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STROKE (H ADAMS, SECTION EDITOR)

Recent Advances in Moyamoya Disease: Pathophysiology and Treatment

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Abstract Moyamoya disease is a progressive intracranial arteriopathy characterized by bilateral stenosis of the distal portion of the internal carotid artery and the proximal anterior and middle cerebral arteries, resulting in transient ischemic attacks or strokes. The pathogenesis of moyamoya disease remains unresolved, but recent advances have suggested exciting new insights into a genetic contribution as well as into other pathophysiological mechanisms. Treatment that may halt progression of the disease or even reverse the intracranial arteriopathy is yet to be found. There are strong indications that neurosurgical intervention, through direct, indirect, or combined revascularization surgery, can reduce the risk of ischemic stroke and possibly also cognitive dysfunction by improving cerebral perfusion, although randomized clinical trials have not been performed. Many questions regarding the indication for and timing of surgery remain unanswered. In this review, we discuss recent developments in the pathogenesis and treatment of moyamoya disease.

Keywords Moyamoya · Latest advancements · Pathophysiology · Genetics · Revascularization · Direct bypass · Cerebral perfusion studies · Neuroimaging · Outcome · Cognition

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Abbreviations

CBF	Cerebral blood flow
CT	Computed tomography
CVR	Cerebrovascular reserve
DSA	Digital subtraction angiography
EPC	Endothelial progenitor cell
ICA	Internal carotid artery
MCA	Middle cerebral artery
MMD	Moyamoya disease
MMP	Matrix metalloproteinase
MMS	Moyamoya syndrome
MMV	Moyamoya vasculopathy
MRI	Magnetic resonance imaging
PET	Positron emission tomography
RCT	Randomized controlled trial
SMC	Smooth muscle cell
STA	Superficial temporal artery
TIA	Transient ischemic attack

Introduction

Moyamoya disease (MMD) is a rare cause of stroke characterized by progressive stenosis of the supraclinoid internal carotid arteries (ICAs) and their proximal branches [1]. The disease was named after the typical appearance on digital subtraction angiography (DSA) of collateral blood vessels that develop at the base of the brain and resemble "something hazy, like a puff of smoke," *moyamoya* in Japanese [2]. Patients with idiopathic moyamoya are diagnosed as having MMD. In a minority of patients, the vasculopathy occurs in association with other conditions, e.g., sickle cell disease or neurofibromatosis, and these patients are categorized as having moyamoya syndrome (MMS) [1]. Patients usually present with transient ischemic attacks (TIAs) or ischemic stroke. In

some regions in Asia, a large proportion of patients (mostly adults) present with intracerebral hemorrhage [3]. Patients may also have headache, seizures, chorea, or cognitive impairment. Infarct patterns on magnetic resonance imaging (MRI) differ depending on age and the severity of the angiographic abnormalities, and suggest a combination of thromboembolism and hemodynamic compromise as the cause of infarcts [4]. Although MMD is most frequently seen in Eastern Asia, it is increasingly recognized in the Western world [1, 3]. Two age peaks are recognized: one during childhood and one in young adults [1, 3]. In most regions, women are more frequently affected than men [3]. In 2009, Scott and Smith [1] reviewed the medical progress that had been made in MMD and MMS. In this review we focus on the very recent advances regarding two important questions in moyamoya vasculopathy (MMV): (1) what causes the disorder and (2) how to treat it.

What Causes Moyamoya Vasculopathy?

Pathological analysis of the affected intracranial vessels in patients with MMD has shown fibrocellular thickening of the intima with an increased number of smooth muscle cells (SMCs), marked undulation of the internal elastic lamina, and attenuation of the media, generally without signs of atherosclerosis or inflammation [5]. Mural thrombi are frequently observed [6]. Recent MRI studies have shown significant outer-diameter narrowing of affected vessels, suggesting vascular constrictive changes that are not observed in intracranial arterial stenosis caused by atherosclerosis [7, 8]. In the typical, dilated collaterals the elastic lamina is fragmented, the media may become thin, and microaneurysms can be present, probably as a result of increased stress on the vessel wall [9]. Collateral moyamoya vessels may also show narrowed, thrombosed lumens [5].

The processes that underlie these abnormal pathological findings remain largely unknown, but the association of the angiographic moyamoya appearance with diverse genetic and acquired conditions, in combination with its idiopathic occurrence, suggests that more than a single factor is responsible. MMD is probably a complex disorder in which genetic and environmental factors play a role, possibly via a so-called double-hit mechanism [10]. In addition to direct disease-causing genetic factors, vessel wall stress and repair factors, angiogenesis- and vasculogenesis-related factors, thrombogenic factors, and autoimmune response processes have all been implicated in MMD. Most likely, multiple factors will be linked in as yet unresolved pathophysiological mechanisms. Histopathological features of collateral moyamoya vessels in a 44-year-old man with proven intracranial atherosclerotic disease were recently reported to be similar to those described in idiopathic MMD [11]. On the basis of these findings, the authors of the study suggested that MMV may develop in two distinct steps: first, a large artery disease that may have different causes, and second, a vasoproliferative response to the large artery disease that may be similar in patients with MMD and in patients with MMS.

Genetic Factors

Recent epidemiological studies found that around 15 % of patients in Japan have a familial form of MMD [12], with pedigree analysis suggesting autosomal dominant inheritance with incomplete penetrance [13]. Familial occurrence in patients of other ethnicity has also been reported but appears less prevalent [14]. In an Algerian family, five male patients were diagnosed with MMS with multisystemic manifestations, suggesting a hereditary syndrome with an X-linked recessive pattern of inheritance [15]. The intracranial vasculopathy associated with smooth muscle actin alpha 2 (*ACTA2*) mutations has been referred to as MMS, but should probably not be regarded as such, since it has distinctive angiographic features, including dilatation of proximal ICAs, an abnormally straight course of intracranial arteries, and absence of typical moyamoya collateral vessels [16•]. Until recently, multiple studies had suggested associations between various genetic loci—including 17q25—and specific genes, but a causal gene for MMD that was involved in independent populations had not been identified [17]. In 2011, two research groups independently found an association between specific variations (predominantly p.R4859K and p.R4810K) in *RNF213*, all leading to an amino acid substitution, and MMD in Japanese, Korean, and Chinese familial and sporadic cases, but not in Caucasian patients [18••, 19••]. Ten other variants in *RNF213* were found in non-p.R4810K East Asian and Caucasian patients, of which some were found in familial cases [18••]. Although the carrier frequency of the p.R4810K mutation was lower in the Chinese Han population than in Korea and Japan, it was still associated with MMD [20, 21]. It is unclear whether these *RNF213* genetic variations are solely associated with MMD or may also be involved in other intracranial vessel diseases [22]. How variants in *RNF213* lead to MMV also remains to be elucidated. *RNF213* knockdown zebra fish show pathological changes in the blood vessels [18••], and gene expression profiles in an in vitro model of vascular endothelial cells of p.R4810K carriers and moyamoya patients have shown downregulation of securin, and lowered angiogenic activity in comparison with vascular endothelial cells from controls without the p.R4810K variant [23]. Recent research also revealed a phenotype–genotype relationship, with patients homozygous for the c.14576G>A variant in *RNF123* having a severer form of the disease than heterozygotes [24]. These results implicate a genetic and phenotypic heterogeneity in MMD [20].

Vessel-Wall-, Angiogenesis-, and Vasculogenesis-Related Factors

In the search for the pathogenesis of MMD, numerous vascular SMC-related molecules and cells and angiogenesis- and vasculogenesis-related molecules and cells have been investigated [25, 26]. Although much research has focused on angiogenesis, i.e., sprouting of endothelial cells from existing vessels—vasculogenesis—i.e., formation of new blood vessels from circulating bone-marrow-derived endothelial progenitor cells (EPCs), which is induced by ischemia—may be equally important [25]. A recent study of plasma samples showed distinctive expression patterns of matrix metalloproteinases (MMPs), their natural inhibitors, tissue inhibitors of MMPs, and several other cytokines and angiogenic factors in MMD patients in comparison with controls [27]. MMPs play a role in both pro-angiogenic and anti-angiogenic processes [28]. In MMD patients, the balance between MMPs and tissue inhibitors of MMPs was disturbed [27]. The level of MMP-9, a proteolytic protein that can degrade the endothelial basal lamina and the extracellular matrix, was increased in MMD patients [29]. Increased levels of MMP-9, vascular endothelial growth factor, and monocyte chemoattractant protein 1 have been shown to result in recruitment of EPCs from the bone marrow into the circulation [30, 31]. Circulating EPCs have been suggested to be a pathogenetic marker of MMD [32]. In addition, a more pronounced expression of basic fibroblast growth factor in MMD patients was seen in the SMCs, intima, and endothelial cells in superficial temporal artery (STA) samples of MMD patients [33]. Basic fibroblast growth factor may be involved in the occlusion of both the ICA and its proximal branches and may also promote the formation of the typical moyamoya collateral blood vessels [33].

Serologic analysis to find key proteins associated with MMD found 22 differently expressed proteomes in comparison with normal controls [34]. Complement C1 inhibitor protein (an upregulated protein possibly associated with the progressive stenosis of affected vessels) and apolipoprotein C-III (a downregulated protein assumed to reduce formation of occlusive lesions) showed clearly different expression and could play a role in MMD [34]. Proteomic analysis has revealed two as yet unidentified proteins in the cerebrospinal fluid of patients with MMD as potential biomarkers [35].

Autoimmune Response and Inflammation

Because of the absence of evidence of inflammation in pathology studies, an inflammatory cause of MMD has long been considered unlikely. However, in a recent immunohistochemical study of three MMD patients who underwent autopsy, involvement of an autoimmune response was suggested by aberrant expression of IgG in the internal elastic lamina of the ICA and the middle cerebral artery (MCA) [36•]. The authors of the study suggested that the IgG deposits may underlie the disruption of the internal elastic lamina and facilitate migration of S100A4-positive SMCs into the intima, which then leads to the typical large intracranial vessel stenosis [36•]. In addition, a high-density autoantibody array identified elevated levels of 165 autoantibodies in the serum of MMD patients in comparison with controls, of which six were suggested to be specific for MMD after the data had been combined with genetic data by novel bioinformatics techniques [37•]. Three of these six proteins were present on loci previously associated with MMD [37•]. A high prevalence of autoimmune diseases, such as diabetes mellitus type I [38] and thyroid dysfunction [39, 40], has been found among patients with MMD, further supporting a possible immunological component in MMD.

Although the recent new insights into the pathogenesis of MMV do not have direct implications for clinical practice yet, they may lead to useful biomarkers of the disease and its course as well as to novel treatments. Alternatively, they may aid in the indication for and timing of currently available treatments.

How Should Patients with Moyamoya Vasculopathy Be Treated?

There is currently no treatment that can halt progression or reverse the intracranial arteriopathy of MMD. Treatment strategies are aimed at alleviating symptoms and preventing recurrent strokes, TIAs, or cognitive deterioration.

Nonsurgical Therapy

It is unclear whether drug therapy using antiplatelet agents improves outcome. Many, mostly non-Asian, practitioners prescribe antiplatelet agents with the aim of improving the microcirculation, preventing (micro)embolism, and maintaining flow through a bypass in patients who were operated on [41]. The guidelines of the Japanese Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis recommend the use of antiplatelet agents in the acute and symptomatic chronic phase in children and adults except in those who present with hemorrhage [42•]. Dehydration must be avoided because hypovolemia may result in a reduced cerebral blood flow (CBF) [43]. Hyperventilation may result in cerebral vasoconstriction, which possibly provokes TIAs or stroke and should thus be avoided [1, 43]. Expert opinion suggests that for the treatment of migraine or other MMV-associated headaches, anticonvulsants such as topiramate may be considered rather than conventional medications such as ibuprofen (interaction with aspirin), triptans (causing vasoconstriction), clonidine, and beta blockers (reduce blood pressure) decreasing cerebral perfusion [44].

Endovascular treatment with angioplasty and stenting of the ICA has not been successful in treatment of MMV [45, 46•].

Neurosurgical Revascularization

Although randomized controlled trials (RCTs) have not been performed, there are strong indications from observational studies that neurosurgical intervention, through direct or indirect revascularization techniques, can reduce the risk of ischemic stroke and possibly cognitive dysfunction by improving CBF [46•, 47]. A meta-analysis of 57 studies in children, including 1,322 who were operated on, concluded that 51.2 % of previously symptomatic patients became asymptomatic, 35.5 % showed improvement in the severity or frequency of symptoms, 10.5 % remained stable, and 2.7 % deteriorated after revascularization procedures [48]. The positive results of surgery were in clear contrast with the previously reported symptomatic progressive disease course in 50-66 % of children who were not surgically treated [48]. The annual ischemic stroke and hemorrhage rates in a North American cohort of untreated adult patients with MMD were 13.3 % and 1.7 %, respectively [49]. Disease progression was reported in 23.8 % of adults in nonsurgically treated hemispheres, and in half of them it was symptomatic [50]. Recently published studies of large cohorts of surgically treated patients confirm the favorable results after revascularization both in children and in adults, with improvement of the modified Rankin Scale after surgery [51, 52], a significant reduction of symptoms [53, 54], and a subsequent stroke or death risk ranging from 0.8 to 13 % within the first 5–10 years postoperatively [53, 55, 56]. Severe headache, a prominent symptom in around 20 % of (often young) patients, may improve after revascularization [57–59].

In light of the above findings, it seems unlikely that RCTs will be performed to test the efficacy of revascularization surgery in improving outcome in patients with MMD who present with TIAs or symptoms of ischemic stroke. Nevertheless, many questions regarding revascularization surgery remain unanswered. There is no consensus on the indication for and timing of revascularization surgery in asymptomatic patients, or for the asymptomatic contralateral hemisphere in symptomatic patients, nor is there consensus on what type of revascularization surgery should preferably be performed. The American Heart Association recommends that surgery should be considered in children who have progressive ischemic symptoms or evidence of inadequate blood flow or cerebral perfusion reserve without contraindications to surgery [47]. Other guidelines recommend surgical treatment in pediatric and adult patients if they have progressive ischemic symptoms (including TIAs) or evidence of inadequate blood flow, as measured with single-photon-emission computed tomography (CT) or positron emission tomography (PET) [42•, 43, 46•]. Careful observation may be justified in asymptomatic patients with undisturbed cerebral hemodynamics. The effect of surgical treatment in patients who present with hemorrhage is less clear and is currently being investigated in an RCT in Japan [60]. A recent study of 97 patients and a review suggested a beneficial effect of direct revascularization on prevention of rebleeding in comparison with conservative treatment [61, 62].

Although surgical therapy in MMV has mostly focused on prevention of recurrent stroke, there is increasing attention for the possible benefit from revascularization therapy in improving cognitive disturbances associated with MMV [46•, 63–65]. Cognitive deficits may also occur in the absence of overt stroke and have been associated with frontal hypoperfusion [65–67].

Little is known about the optimal timing of surgery. From the perspective of secondary prevention, early surgery may be beneficial, but recent stroke and infection may be a reason to postpone the procedure [46•].

The measurement of CBF and cerebrovascular reserve (CVR) assessed by PET or single-photon-emission CT scan is not only helpful to determine the indication for surgery, but can also aid the neurosurgeon in deciding which parts of the brain may benefit from revascularization [68, 69]. Recently, less invasive alternatives have become available to measure quantitative maps of CBF and CVR in the brain such as blood-oxygen-level-dependent MRI [70], arterial spin labeling MRI [71, 72], and CT perfusion [73, 74].

Techniques

The goal of both direct and indirect revascularization techniques is to improve the blood flow to the brain. Although after direct bypass surgery the CBF is augmented immediately, indirect revascularization may result in improved collateralization within weeks [75]. A direct bypass consists most commonly of a microsurgical anastomosis between the frontal or the parietal branch of the STA, with a minimal STA diameter of 0.6 mm, and a cortical artery, most often a branch of the MCA. In young children, direct bypass surgery is particularly challenging owing to the small caliber of the blood vessels [75]. The STA is also used for direct connection to the anterior cerebral artery [76]. Furthermore, anastomoses between the occipital artery or the middle meningeal media artery and the MCA have been described [75]. Indirect techniques approximate richly vascularized tissue such as the temporal muscle (encephalomyosynangiosis), the pericranium [encephalogaleo(periosteo)synangiosis], the dura (encephalodurosynangiosis), the STA (encephaloarteriosynangiosis), or combinations of these on the affected cortex in order to promote angiogenesis over time [77]. Burr holes, placed either solely or in combination with other techniques, may also result in

neoangiogenesis, in particular in children, with the most important advantage that technically this is the least challenging operation [78, 79]. Direct and indirect techniques may also be combined to obtain immediate increased blood flow and benefit from the diffuse neovascularization that develops over time [75]. It remains unclear which technique results in the most favorable outcome, as randomized studies comparing the various techniques have not been performed. Naturally, the expertise of the surgeon is the key factor to a successful outcome [46•, 47]. A meta-analysis of 1,156 children with MMD who were operated on with various techniques concluded that direct and combined procedures provide better revascularization on DSA than solely indirect procedures [48]. However a difference in functional outcome could not be demonstrated [48]. Similar results were found in adults [48, 80].

Recently developed revascularization techniques are mostly modifications from already existing methods, aiming to refine the procedures, to provide blood flow to territories other than the MCA and anterior cerebral artery territories, or to perform additional surgery after insufficient revascularization [54, 81–87] (Table 1).

Complications

Potential perioperative complications in revascularization surgery include infection, intracranial hemorrhage, ischemic stroke, and hyperperfusion syndrome [1, 88]. Hypotension, hypovolemia, hyperthermia, hypocarbia, and hypercarbia must be avoided in the perioperative period with postoperative administration of ample intravenous fluids for 24-72 h [1]. Data on complications of the various surgical series are difficult to compare because patient characteristics and revascularization methods differ and the studies do not always distinguish between complications with transient symptoms and those with permanent loss of function. Large series or reviews report rates of perioperative stroke ranging from 4.4 % [48] to 10 % [43], and a rate of reversible ischemic events of 6.1 % [48] in direct, indirect, and combined revascularization procedures. In a series of 450 procedures in adult and pediatric patients, the reported morbidity rate was 3.5 % and the authors of the study reported the mortality rate was 0.7 % [52]. Postoperative (symptomatic) cerebral hyperperfusion is an important complication after a direct bypass has been performed, with reported incidences of 20-40 % [88]. Patients may complain of headache and may develop seizures and

Table 1 Recently developed modifications of revascularization techniques in moyamoya disease

Study	Technique	Procedure	Indication	Advantage
Hayashi et al. [81] ($n=3$)	Combined	OA–PCA bypass with EDPS and burr holes	Additional surgery in postoperative ischemia due to progressive PCA lesions	Direct revascularization in ischemic area
Muto and Oi [87] ($n=1$)	Indirect	IDAS: STA anastomosed into inner layer dura sandwiched by the outer layer	Maximizing preservation of existing neovascular network	Simplicity, reduced invasiveness, preservation of collaterals, small skin incision
Kuroda et al. [84] ($n=75$)	Combined	Standard STA–MCA bypass plus EMS plus EDMAPS using a frontal pericranial flap covering the frontal area unilaterally	Disturbed frontal hemodynamics	Safe and effective with frontal revascularization
Kawashima et al. [83] ($n=7$)	Direct	Simultaneous STA–ACA/STA–MCA bypass using a long STA graft with two craniotomies	Disturbed ACA hemodynamics and cognitive functions	Immediate revascularization in two areas
Horiuchi et al. [82] ($n=1$)	Combined	PAA–MCA bypass plus EPS	Additional surgery in refractory moyamoya	Direct revascularization after already performed combined procedures
McLaughlin and Martin [85] ($n=65$)	Indirect	EDAS with splitting and resection of the innermost vascularized dural layer	Indirect revascularization	Protects the MMA branches, optimizes arterioduropial synangiosis
Kronenburg et al. [86] ($n=1$)	Combined	Standard STA–MCA bypass plus EDMS plus bifrontal EDPS	Patients with disturbed frontal hemodynamics and cognitive and lower extremity dysfunction	One-stage direct unilateral and indirect bifrontal revascularization

ACA anterior cerebral artery, *EDAS* encephaloduroarteriosynangiosis, *EDMAPS* encephaloduromyoarteriopericraniosynangiosis, *EDMS* encephaloduromyosynangiosis, *EDPS* encephaloduroperiosteosynangiosis, *EMS* encephalomyosynagiosis, *EPS* encephaloperiosteosynangiosis, *IDAS* intradural arteriosynangiosis, *MCA* middle cerebral artery, *MMA* middle meningeal artery, *OA* occipital artery, *PAA* posterior auricular artery, *PCA* posterior cerebral artery, *STA* superficial temporal artery

focal neurological deficits. Recognition of hyperperfusion syndrome is important because treatment is with strict blood pressure control [89].

How Do We Do It?

In patients in whom MMV is suspected, we perform DSA to confirm the diagnosis and study the extent of the disease, the collateral blood vessels, and the possibilities for revascularization surgery. With an ^{15}O-labeled water PET scan before and after administration of acetazolamide, we assess in which parts of the brain CBF and CVR are compromised. In addition, all patients undergo a formal neuropsychological assessment. In multidisciplinary consultation, an individual treatment plan is made for each patient. On the basis of the clinical symptoms, including TIAs, stroke, and cognitive disturbances, the extent and severity of hemodynamic disturbances, and the technical possibilities, we decide whether, when, where, and how to perform revascularization surgery. When technically feasible, we perform a direct STA–MCA bypass to the most severely affected hemisphere with encephaloduromyosynangiosis at the site of trepanation. If there are indications of poor frontal vascularization, a one-stage indirect bifrontal or unifrontal procedure through encephaloduroperiosteosynangiosis is considered (Fig. 1) [86]. In this way, the MCA as well as one or both of the frontal territories can be revascularized. In patients who do not develop symptoms of the contralateral hemisphere and in whom the PET scan does not show severe hemodynamic compromise, we will, in general, not recommend a revascularization operation on the contralateral side, but will closely follow the patient for development of new symptoms. In patients with symptoms from both hemispheres or in the case of severe hemodynamic compromise, revascularization of the contralateral side will be performed, with the timing of the surgery depending on the patient's symptoms. We are reluctant to perform surgery on both sides on the same day and will generally perform the revascularization operation on the contralateral side 6 weeks later. In all patients we repeat the neuropsychological assessment, MRI, PET, and DSA 1 year postoperatively. In the case of a stable clinical, radiological, and hemodynamic situation (including the non-operated-on asymptomatic hemisphere), we follow children and adult patients at least annually at outpatient clinics. Additional imaging is performed in the case of new symptoms.

Conclusion

MMV is a rare cerebrovascular condition with an as yet largely unknown and probably multifactorial cause. Recent

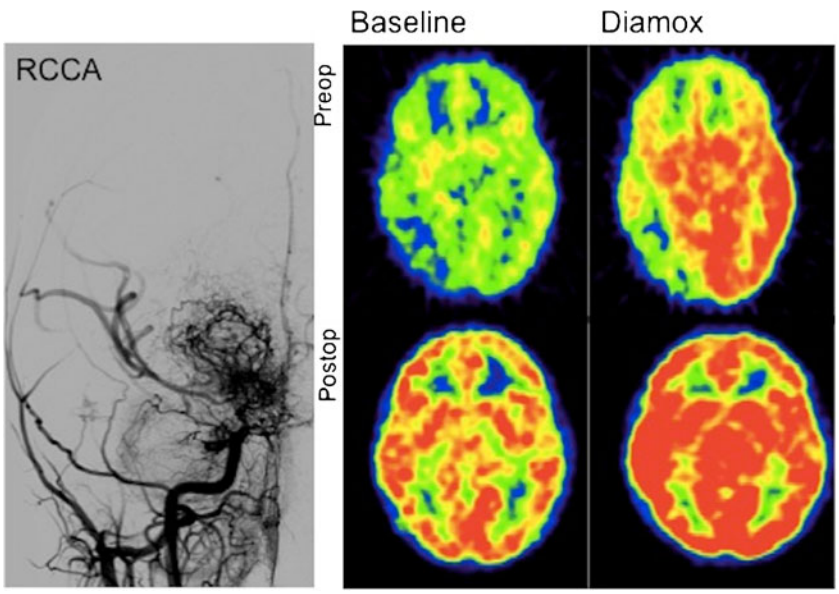

Fig. 1 Digital subtraction angiography and [^{15}O]H_2O positron emission tomography (PET) scan of a 9-year-old girl diagnosed with bilateral moyamoya syndrome associated with neurofibromatosis type I manifesting as frequent transient ischemic attacks, consisting of either a diplegia with paralysis of both legs and intact consciousness or a monoparesis of the arm. Furthermore, she had severe migraine attacks. The *left panel* shows stenosis of the right terminal internal carotid artery, M1, and A1 with extensive moyamoya collaterals. The *right panel* shows preoperative and postoperative results of the [^{15}O]H_2O PET scan before and after administration of acetazolamide. Before surgery, cerebral blood flow and cerebrovascular reserve in the entire right hemisphere and in the left frontal and parietal area were decreased, with preserved CVR in the left middle cerebral artery and posterior cerebral artery territory. After a direct right-sided superficial temporal artery to middle cerebral artery bypass, combined with encephaloduromyosynangiosis and bifrontal encephaloduroperiosteosynangiosis, the postoperative [^{15}O]H_2O PET scan showed improvement of baseline CBF and CVR in the right hemisphere and the left frontal regions. A color scale indicates CBF with blue at the low end of the scale and red at the high end of the scale. *RCCA* right common carotid artery

new evidence has shown involvement of *RNF123*, several vessel wall stress and repair factors, and a possible role of an autoimmune response, which have the potential to lead to new biomarkers of the disease and of disease progression, as well as to new treatment options. Early recognition of MMD and MMS and their timely treatment by revascularization surgery are essential to minimize the risk of future strokes. Future research should be directed at finding treatment that may halt progression of the vasculopathy and at refining the indications for and the timing of revascularization surgery.

Compliance with Ethics Guidelines

Conflict of Interest Annick Kronenburg, Kees P.J. Braun, and Albert van der Zwan declare that they have no conflict of interest.

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