and hyperlipidemia-induced neointimal hyperplasia. Angioplasty is known to cause direct vessel wall injury, which induces SMCs to proliferate with subsequent overproduction of extracellular matrix. Transplant-associated vasculopathy occurs secondary to immunological targeting of the allograft by the recipient. Atherogenic substances (for example, oxidized low-density lipoprotein, homocysteine, angiotensin II, and lipopolysaccharides) can induce apoptosis and abnormal vascular wall remodeling, resulting in neointimal formation. Similar mechanisms have been proposed for the development of stenosis or occlusion in moyamoya disease, that is, direct vessel wall injury, immunological targeting, and caspase-3-mediated apoptosis [22,23].

ENDOTHELIAL PROGENITOR CELLS IN VASCULAR ANOMALIES

The majority of MMD research has focused on abnormal angiogenesis, that is, endothelial cell sprouting from existing vessels, in the underlying pathogenesis of moyamoya disease. However, adult vasculogenesis is increasingly being understood as the pathway for adult neovascularization. Vasculogenesis differs from angiogenesis in that new blood vessels arise from circulating bone marrow-derived endothelial progenitor cells (EPCs) rather than from local endothelial cells [2]. Vasculogenesis begins during tissue ischemia with increased expression and stabilization of the transcription factor HIF-1, which promotes local production of stromal cell-derived factor 1 (SDF-1) and VEGF-A by hypoxic endothelial cells. It is hypothesized that release of SDF-1 ligand results in reversal of a marrow/periphery gradient that normally inhibits EPC migration. As a result, EPCs can mobilize to the periphery where they are preferentially recruited to SDF-1-expressing ischemic tissue during adult vasculogenesis.

There is recent evidence that circulating stem and progenitor cells and aberrant vasculogenesis may contribute to the development of other vascular abnormalities. Children with proliferating infantile hemangioma harbor increased levels of mobilized EPCs, and surgical specimens of infantile hemangioma specimen are positive for progenitor-specific markers including CD34, AC133, and VEGF.

Consistent with aberrant vasculogenesis as a shared final common pathway among vascular anomalies, MMD has been associated with co-occurrence of other vascular malformations, including cerebral cavernous malformations and brain arteriovenous malformations (AVMs). The paracrine chemical bFGF stimulates endothelial cell growth and promotes angiogenesis and is found in histochemical association with cerebral cavernous malformations. Elevated levels of bFGF have been observed in the CSF of patients with moyamoya disease,

which is one proposed mechanism explaining the cooccurrence of cerebral cavernous malformation with moyamoya disease. Brain AVMs associated with MMD have been reported in patients ranging in age from 8 to 54 years, occurring in both unilateral and bilateral disease. Fuse *et al*. have reported the diagnosis of a brain AVM in a 9-year-old girl 4 years after undergoing indirect bilateral revascularization surgery for a diagnosis of moyamoya disease. The exact mechanism for this rare *de novo* brain AVM formation is unknown. The authors proposed decreased cerebral perfusion pressure and hypoxia in the setting of MMD as one possible mechanism, acting through elaboration of angiogenic cascades. However, this seems less likely given that revascularization was deemed effective on pan cerebral angiography. It may be more likely that de novo brain AVM formation occurred in the setting of an increased angiogenic environment induced by the bilateral indirect revascularization surgery.

The cooccurrence of brain AVM with MMD may support the theory of a shared final common pathway in the pathogenesis of these 2 diseases. Indeed, similar angiogenic factors are expressed in both diseases, including increased expression of HIF-1, VEGF, and VEGF receptors. It has been shown that MMP-9 is responsive to hypoxia and may result in release of EPCs by cleavage of membrane-bound kit ligand in the bone marrow. Interestingly, MMP-9 has been shown to be increased in patients with MMD as well as in those with a brain AVM. Of note, an SNP in the gene encoding TIMP-2, a candidate SNP within a location identified in linkage studies of familial moyamoya, has been implicated as a genetic predisposing factor for familial moyamoya. However, subsequent studies have been unable to replicate this finding [24].

Recently, Jung *et al*. provided the first demonstration of aberrant vasculogenesis in moyamoya disease although future studies are needed to enumerate circulating EPCs in MMD patients *in vivo* using FACS and to perform blood genomic analysis on these and other circulating cell populations. Data are lacking on progenitor-specific markers and SDF-1 expression in cerebrovascular disease tissue and on levels of circulating EPCs and other markers of vasculogenesis in the peripheral blood of patients with cerebrovascular disease, including moyamoya disease. Future studies to define basal EPC profiles in MMD and other cerebrovascular diseases, changes in EPC profiles after stroke or intracerebral hemorrhage, as well as changes in EPC profiles following revascularization procedures (direct versus indirect), will aid in the understanding of vascular stem cell biology, validate the utility of EPCs as a marker of MMD progression, and shed light on novel therapeutic strategies for the medical management of cerebrovascular disease [25].

MORPHOLOGICAL LESIONS AND IMAGING DIAGNOSTICS IN THE MOYAMOYA DISEASE

Changes appearing in the course of the disease include mainly the terminal parts of internal carotid arteries and or proximal parts of middle and anterior cerebral arteries [4]. In the affected cerebral vessels, pathological examinations do not show atherosclerotic or inflammatory lesions, and the cause of stenosis is the overgrowth of the smooth muscle layer, with thrombotic changes.

The disease leads not only to a different degree of stenosis and occlusions of large arteries of the anterior part of the Willis circle but also to the development of the collateral vasculature that produces a typical angiographic image, called "clouds of smoke" or "puff of cigarette smoke." The vessels of the collateral circulation are formed as a result of widening of the existing vessels or development of new perforating arteries. These arteries are small or medium-sized muscular arteries, branching from intracranial parts of internal carotid arteries, posterior cerebral arteries, or anterior choroidal arteries. The vessels of the collateral circulation combine with distal branches of the middle cerebral arteries. There are three main pathways of collateral circulation - parenchymal, meningeal, and transdural.

Collateral parenchymal vessels (described as vessels of "moyamoya" type) are small, twisting, wide vessels penetrating toward the base of the

brain, along the course of thalamostriatal arteries and lenticulostriatal arteries. Transscleral anastomoses develop between the superficial temporal artery (STA) and the middle meningeal artery or the optic artery and the anterior or middle cerebral artery, perforating the dura mater.

In the vessels of the collateral circulation, there may appear thrombotic changes, which are the cause of ischemic symptoms. An increased blood flow through thin collateral walls during stress, as well as the presence of microaneurysms, is the probable cause of intracranial hemorrhages.

Angiographic criteria of the diagnosis of MMD were established in 1998. They include stenosis or occlusion of the distal parts of intracranial internal carotid arteries and proximal parts of anterior and middle arteries, as well as the presence of collateral vasculature in the regions of the brain base, without causal disease. In case of bilateral changes, the diagnosis is considered as sure. Unilateral changes are qualified as probable.

Naturally, CT examination is sufficient to diagnose ischemic or hemorrhagic stroke in the course of the disease (Fig. 1). Ischemic foci may be present in basal ganglia and in the white matter - periventricular and subcortical. In case of patients with TIA symptoms, the results of the studies are negative.

The presence of occlusions or stenoses of large intracranial vessels and the presence of collateral vasculature in a routine contrast-enhanced CT should suggest a suspicion of the disease, especially in young individuals. In ambiguous cases, it is indicated to carry out MRI, which not only helps in establishing the diagnosis but also allows for a better evaluation of the range and time phase of ischemic lesions (Fig. 2). The use of diffusion techniques substantially increases the diagnostic value of the MRI studies in these cases. Fluid-attenuated inversion recovery sequence is also very useful, as it helps to diagnose the "ivy sign," i.e., an increase in signal intensity along the fissures and gyri of cerebral hemispheres, resulting most probably from the reduction of the cortical flow (Fig. 3). The MRI study is also very useful in visualizing late sequelae of the previous strokes, i.e., brain atrophy and widening of the ventricular system and of the pericerebral fluid spaces.

Before modern angiographic examinations (such as computed tomography angiography [CTA] or magnetic resonance angiography [MRA]) were introduced to a wide clinical practice, the final diagnosis of the vascular changes was based on conventional angiography or digital subtraction angiography. At present, the diagnosis of the whole range of vascular changes in the course of the disease is based mainly on MRA and CTA, using multi-row systems (Fig. 4a and b). There were also single reports on the use of transcranial Doppler ultrasonography. However, this method does not have any significance in disease diagnostics.

Angiographic examinations distinguish 6° of the severity of vascular changes. The first degree includes only stenosis of the carotid artery. In the 2° and 3°, the collateral vasculature of moyamoya type develops and increases its range (Fig. 5). In the fourth and fifth degree, these vessels start disappearing, and in the sixth degree they become invisible (Fig. 7) - the collateral vessels branch only from external carotid arteries.

An important issue reported on in the literature is also the quantitative evaluation of hemodynamic disturbances of the cerebral circulation in the course of the moyamoya disease, evaluated on the basis of PET, SPECT, and perfusion CT and MRI.

Comparative studies, including vascular and perfusion examinations, have shown significant correlations between the angiographic image and the regional perfusion. As the disease normally affects both internal carotid arteries, and not the posterior part of the arterial circle of Willis, the individuals with MMD experience a decrease in frontal blood flow (dominant in normal conditions), with normal or increased blood flow in occipital lobes.
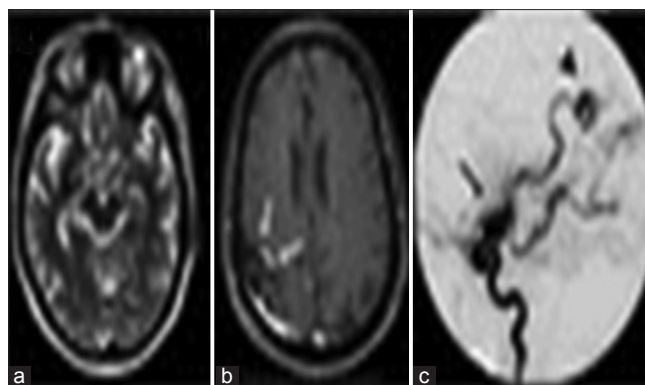

Fig. 1: Imaging studies acquired in a 47-year-old woman who suffered a hemorrhage from a right parietal arteriovenous malformation (AVM). (a and b) Axial T2-weighted (a) and a T1-weighted (b) magnetic resonance images obtained after contrast agent injection. (c) Lateral cerebral angiogram. Flow voids are detected on the T2-weighted image (arrow in A), which correlate with the finding of moyamoya vessels and occlusion of the middle cerebral artery on the cerebral angiogram (arrow in C). The right parietal AVM is detected on the contrastenhanced image (arrows in B) and correlates with the AVM on the angiogram (arrowhead in C) with an early draining vein. The patient was first treated for the AVM after the hemorrhage occurred and then underwent right superficial temporal artery-middle cerebral artery bypass surgery
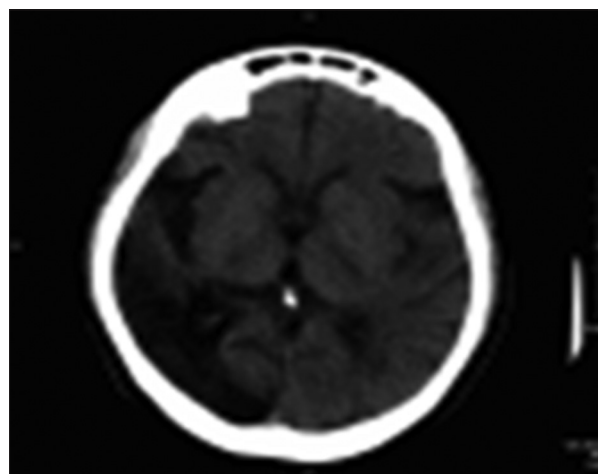

Fig. 2: A 39-year-old women, 3 years after stroke, preceded by transient ischemic attacks (Case 1). Computed tomography examination - hypodense area attributable to malacia after stroke in the right temporal and occipital lobe

On the basis of perfusion studies, it was also found out that in children with MMD there is a decrease in CBF and increase in cerebral blood volume (CBV) and in O_2 extraction fraction (OEF), much more pronounced than in adult populations. Moreover, it was reported that the reduction of cerebrovascular reserve (CVR) is higher in children, which was evaluated on the basis of tests with acetazolamide or CO_2. Such differences may explain higher incidence of ischemic lesions in pediatric populations - as opposed to intracranial hemorrhages, which are more often in adults.

The results of the studies on hemodynamic disturbances in adults are not homogeneous. The majority of papers reported disturbances similar to changes observed in children. However, some of the reports did not confirm the presence of significant changes in perfusion parameters in adults. These differences follow most probably from
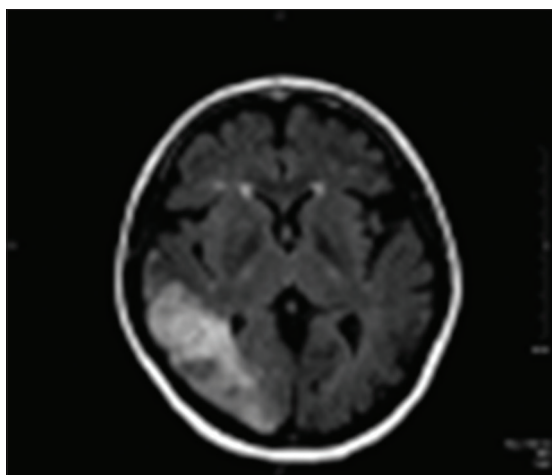
Fig. 3: Case 1. Magnetic resonance study, fluid-attenuated inversion recovery image in axial plane. Hyperintense lesion in the right temporal and occipital lobe
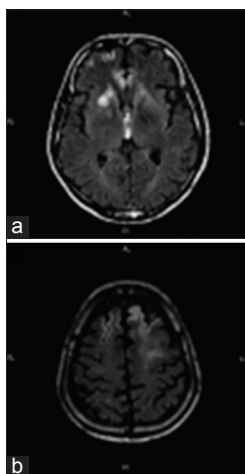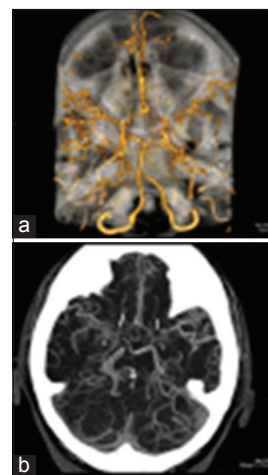

Fig. 5: Case 1. Suzuki grades III/IV. Computed tomography angiography, three-dimensional reconstruction. Narrowing of the distal segments of both internal carotid arterys. Narrow or locally not visible segments A1 of the anterior cerebral arteries and M1 of the middle cerebral arteries (a). Moyamoya collaterals

Fig. 4: Case 2. A 35-year-old man with facial and arm paresis. Magnetic resonance study, fluid-attenuated inversion recovery image in axial plane. Hyperintense lesion in the right basal ganglia (a). Cortical stroke in the left frontal lobe and ivy sign in the right frontal lobe (b)
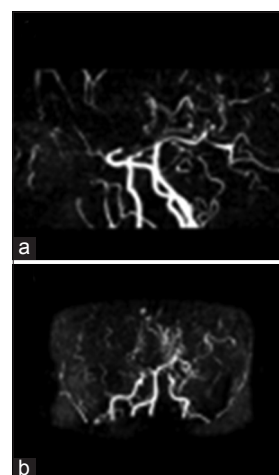

Fig. 6: Case 1. Suzuki Grades III/IV. Magnetic resonance angiography, time-of-flight technique, maximum intensity projection reconstructions in sagittal (a) and axial plane (b). No signal from either of the anterior cerebral and middle cerebral arteries. Collateral vessels of "moyamoya"

heterogeneity of the studied groups and depend on the severity of changes and the presence of the collateral circulation. Piao *et al.* found that patients with clinical symptoms of ischemia or with collateral circulation experience an increase in CBV and decrease in CVR, as opposed to the group of patients without a well-developed collateral vasculature. On the other hand, Nariai *et al.* showed that in cases with ischemic stroke or TIA; there followed an increase of CBV and OEF, while in patients with hemorrhages or TIA, there were no changes in perfusion parameters [4,6,26-28].

TREATMENT

Treatment of MMD often depends on the aggressiveness of its course. Cases with milder symptoms are usually treated more conservatively. More severe symptomatic cases are usually treated using revascularization procedures. The most cases (77%) are treated surgically because this has been shown to be more effective than nonsurgical treatment.

Medical treatments that have been proposed include vasodilators, antiplatelet agents, antifibrolytic agents, and fibrinolytic agents. However, the efficacy of medical treatments has yet to be proven in clinical trials. Epileptic cases have been managed using anticonvulsants.

Ischemic episodes and thrombosis can be managed using antiplatelets, thus possibly preventing the progression of MMD as well [13].

Surgical treatments are divided into three groups: Direct, indirect, and combined/other methods. Direct bypass includes vein grafts and extracranial-intracranial anastomosis of the STA to the MCA (STA-MCA anastomosis). Extracranial-intracranial bypass was first performed in 1972 by Yaşargil. Indirect bypass can involve any of several procedures including encephaloduroarteriosynangiosis, encephalomyosynangiosis, encephalomyoarteriosynangiosis, encephaloarteriosynangiosis, durapexy, multiple cranial bur holes, and transplantation of omentum. The indirect procedures bring in circulation to the intracranial regions by introducing newly developed vasculature from sutured tissue. Indirect surgeries are better for patients without good candidate cortical branches for anastomosis. These procedures may not be enough to prevent further ischemia, and therefore, a combination of direct and indirect procedures is generally preferred [29-31].

Direct revascularization has been shown to drastically improve CBF and thus potentially prevent brain infarction. Bypass also offloads stressed moyamoya vessels, thus potentially decreasing the risk of hemorrhage.
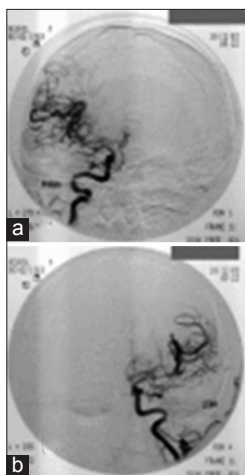
Fig. 7: Case 3. Suzuki Grade III. A 33-year-old man with seizures, aphasia and right-sided hemiparesis. Angiogram of the right (a) and of the left (b) internal carotid artery. Stenosis of the distal parts of the internal carotid arteries; proximal stenosis of
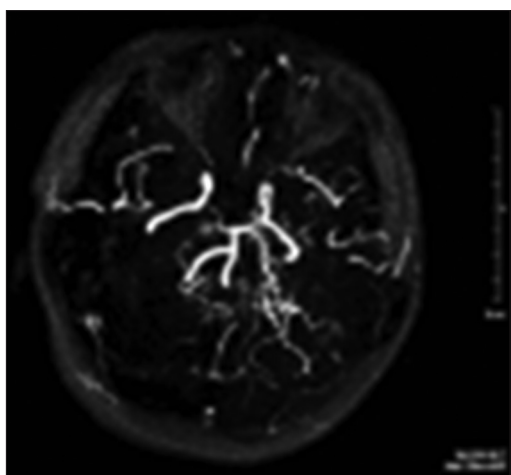

Fig. 8: Case 2. Suzuki grades V/VI. Magnetic resonance angiography, maximum intensity projection reconstruction in axial plane. No signal from either of the anterior or middle cerebral arteries; collateral circulation vessels not visible

Direct bypass is generally limited to adults or older children due to the small caliber of the STA in younger children. Younger children are thus better candidates for combined indirect bypass methods such as encephaloduroarteriosynangiosis with encephalomyosynangiosis and/or encephalomyoarteriosynangiosis. However, recent research by Fujimura *et al*. has suggested that direct STA-MCA anastomosis is safe and effective in children of all ages, and these authors have reported good and excellent outcomes in patients with a mean age of 6.2 years.

Extracranial-intracranial bypass procedures have come under scrutiny since the extracranial-intracranial study group in 1985 reported failure of such surgery to reduce the risk of stroke. However, physiological PET imaging (rCBF and OEF) did not constitute a requirement for entry. More recent Japanese and US studies have shown that those patients who underwent surgical revascularization had no ischemic episodes following surgery in the Japanese study, and fewer ischemic episodes than preoperatively in the US study [32]. In children with MMD, direct and indirect extracranial-intracranial bypass has been shown to improve symptoms, reverse neurological deficits, prevent further ischemic episodes, allow normal intelligence development, decrease seizure activity, and result in the disappearance of involuntary movements. In adults, these procedures have resulted in the prevention

of ischemic episodes and improvement in symptoms and cerebral hemodynamics.

The effectiveness of these procedures in hemorrhagic cases is not as well studied for ischemia. It has been suggested that bypass procedures may offload the "stress" onto perforating vessels and hence decrease subsequent risk of hemorrhage. Some data do exist, however, to justify revascularization for hemorrhage prevention. A 1997 study of patients with hemorrhagic MMD showed that 28.3% of patients without surgery had recurrent hemorrhage during follow-up compared with 19.1% of those who received surgery. Yoshida *et al.* conducted a survey of 28 patients with hemorrhagic MMD with a mean follow-up period of 14.2 years. Rebleeding was observed in 1 of 8 patients who underwent bypass surgery and in 5 of 13 who did not. This finding suggests that rebleeding was less likely to occur in patients who had undergone bypass surgery. However, there was no significant difference in the rebleeding ratio or death rate between patients with and those without revascularization surgery. The role of extracranial-intracranial bypass surgery in hemorrhagic MMD does appear promising. In 1 study, 11 of 22 patients were surgically treated, with 6 undergoing STA-MCA bypass and the other 5 undergoing encephaloduroarteriosynangiosis. The patients were followed up between 0.8 and 15.1 years. The incidence of hemorrhagic and ischemic stroke was significantly lower in patients who underwent STA-MCA bypass when compared with patients who underwent encephaloduroarteriosynangiosis or conservative therapy. In the pediatric population, there may be also a benefit of revascularization; Suyama *et al.* reported on 3 patients with hemorrhagic MMD, 2 of whom underwent STA-MCA anastomoses with encephalomyosynangiosis. No subsequent evidence of ischemic episodes or hemorrhage was noted at follow-up in these 2 patients. There are more studies currently underway examining extracranial-intracranial procedures in MMD [33,34].

Among 1 of the most recent studies from Japan, Byval'tsev and Suzuki reported findings on direct and indirect treatments in 140 patients with MMD [35]. Their findings show good and excellent clinical results in 92.9% of cases and cerebral circulation normalization in 97.1% of patients. These results from 2007 suggest the benefit of surgical treatment tailored to the individual case of MMD.

Better outcomes in revascularization surgery may now be feasible due to improvements in operative methods. Intraoperatively, there have been several developments to assess bypass graft patency. One promising method is using intraoperative video fluorescence angiography, which involves using a fluorescent tracer (indocyanine green) and specially equipped surgical microscopes that are able to view light in the near-infrared spectra. Woitzik *et al.* demonstrated that intraoperative angiography was useful in identifying both nonfunctioning and stenotic bypass grafts. Postoperatively, improvements in imaging techniques allow for diagnosis of hyperperfusion and other possible side effects from surgery, enabling prompt treatment [36-38].

CONCLUSION

MMD is an important cause of stroke in children and young adults. Further investigations are needed to identify the underlying cause of moyamoya disease. High-throughput proteome-wide approaches promise to provide a better insight into global pathways and interactions at play in moyamoya disease. Surgery is the only successful method of treatment, preventing from disease recurrence. A proper qualification for surgery should base on a comprehensive angiographic and imaging evaluation of brain structures. With advances in imaging and other diagnostic tools, the incidence and prevalence of MMD is increasing. It is anticipated that bypass procedures for MMD will be increasingly required at main treatment centers.

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