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REVIEW

Moyamoya disease and syndromes: from genetics to clinical management

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Abstract: Moyamoya angiopathy is characterized by a progressive stenosis of the terminal portion of the internal carotid arteries and the development of a network of abnormal collateral vessels. This chronic cerebral angiopathy is observed in children and adults. It mainly leads to brain ischemic events in children, and to ischemic and hemorrhagic events in adults. This is a rare condition, with a marked prevalence gradient between Asian countries and Western countries. Two main nosological entities are identified. On the one hand, moyamoya disease corresponds to isolated moyamoya angiopathy, defined as being "idiopathic" according to the Guidelines of the Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis. This entity is probably multifactorial and polygenic in most patients. On the other hand, moyamoya syndrome is a moyamoya angiopathy associated with an underlying condition and forms a very heterogeneous group with various clinical presentations, various modes of inheritance, and a variable penetrance of the cerebrovascular phenotype. Diagnostic and evaluation techniques rely on magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) conventional angiography, and cerebral hemodynamics measurements. Revascularization surgery can be indicated, with several techniques. Characteristics of genetic moyamoya syndromes are presented, with a focus on recently reported mutations in *BRCC3/MTCP1* and *GUCY1A3* genes. Identification of the genes involved in moyamoya disease and several monogenic moyamoya syndromes unraveled different pathways involved in the development of this angiopathy. Studying genes and pathways involved in monogenic moyamoya syndromes may help to give insights into pathophysiological models and discover potential candidates for medical treatment strategies.

Keywords: moyamoya disease, moyamoya syndrome, stroke, surgical revascularization, genetics

Introduction

Moyamoya cerebral angiopathy is characterized by a progressive stenosis or occlusion of the intracranial internal carotid artery (ICA) and/or the proximal portion of the anterior cerebral artery (ACA) and middle cerebral artery (MCA). This steno-occlusive pattern is associated with a compensatory development of a collateral network of vessels at the base of the brain, appearing as a "puff of smoke" on conventional angiography ("moyamoya" in Japanese).

This angiopathy was first described in Japan in 1957,[1] and was called "moyamoya disease" for the first time by Suzuki and Takaku in 1969.[2]

When used alone, the term "moyamoya phenomenon" refers to this cerebral angiopathy regardless of its cause, although this angiographic pattern can have multiple

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causes. Moyamoya disease (MMD) refers to isolated and primary moyamoya angiopathy, usually bilateral. Moyamoya syndromes (MMS) correspond to moyamoya angiopathy associated with other neurological or extra-neurological manifestations, with or without a well-known associated inherited or acquired condition. Hereditary MMS constitute a heterogeneous group that tends to be clarified with advances in genetic research. It includes Mendelian and non-Mendelian genetic causes that will be detailed below.

Whatever the cause, moyamoya angiopathy increases the risk of ischemic and hemorrhagic brain damage. The specific treatment to prevent such complications is usually revascularization surgery, associated or not with therapeutics relating to the underlying disease.

Pathophysiology of moyamoya remains unknown to date. The identification of genes involved in MMD/MMS provides clues to understand the pathophysiology and gives hope for the development of treatments that could limit vascular damage.

Moyamoya disease

Epidemiological data

Epidemiological studies on MMD are heterogeneous, using various methodologies, making valid comparisons between these studies difficult. In Japan, where MMD is frequent, numerous epidemiological nationwide surveys were performed.[3] In other countries, data were derived from smaller studies which sometimes mixed MMD and MMS and are therefore more heterogeneous.

MMD is found in all ethnicities, but there is a marked East-West gradient: if MMD is a rare condition in Western countries, its occurrence is about ten times higher in East Asian countries.[4–6] The highest prevalence of MMD is found in Japan.[7–10] High standard epidemiological studies found an MMD prevalence of 3.16–10.5/100,000 and an incidence of 0.35–1.13/100,000/year in this country.[7–10] All studies showed a female preponderance with twice as many females as males.

Age of MMD onset follows a bimodal distribution with a first peak in childhood between 5 and 10 years of age and a second peak during the fourth decade.[11] A familial history is noted in 10% to 15% of cases in Japan.

Incidence does not seem to be uniform across East Asian countries. The People's Republic of China or Korea have high incidence and prevalence rates, close to those observed in Japan. In contrast, the incidence rate in Taiwan is similar to that found in Western countries.[12–15]

In Western countries, incidence and prevalence of MMD are much lower than those in East Asian countries. A study conducted in California and Washington State showed that the annual incidence rate of MMD/MMS was 0.086/100,000 persons, ie, 4–13 times lower than incidence of MMD in Japan.[5] However, the observation of an ethnicity-related pattern suggests a strong genetic determinism in MMD: the incidence in Californian people originating from Asia was similar to the Japanese incidence. In line with this observation, in Hawaiian patients of Japanese descent a significantly higher prevalence was observed than in those of Caucasian origin.[14–16]

In Europe, MMD incidence was estimated 1/10 of MMD incidence in Japan.[6] In French pediatric patients, the prevalence of pediatric MMD/MMS was approximately 1/20 of that estimated in Asia, with a less frequent familial history, around 7.5%.[17]

Data about MMD for African and African American population are scarce. A study conducted in California showed that ethnicity-specific incidence of moyamoya was higher among African American people (0.13/100,000 person-years) than among Caucasian people (0.06/100,000 person-years), but these two incidences became similar when patients with a diagnosis of sickle cell disease were removed.[5]

Clinical presentation

Clinical presentation of MMD differs between adults and children. Adults present with transient or permanent cerebral infarction and intracranial hemorrhage, whereas children present mainly with ischemic events.[18–20] However, in occidental countries, adults seem to present with a lower rate of hemorrhage than in Asian countries.[21–23]

Ischemic manifestations, due to steno-occlusive lesions, are usually multiple and recurrent. Patients present with acute transient or permanent symptoms related with cerebral ischemia in the carotid branches territories or in watershed regions: mono or hemiparesis, sensory impairment, or aphasia/dysarthria. Rarely, patients may develop atypical symptoms such as syncope, visual symptoms, or pseudo-psychiatric symptoms. Ischemic events can be triggered by hyperventilation due to physical or intellectual activity, dehydration, fever, and crying in babies.[24] In these patients, cortical vessels are most often maximally dilated at steady state to compensate for chronic cerebral ischemia. Vasoconstriction in response to carbon dioxide decrease related to hyperventilation results in reduced cerebral perfusion.

While more than 20% of adult patients with MMD present with intracranial hemorrhage, intracranial bleeding is rare in MMD children.[25,26] Cerebral hemorrhage is mainly due to rupture of fragile deep collateral vessels with

deep intraparenchymal (basal ganglia region or periventricular deep white matter) or intraventricular hemorrhage. Subarachnoid hemorrhage is rare and, sometimes due to the rupture of saccular aneurysms located in the circle of Willis – most often in the vertebrobasilar system – developed in response to shifting circulatory patterns.

Intellectual disability is often reported in children with MMD. This cognitive disability was reported even among patients without history of stroke, suggesting the deleterious effect of cerebral chronic hypoxemia on cognitive functions, but tended to be greater in children who have had a stroke.[27,28] Bilateral disease and duration of symptoms are the main factors associated with cognitive deficits.

Migraine-like headache is also a common symptom in MMD, probably due to stimulation of dural nociceptors by dilated transdural collaterals, or can be a symptom of chronic hypoxemia. It is sometimes difficult to establish if headache is related to the disease or not. Epilepsy is frequent in pediatric patients, related to cortical ischemia. More rarely, choreic movement disorders occur in pediatric or adult patients, secondary to basal ganglia damage.

Imaging data

Diagnosis of moyamoya angiopathy relies on both the visualization of distal stenosis of one or both internal carotid arteries and/or their branches (ACA and MCA), and on neovascularization reflecting the progressive nature of the stenoting process. Accurate radiological assessment is crucial for diagnosis and treatment planning.

Magnetic resonance imaging and magnetic resonance angiography

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) provides information on cerebral arteries, brain parenchyma, and cerebral perfusion, making it a key of the diagnostic assessment and follow-up of patients. Easy to perform, in a non-invasive way and without any radiation, MRI-MRA may be sufficient to diagnose MMD when the following criteria (which were first established on conventional angiography) are met (Figure 1):[11]

- stenosis or occlusion of the terminal part of the ICA and/or the proximal portion of the ACA and/or MCA;
- visualization of an abnormal arterial vascular network seen in the vicinity of the steno-occlusive lesions, ie, in the basal

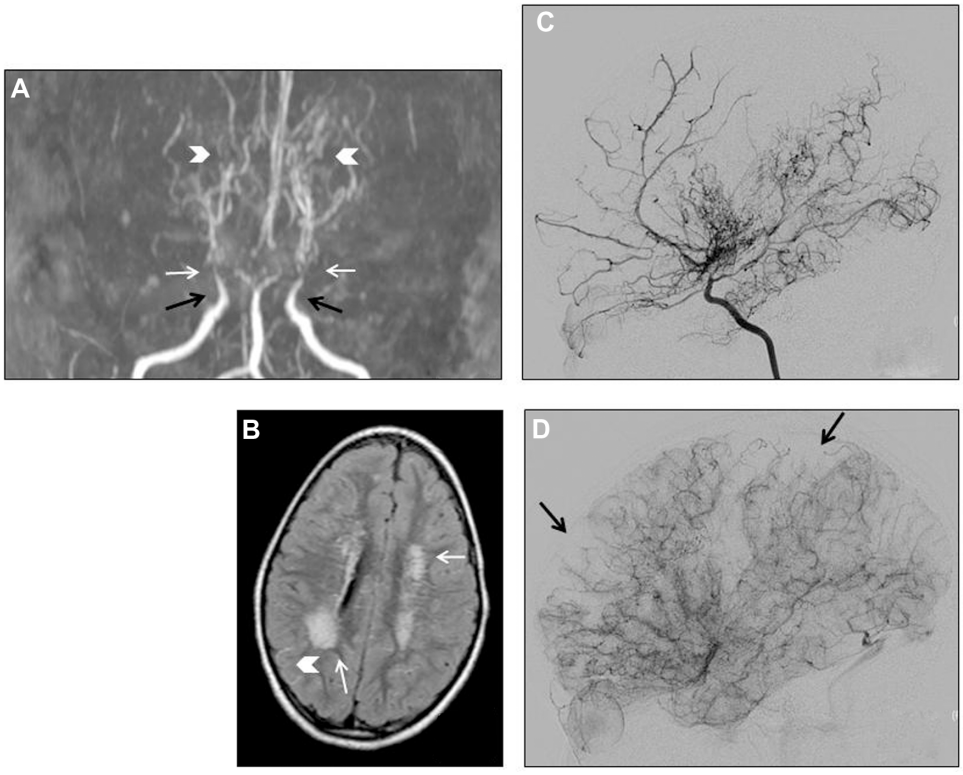

Figure 1 Moyamoya angiopathy imaging in a 4-year-old girl.
Notes: (**A**) MR angiography. Bilateral ICA stenosis (black arrows), occlusion of MCA (white arrows), moyamoya collaterals (arrow heads); (**B**) MRI FLAIR sequence. White matter ischemic lesions (white arrows) and flow void visualization (arrow head); (**C**) conventional angiography. Arterial stenoses and visualization of moyamoya collaterals; (**D**) conventional angiography. Parenchymal image: vascular defects (arrows).
Abbreviations: MR, magnetic resonance; ICA, internal carotid artery; MCA, middle cerebral artery; MRI FLAIR, magnetic resonance imaging Fluid Attenuation Inversion Recovery.

ganglia and thalamus, and with the appearance of a "puff of smoke". These deep perforating dilated moyamoya vessels are usually seen on MRA, and they can also be identified on T1 and T2-weighted MRI when more than two apparent flow voids are seen in basal ganglia and thalamus;
- the diagnosis is "definite MMD" if these findings are bilateral and is "probable MMD" if they are unilateral; and
- the posterior circulation is spared.

MRI shows recent and old ischemic and hemorrhagic lesions (T1-, T2-, T2*-weighted sequences) in the brain parenchyma. White matter hyperintensities located in the distal vascular bed supplied by penetrating branches of MCA/ACA and related to border-zone infarcts are frequently seen.

Asymptomatic microbleeds are seen in a large proportion of adult patients, and may be predictive of the risks of developing a hemorrhagic stroke.[29,30] Microbleeds are much more frequent in adult patients (from 28% to 46% according to MRI modalities) than in pediatric patients.[30–32]

Slowed cortical blood flow can be inferred from FLAIR sequences, showing linear hypersignals that follow a sulcal pattern and which are called the "ivy sign".[33]

MRI perfusion sequences called dynamic susceptibility contrast and more recently arterial spin labeling allow the estimation of the degree of cerebral hypoperfusion (see the "Cerebral hemodynamics measurement" section).[34]

Conventional angiography

Cerebral conventional angiography (Figure 1) – with ICA, external carotid arteries (ECA) and vertebral arteries injection – is the gold standard for diagnosis (see criteria in the "MRI and MRA" section), and classification of MMD according to Suzuki grades.[2,24]

However, because of the invasivity of the technique, conventional angiography is realized in limited circumstances: uncertain diagnosis or progression of the angiopathy during follow-up with non-invasive techniques, pre-surgical management, and sometimes evaluation after surgical revascularization.

Disease severity is classified into six progressive stages according to Suzuki's classification (Table 1).[2] It is important to note that MMD is a progressive condition and that some imaging criteria can appear or disappear during the course of the disease. For example, deep collateral vessels can be missing in the early and end stages. Moreover, contralateral lesions can develop in patients initially presenting with unilateral findings. This progressive bilateralization is more frequent in pediatric patients.[35–37]

Table 1 Angiographic grades according to Suzuki classification

Grades	Definition
I	Narrowing of ICA apex
II	Apparition of deep "moyamoya" collateral vessels
III	Progression of moyamoya collateral vessels
IV	Apparition of transdural collateral vessels originating from ECA
V	Progression of transdural collateral vessels and reduction of moyamoya vessels
VI	Occlusion of ICA and disappearance of moyamoya collateral vessels

Note: Data from Suzuki et al.[2]
Abbreviations: ICA, internal carotid artery; ECA, external carotid arteries.

Conventional angiography is the most accurate procedure to obtain a detailed mapping of collateral networks, which is essential for planning surgical treatment and avoiding disrupting existing collaterals during revascularization procedure. Indeed, several types of collateral networks typically develop in response to progressive occlusion of distal ICA: collateral deep vessel developed from thalamoperforating and lenticulostriate perforating arteries, that have the appearance of a puff of smoke on angiography imaging and are called "moyamoya vessels", but also pial collateral arteries developed from the posterior circulation and transdural collateral arteries most often developed from ECA branches.

At late stages of the disease, ICAs are totally occluded and anterior parenchymal vascularization relies essentially on these collateral networks.

Cerebral hemodynamics measurement

Assessment of cerebral perfusion is useful for diagnosis, treatment decision, and follow-up of patients with moyamoya angiopathy.[34]

Cerebral hemodynamic (single photon emission computed tomography [SPECT], perfusion computed tomography [CT], xenon-enhanced CT and MRI-based methods: dynamic susceptibility contrast and arterial spin labeling) and metabolic (positron emission tomography [PET]-scan) patterns observed in pediatric patients with MMD are:
- decrease of global cerebral blood flow compared with controls, with a predominant posterior cerebral blood flow distribution;
- impaired cerebrovascular reactivity to acetazolamide or carbon dioxide in the ICA territory, suggesting reduced cerebrovascular reserve; and
- compensatory increase of cerebral blood volume by cerebral vessels' vasodilation, and increase of oxygen fraction extraction.

These modifications are usually more prominent in pediatric than adult patients.

Transcranial Doppler ultrasonography

Transcranial Doppler (TCD) may be helpful in the monitoring of intracerebral hemodynamics in moyamoya angiopathy.[38,39] However, data are scarce in literature and parameters assessed in ultrasonography differed across studies, although the main TCD parameters are the mean flow velocities and the pulsatility index. Moreover, TCD is a very operator-dependent tool. Therefore, TCD cannot be a sufficient tool for evaluation and follow-up in moyamoya angiopathy. In the same way, additional studies are needed to validate TCD in postoperative follow-up.[40]

Electroencephalography

Electroencephalography can show a specific pattern in pediatric patients with moyamoya, called "rebuild-up" phenomenon. This pattern consists of the reappearance of high amplitude slow waves after hyperventilation, indicating a cerebral hypoxemia induced by hyperventilation, and corresponds to a reduced cerebral perfusion reserve.[41] However, because of the risk of hyperventilation-induced cerebral infarction, many physicians consider that electroencephalography hyperventilation should not be performed in these patients.

Investigations for usual causes of acquired or inherited moyamoya syndrome

A crucial step in the examination of patients who have moyamoya angiopathy is the research of underlying condition or neurological and extra-neurological signs that would suggest MMS. Acquired causes of MMS, including cranial irradiation which is the most frequently associated feature, should be screened by physicians (Table 2).[110–114] Numerous other acquired conditions have been associated with moyamoya angiopathy but it is often difficult to determine whether the association is causal or incidental, as the number of cases is most often very limited. There are various clinical features associated with inherited MMS. (See "MMS" section and Table 3, where the main clinical symptoms found in inherited MMS are detailed).[115–152]

Practically, the etiological investigation should include a rigorous interview of the patient, detailed physical examination, and a minimal set of complementary exams in order to rule out the main causes of MMS (Table 2).

Table 2 Main acquired and inherited MMS and minimal etiologic investigations when discovering a moyamoya angiopathy

Current causes of acquired MMS	Key diagnosis features
Cephalic or neck irradiation[112]	Interview
Skull base tumor[111]	Imaging of the skull base
Atherosclerosis of skull base arteries	Complete imaging of cervical arteries
Chronic meningitis (especially tuberculosis meningitis), cerebral vasculitis[110]	Cerebrospinal fluid analysis
Autoimmune angiitis[113]	Autoimmune blood tests (anti-nuclear antibodies)
Prothrombotic disorders[114]	Antithrombin, protein C/protein S, activated protein C resistance, factor V Leiden mutation, prothrombin mutation
Current causes of inherited MMS	
Sickle cell disease or trait[136–138]	Hemoglobin electrophoresis (if from African or Caribbean origin)

Abbreviation: MMS, moyamoya syndromes.

Clinical course of MMD

The natural history of MMD in non-operated cases is not well described. Studies addressing natural history had limited patient samples and no systematic brain imaging follow-up.[42] The course of the disease is variable and could go from a rapid progression leading to severe disabilities to clinical silence during several years. In most pediatric patients, there is a progressive worsening of the occlusive arterial lesions, even among asymptomatic patients or among patients with unilateral lesions.[43,44] Studies addressing the prevalence of stroke in children with moyamoya are scarce but autonomy loss was observed in 60% of patients after a 5-year follow-up. In adults, the disease's natural course seems to be less severe, as autonomy loss was observed in 20% of patients. However, the overall stroke rate in adults appears to be high, an estimated 10%–15% per year in symptomatic cases and 3% per year in asymptomatic cases.

The risk of developing an ischemic or hemorrhagic stroke increases in line with the progression of vascular lesions. In conservatively treated children, neurologic deterioration is most often due to repeated ischemic strokes that occur with progression of arterial occlusion. Non-operated MMD adult patients present a high risk of developing both ischemic and hemorrhagic stroke, and the latter is an important cause of functional deterioration or mortality in these patients. A regular follow-up of conservatively treated patients is crucial, even if they are asymptomatic or have unilateral lesions.[26,45]

Treatments in MMD

No curative treatment allowing regression of the occlusive arterial lesions has been proved in moyamoya vasculopathy. Treatments in the acute phase of ischemic or hemorrhagic stroke are symptomatic, but the use of intravenous

Table 3 Characteristics of genetic moyamoya syndromes (and pseudo-moyamoya syndromes)

Disease name and mutated gene(s)	Disease prevalence	Frequency of MMA/ cerebral angiopathy in the disease	Characteristics of the cerebral angiopathy	Hallmark symptoms of the disease
MMS with autosomal dominant transmission				
Type 1 Neurofibromatosis[115–121] Gene: NF1 (17q11.2) Protein: neurofibromin LOF mutations in NF1, leading to endothelial cell proliferation through activation of RAS pathway	1/3,000	2.5%–6%	– Intracranial arteries: MMA, stenosis, occlusion, ectasia, aneurysm, arteriovenous fistula Involvement of anterior and/or posterior circulation – Possible involvement of extracranial carotid or vertebral arteries – Mean age of onset of cerebral angiopathy: 5–11 years	– "Café au lait" macules – Cutaneous/subcutaneous and/or plexiform neurofibroma – Axillary or groin freckling – Optic pathway glioma – Lisch nodules (iris hamartomas seen on slit lamp examination) – Bone dysplasia – Possible systemic vasculopathy (aortic coarctation, renal artery stenosis, etc)
Noonan syndrome[122–126] Genes: – PTPN11 (12q24.13): 50% of cases – SOS1 (2p22.1): 10%–13% of cases – RAF1 (3p25.2): 3%–17% of cases – More rarely: KRAS (12p12.1), NRAS (1p13.2), BRAF (7q34), MAP2K1 (15q22.31) GOF mutations in these genes, leading to enhanced cellular proliferation through activation of RAS pathway	1/1,000–1/2,500	?	MMA	– Short stature – Congenital heart defect (pulmonary valve stenosis, hypertrophic cardiomyopathy, etc) – Developmental delay – Dysmorphism (broad or webbed neck, unusual chest shape, low set nipple, facial dysmorphism) – Cryptorchidism, male infertility – Ocular abnormalities – Cutaneous abnormalities (café au lait macules, lentigines)
Costello syndrome[127] Gene: HRAS (11p15.5) GOF mutation affecting p.Gly12 or p.Gly13, leading to dysregulation of the RAS pathway	Rare	?	MMA	– Failure to thrive (infants) – Short stature – Coarse facial appearance – Cutaneous abnormalities: loose and soft skin. Hyperpigmentation. Excessive skin in neck, hands, and feet. Papilloma – Joint laxity – Cardiomyopathy/cardiac defect – Mild intellectual deficiency – Malignant tumor predisposition
Alagille syndrome[128–135] Genes: – JAG1 (20p12.2) in most of cases (60% de novo mutations) – NOTCH2 (1p12-p11) in less than 1% of cases	1/70,000	1/268 in one study[129]	– Unilateral or bilateral MMA – Other abnormalities of distal ICA or MCA (stenosis, occlusion, aneurysm) – Basilar aneurysm	Quasi-constant symptoms (>80%): – Cholestasis – Congenital heart disease (pulmonary artery stenosis > others) – Butterfly vertebrae – Posterior embryotoxon

				Less frequent symptoms: – Dysmorphic face – Systemic angiopathy (aortic coarctation or aneurysms, renal artery stenosis, etc) – Renal anomalies – Growth retardation – Pancreatic insufficiency – Learning difficulties
MMS with autosomal recessive transmission				
Sickle cell disease[136–138] Gene: HBB (11p15.5)	Variable according to ethnic origins 1/3,000 in France Higher prevalence in African, Afro-American, Caribbean, or Mediterranean populations	Moyamoya collateral vessels exist in 20%–40% of patients with sickle cell disease who have history of stroke	– Distal ICA and/or proximal ACA/ACM stenosis – Moyamoya collateral vessels – Rare involvement of posterior circulation – Posterior aneurysm(s)	– Vaso-occlusive events (bone and organs) leading to acute or chronic pain and organ dysfunction – Chronic hemolytic anemia – Increased risk of bacterial infections
GUCY1A3 mutations[109] Gene: GUCY1A3 (4q32.1) Protein: α1 subunit of sGC LOF mutations leading to alteration of NO pathway in smooth muscle cells	Three families reported	MMA in one-third of subjects (3/9) and non-MMA angiopathy in one subject	– Unilateral or bilateral MMA – Possible involvement of posterior circulation – Isolated stenosis of MCA and ACA – First ischemic event before 5 years of age	Constant symptoms – Severe achalasia Less frequent symptoms (<50%) – Arterial hypertension – Raynaud syndrome, livedo – Erectile dysfunction – Low platelet count
SAMHD1 mutations[139,140] Gene: SAMHD1 (20q11.3) LOF mutations leading to a lack of expression of mutant protein in cells	–	MMA in about 50% of subjects according to series	– MMA – Distal ICA and/or proximal ACM/ACA stenosis – Intracerebral sacciform aneurysms	Aicardi-Goutieres syndrome: Aseptic subacute relapsing encephalopathy in early childhood leading to psychomotor regression and epilepsy, Chilblains, poor adaptation to cold; MRI: leukodystrophy, cerebral calcifications; CSF: Lymphocytic meningitis, High interferon alpha and neopterin levels Other symptoms in SAMHD1 mutations: congenital glaucoma, arthritis, chilblain lupus
MOPDII or Majewski syndrome (microcephalic primordial dwarfism)[141–143] Gene: PCNT (21q22.3) Protein: Pericentrin, a centrosomal protein involved in cell cycle progression LOF mutations	–	Cerebral arteriopathy in 19%-52% of subjects	– Intracranial aneurysm – MMA	– Intrauterine growth retardation – Severe proportionate short stature – Microcephaly – Bone radiologic abnormalities (skeletal dysplasia) – Absent or mild mental retardation – Insulin resistance

(*Continued*)

Table 3 (*Continued*)

Disease name and mutated gene(s)	Disease prevalence	Frequency of MMA/ cerebral angiopathy in the disease	Characteristics of the cerebral angiopathy	Hallmark symptoms of the disease
Seckel syndrome (microcephalic primordial dwarfism)[143,144] Six genes involved in cycle cell progression, centrosomal function or DNA repair: – ATR (3q23) – RBBP8 (18q11.2) – CENPJ (13q12.12) – CEP152 (15q21.1) – CEP63 (3q22.2) – NIN (14q22.1)	1/10,000	Two case reports of MMA in Seckel syndrome	– Intracranial aneurysm, frequent – MMA, rare	– IUGR – Severe proportionate short stature – Microcephaly – Characteristic "bird-headed" facial appearance – Absence of skeletal dysplasia – Mental retardation
MMS with recessive X-linked transmission				
Loss of expression of BRCC3/MTCP1[107,108] Deletion of BRCC3/MTCP1 (Xq28), leading to loss of expression of these genes	3 families reported	8/9 subjects had MMA	– Bilateral anterior MMA – Onset of acute neurological symptoms: 4–32 years of age	Constant or frequent (>50%) symptoms: – Short stature – Facial dysmorphism (hypertelorism, long philtrum, mild ptosis) – Hypergonadotropic hypogonadism (delayed puberty, azoospermia) – Premature hair graying Less frequent symptoms (<50%): – Dilated myocardiopathy – Arterial hypertension – Early onset cataract – Developmental delay – Premature coronary heart disease
Aneuploidy disorders				
Down syndrome[145,146] (47 XY + 21) in males (47 XX + 21) in females or mosaicism	1/800	Prevalence of Down syndrome 26 times higher in patients with MMA than in the general population	– Similar characteristics to MMD	– Intellectual deficiency – Muscular hypotonia, joint laxity – Facial dysmorphism – Heart defect (atrio-ventricular canal) – Duodenal atresia, Hirschsprung's disease – Congenital cataract – Small size – Epilepsy – Endocrine disorders – Leukemia predisposition
Turner syndrome[147–150] 45 (X;0) or mosaicism	1/2,500 females	–	– MMA – Fibromuscular dysplasia	– IUGR, growth retardation – Ovarian insufficiency – Skeletal abnormalities – Facial dysmorphism, Pterygium colli

				– Congenital malformative cardiopathy, systemic hypertension, aortic dissection, myocardial ischemia – Multiple cutaneous nevi – Diabetes, hypothyroidism – Renal and ENT malformations – Learning difficulties
Other				
PHACE syndrome[151,152] Unknown	<1/1,000,000	8/115 in one study	Congenital arterial lesions > progressive steno-occlusive arterial lesions – Congenital arterial lesions: dysplasia-hypoplasia, aneurysms, aberrant course of arteries – Progressive arterial lesions: stenosis and occlusions, MMA	– Posterior fossa brain malformations – Facial or cervical hemangiomas – Arterial cerebrovascular anomalies – Coarctation of the aorta and cardiac defects – Eye abnormalities
Pseudo-moyamoya angiopathy				
ACTA 2 mutations[104,105,155] Gene: ACTA 2 (10q23.31) Autosomal dominant transmission or de novo mutations		Quasi-constant cerebral angiopathy in Arg179 mutations	– Bilateral pseudo-MMA: ectasia of the proximal ICA, stenosis of the terminal ICA, bilateral dolichoectatic ICA, straight course of intracranial arteries – Absent basal collateral vessels – Possible posterior circulation involvement	– TAAD – Premature coronary heart disease – Livedo reticularis Features specific to Arg179H mutations: – Persistent ductus arteriosus (constant) – Congenital mydriasis (constant) – Arterial pulmonary hypertension – Hypotonic bladder – Malrotation and hypoperistalsis of the gut – Cerebral leukopathy

Abbreviations: ACA, anterior cerebral artery; CSF, cerebrospinal fluid; GOF, gain of function; ICA, internal carotid artery; LOF, loss of function; MCA, middle cerebral artery; MMA, moyamoya angiopathy; MMS, moyamoya syndromes; MRI, magnetic resonance imaging; TAAD, thoracic aortic aneurysms and dissections; sGC, soluble guanylate cyclase; IUGR, Intrauterine Growth Retardation; ENT, ear, nose and throat; MMD, moyamoya disease; PHACE, Posterior fossa Hemangioma Arterial lesions Cardiac abnormalities Eye abnormalities.

tissue plasminogen activator is contraindicated for MMD manifesting as cerebral ischemia, because of the high risk of intracranial bleeding.[46] After managing acute complications, patients should be referred to a reference center.

Common general measures are recommended in order to prevent deterioration of cerebral hemodynamics, such as avoidance of hypotension, dehydration, and hyperventilation, because of these patients' deficit in cerebrovascular reserve. A very important point is specific care during the perioperative period, especially concerning the management of anesthetic risk to minimize the risk of perioperative stroke.[47,48]

Non-ischemic symptoms such as headache and seizure should be treated symptomatically with antiepileptic drugs and analgesics.

Medical therapy is usually started in every patient with ischemic moyamoya angiopathy. Long-term oral antiplatelet therapy is prescribed in children and adults to prevent thrombosis and thromboembolism at sites of arterial stenosis.[26,46,48] Aspirin is most often used at the usual dose of 50–100 mg daily in children.[24] Antiplatelet therapy may be the sole treatment when surgery revascularization is postponed because of recent infarction, or when surgical bypass is not indicated because the patient has relatively mild disease or good spontaneous revascularization. Data addressing aspirin's short-term or long-term efficacy are scarce. Antiplatelet bitherapy is not recommended because of the increased risk of intracerebral bleeding.[46]

The mainstay of treatment is based on surgical revascularization. The revascularization goal is to improve cerebral hemodynamics and to reduce moyamoya collateral network, thus reducing the risk of new ischemic or hemorrhagic events.[26,45,49,50]

The efficacy of surgical revascularization in moyamoya patients with ischemic stroke has not been evaluated in a randomized trial. In several non-comparative studies, the occurrence of ischemic events decreases after revascularization surgery, suggesting possible efficacy. In children, most symptomatic cases are operated on, because deteriorating natural course is frequent. In adults, surgery indications are variable between centers and considered on a case-by-case basis.

According to Japanese and US guidelines, indications for revascularization surgery include clinical ischemic symptoms or a decreased regional cerebral blood flow, vascular response and perfusion reserve, retrieved from cerebral circulation and metabolism studies.[24,46,48] Moreover, the occurrence of transient ischemic attacks usually requires a short-term revascularization. However, the guidelines are unclear regarding the timing of surgery, "although the general principle of minimizing the time between diagnosis and revascularization is supported", except in cases where there are immediate contraindications such as recent infarction or hemorrhage.[24]

After surgical revascularization, antiplatelet medication is usually sustained, in order to prevent cerebral embolization due to thrombi formation at sites of stenosis.[26] Treatment in hemorrhagic moyamoya disease is more controversial.

There is no strong recommendation for the selection of surgical revascularization procedure. According to experts' consensus, indirect revascularization is preferred in children because direct bypass is technically difficult on small-diameter vessels, whereas direct bypass is preferred in adult patients.[48]

Indirect revascularization is based on moyamoya physiopathology, which spares ECA and its branches. The development of cerebral neovascularization from ECA branches allows brain revascularization.[51] Several techniques of indirect revascularization have been developed, all based on a synangiosis procedure. During synangiosis, tissues containing ECA branches (dura mater, temporal muscle, galeal tissue, or superficial temporal artery) are directly put in contact with the surface of the ischemic brain. Development of neovascularization from these tissues is supposed to be enhanced by angiogenic factors' secretion from ischemic brain parenchyma. This procedure does not provide immediate benefit, since efficient neoangiogenesis requires at least 3 months to develop, and thus there is a risk of stroke during the perioperative period. On the contrary, in the direct revascularization technique, the superficial temporal artery – a branch of the ECA – is directly anastomosed with MCA or ACA.[51] This allows an immediate improvement of cerebral hemodynamics and minimizes the risk of perioperative ischemic stroke when compared with indirect techniques. Conversely, direct bypass induces a higher risk of brain hemorrhage secondary to hyperperfusion syndrome, especially in patients with severe cerebral ischemia before surgery. Pre-surgery SPECT evaluation of brain perfusion allows risk estimation. In some cases, direct and indirect approaches can be combined.

Before surgical revascularization, an accurate assessment of vascular status by conventional angiography is required, to avoid disruption of pre-existing collateral vessels naturally developed from ECA.

Because of the possibility of angiopathy progression and persistent stroke risk, a clinical and imaging follow-up should be continued after surgical treatment, especially for patients with unilateral angiopathy who present a risk of bilateralization.

Table 4 Main studies on MMD genetics

Author	Year	Ethnic origin	Study design	Results: identified loci/markers
Kihatara et al[80]	1982	Japanese	Type I HLA genotyping (HLA A/B/C) and association study	Association of MMD with HLA A*24 , HLA B*46 and HLA B*54 alleles
Aoyagi et al[81]	1995	Japanese	Type I and II HLA genotyping (HLA A/B/C/DR/DQ) and association study	Association of MMD with HLA B*51 allele
Inoue et al[82]	1997	Japanese	HLA genotyping (HLA A, DRB1/DQA1/DQB1/DPA1) and association study	Association of MMD with HLA DRB1*0502, HLA DRBI*0405 and HLA DQBI*0401 alleles
Ikeda et al[73]	1999	Japanese	Genome-wide linkage analysis	Linkage to 3p24.2-26
Inoue et al[75]	2000	Japanese	Chromosome 6 linkage analysis	Linkage to D6S441 (6q25)
Yamauchi et al[77]	2000	Japanese	Chromosome 17 linkage analysis	Linkage to 17q25
Han et al[83]	2003	Korean	HLA genotyping	Association of MMD with HLA-B35 allele
Sakurai et al[76]	2004	Japanese	Genome-wide linkage analysis	Linkage to 8q23 Suggestive evidence for linkage to 12p12
Kang et al[66]	2006	Korean	Association study focused on TIMP2 (3p24.2-p26) and TIMP4 (17q25)	Association of familial MMD with rs8179090 polymorphism (in TIMP2 gene promotor)
Mineharu et al[78]	2008	Japanese	Genome-wide linkage analysis	Linkage to 17q25.3
Hong et al[84]	2009	Korean	HLA genotyping	Association of familial MMD with HLA-DRB1*1302 and HLA-DQB1*0609 alleles
Liu et al[79]	2010	Japanese, Korean, Chinese, Caucasian	17q25.3 linkage analysis Segregation analysis and case control study for ss161110142 polymorphism	2,1 Mb candidate region on 17q25 3 Association of Asian MMD (but not Caucasian MMD) with ss161110142 polymorphism (in Raptor gene)
Li et al[65]	2010	Chinese Han	Case-control study focused on polymorphisms in MMP2/3/9/13 and TIMP2 genes	Protective effect of the MMP3-1171 5A/6A and 5A/5A genotypes
Roder et al[62]	2010	Central European	Candidate gene association study (B-FGF, CRABP1, PDGFRB, TGFB1), located in 5q31-q32 and 19q13.1	Association of MMD with rs382861 (in PDGFRB gene) and rs1800471 (in the first exon of TGFB1 gene) polymorphisms
Kamada et al[89]	2011	Japanese	Linkage analysis focused on candidate regions 3p24–26, 6q25, 8q13–24, 12p12–13 and 17q25 GWAS Locus specific association study Association study for c.14576G>A RNF213 polymorphism	Association of MMD with locus 17q25-ter Strong association with the RNF213 locus Strong association with the c.14576G>A (p.R4859K) RNF213 variant
Liu et al[74]	2011	Japanese, Korean, Chinese, Caucasian	Genome wide Linkage analysis WES to identify rare functional variants in the candidate region Case control association study according to ethnicity	Linkage to 17q25.3. Candidate region of 1.5 Mb p.R4810K RNF213 variant (located within a founder haplotype) is a susceptibility gene of MMD in Asian MMD (Maximum OR = 111.8 in Asian MMD [95% CI= 64-195], 338.9 in Japanese [95% CI= 148-777], 135.6 in Korean [95% CI= 43-428], 14.7 in Chinese [95% CI= 3-71]) p.R4810K RNF213 variant present in 2.4% of Asian controls p.R4810K absent in Caucasians (cases and controls)
Park et al[153]	2011	Korean	Association study focused on polymorphisms in eNOS gene (7q36)	No significant association with MMD
Roder et al[102]	2011	Central European	Association study focused on polymorphisms in the following genes: ELN, LIMK1, CDKN2A/B, CXCL12, PSRC1, MTHFD1L, SMAD3, MIA3, PDGF-B, TIMP2 and the pseudogene ENSG00000197218	Association with rs599839 (PSRC-1 gene)

(*Continued*)

Table 4 (*Continued*)

Author	Year	Ethnic origin	Study design	Results: identified loci/markers
Kraemer et al[85]	2012	Caucasian	HLA genotyping and association study	High significant association of MMD with HLA DRB1*03 and HLA DRB1*13 alleles Weaker significant association of MMD with HLA A*02, HLA B*08, HLA DQB1*03, HLA A*24, HLA B*44, HLA B*35 and HLA DRB1*11 alleles
Liu et al[63]	2012	European and Japanese	Association study focused on polymorphisms of the first exon of TGFB1 gene	No association found (absence of reproduction of association with rs1800471[61])
Miyatake et al[91]	2012	Japanese	Association study for the RNF213 c.14576G>A polymorphism Analysis of genotype-phenotype correlation	c.14576G>A RNF213 allele found in 95.1% of familial MMD cases, in 79.2% of non-familial MMD cases and in 1.8% of controls (OR = 259 [95% CI= 100-674, $P<0.001$]) Patients HMZ for this variant present with an earlier age at onset, an increased risk of infarction at initial presentation and an increased rate of PCA involvement
Miyawaki et al[92]	2012	Japanese	Association study for the RNF213 c.14576G>A polymorphism Analysis of genotype-phenotype correlation	c.14576G>A RNF213 allele found in 85.4% of MMD patients, in 21.9% of non-MMD ICASO patients, in 1.6% of patients with cerebral aneurysm, in no patients with cervical disease, in no controls Significant association of c.14576G>A allele with MMD (OR= 292.8, 95% CI= 15.4–5153, $P<0.0001$) and non-MMD ICASO (OR= 14.9, 95% CI= 0.82–268.4, $P=0.01$)
Miyatake et al[95]	2012	Japanese	Case-control study for the c.14576G>A RNF213 polymorphism	Earlier onset and more severe course in patients HMZ for c.14576G>A RNF213 variant
Wu et al[94]	2012	Chinese Han	Case-control study focused on the p.R4810K RNF213 polymorphism	Association of MMD with p.R4810K RNF213 variant (OR= 36.7, 95% CI=8.6-156.6, $P=6.10–15$) p.R4810K RNF213 variant found in 0.4% of the controls p.R4810K RNF213 variant more frequently found in ischemic versus hemorrhagic MMD
Mineharu[96]	2013	Japanese	Case report of one family	Bilateral MMD in patients with HMZ p.R4810K RNF213 variant Unilateral MMD or no MMD in subjects with HTZ p.R4810K variant
Wang et al[154]	2013	Chinese Han	Genotyping for candidates polymorphisms in the PDFRBR/MMP3/TIMP2/RNF213/Raptor genes, and searching for gene-gene interactions	Association of MMD with rs112735431 and rs148731719 (RNF213 gene) No significant gene–gene interaction detected
Liu et al[90]	2013	Central European	GWAS Sequencing of candidate genes included in candidate regions	Association of MMD with rs1023115 on 1q23.3, rs11681583 on 2p22.1, rs3742257 on 13q14.11 (protecting effect), rs2058364 on 17p13.3 and rs720607 on 20q13.33 (protecting effect) No significant association with polymorphisms in RNF 213 and ACTA2 genes

Abbreviations: CI, confidence interval; HLA, human leukocyte antigen; HMZ, homozygous; HTZ, heterozygous; ICASO, intracranial major artery stenosis/occlusion; MMD, moyamoya disease; OR, odd ratio; PCA, posterior cerebral artery; WES, whole exome sequencing; GWAS, Genome Wide Association Study.

Of course, as mentioned before, as part of the general measures applying to MMD patients, revascularization surgery must be performed in a center experienced in the management of moyamoya, especially for the anesthetic procedures and the perioperative management.

Finally, to date, it is not recommended to use endovascular treatment such as angioplasty, intra-arterial vasodilators or thrombolytic agents in moyamoya vasculopathy.[24]

Pathophysiological features and genetics of MMD

Pathological studies showed a concentric and eccentric fibrocellular thickening of the intima in the terminal portion of ICA, leading to lumen stenosis, and fragmentation of internal elastic lamina.[52] Immunohistochemical studies have shown that this intimal fibrocellular thickening contains alpha-actin-positive smooth muscle cells (SMCs) with a proliferative phenotype, while the media appears thinner.[53] Inflammatory or atherosclerotic changes are absent.

Typical deep moyamoya collateral vessels result from the combination of a dilation of pre-existing penetrating vessels (thalamoperforating and lenticulostriate perforating arteries) and development of new vessels. They form a fragile vascular network with a thin media, a fragmented elastic lamina and microaneurysms, with an increased risk of rupture.[54] Development of collateral vessels is thought to be the result of compensatory mechanisms in reaction to chronic brain ischemia, facilitated by secretion of pro-angiogenic factors by ischemic parenchyma.[55] For others, these collateral vessels result from an abnormal neoangiogenesis in MMD.[55,56] Patients also develop compensatory transdural and leptomeningeal collateral vessels. Stimulation of dural nociceptor by dilated transdural collaterals have been implicated in the genesis of headaches in moyamoya.

Pathophysiological mechanisms of MMD are unknown, and only hypotheses can be raised so far.[57] A genetic contribution is strongly suspected, based on the existence of familial cases and the observation of a strong ethnicity effect. This genetic susceptibility has been confirmed by recent molecular data obtained in MMD (see Table 4). However, MMD appears to have a complex determinism, with both genetic predisposition and environmental triggers, as suggested by the observation of discordant monozygotic twins.

Many studies highlighted an overexpression of proangiogenic factors in patients' cerebrospinal fluid, blood, or tissues, but did not permit to determine whether this overexpression was primary or secondary to chronic cerebral ischemia.[58,59]

Two studies have shown that the expression of two angiogenic factors, fibroblast growth factor and hepatocyte growth factor, was significantly higher in cerebrospinal fluid of MMD patients compared to patients with atherosclerotic occlusion of ICA, suggesting that this overexpression was not a simple consequence of chronic brain ischemia in MMD, but a potential etiopathogenical factor.[60,61]

Based on these observations, it has been hypothesized that polymorphisms in genes coding for these factors would increase their expression or stability, leading to development of vascular abnormalities. However, association studies failed to show any correlation between the occurrence of MMD and polymorphisms in fibroblast growth factor and hepatocyte growth factor genes. One study showed an association between an increased risk of MMD and polymorphisms located in the promoter region of the platelet-derived growth factor (PDGF) receptor B gene and in the transforming growth factor beta 1 gene, two genes broadly implicated in cell growth and differentiation and thus potentially implicated in vascular growth.[62] However, these results were not confirmed in other studies (Table 4).[63] Increased plasmatic levels of PDGF were also hypothesized to be a compensatory mechanism to a decreased number of PDGF B receptors on vascular SMCs of MMD patients, and that over-exposition to this cytokine would lead to intimal thickening in MMD.[59]

Metalloproteinases and tissue inhibitor of metalloproteinases, extracellular matrix remodeling enzymes involved in angiogenesis and vasculopathies such as atherosclerosis, were also studied in MMD. A differential expression of metalloproteinases and tissue inhibitor of metalloproteinases between patients and controls and an association between polymorphisms in genes coding for these enzymes and the occurrence of MMD was shown in some studies, but not further confirmed (Table 4).[58,64–66]

Some studies showed intimal accumulation of cells expressing vascular smooth muscle actin, an antigen usually expressed by SMCs in the media. The exact nature of these intimal cells is not clear – SMCs or myofibroblasts – and they may be part of the pathophysiological process of moyamoya angiopathy. These cells could originate from circulating progenitors, as demonstrated in other stenotic vasculopathies (post-angioplasty restenosis, atherosclerosis).[55,67] They could also originate from the underlying media through an endothelial-to-mesenchymal transition, in which SMCs would transit from media to intima while losing their contractile phenotype. Milewicz et al raised the hypothesis that moyamoya should be considered as a hyperplastic vasculomyopathy and that moyamoya physiopathology would be based on genetic

predisposition that promotes migration and proliferation of SMCs and matrix production, in addition to an environmental trigger factor, such as cervical irradiation.[68]

Genetic factors are strongly suspected, based on a strong ethnicity-related effect, a high concordance rate of the disease in monozygotic twins, and the 10% proportion of familial cases. A polygenic inheritance combined with environmental factors may be involved in most cases. However, various Mendelian patterns of transmission have also been suggested in familial MMD. Transmission of the disease in multiple generations is the most frequently reported pattern of inheritance.[69–72] Mineharu et al reported 15 large multigenerational pedigrees consistent with an autosomal dominant disorder with an incomplete penetrance.[69] Mother-to-child transmission was the most common mode of inheritance in this paper but a few cases of father-to-child transmission were also observed, including father-to-son. A number of Japanese families suggesting a possible autosomal recessive inheritance were also reported.[72,73] Whatever the mode of transmission, a larger preponderance of female patients was observed in both familial and sporadic cases.[69–72]

Since the 1990s, several genome-wide linkage analyses and Genome wide associations studies (GWAS) have been performed, mostly in East Asian populations in order to map and identify MMD genes.[59,73–79,89,90] Five main loci were reported: 3p24.2–p26, 6q25, 8q23, 12p12, and 17q25.[73,75–79] So far, the sole locus which has been confirmed is located at 17q25 (Table 4).

With the discovery of linkage with the 6q25 loci, several studies conducted in Asian and Caucasian European populations showed an association between various HLA alleles and MMD.[80–85] However, these results were conflicting, except for HLA-DRB1*13, that was found to be associated with MMD with a high level of significance in a Korean and a European study (Table 4).[84,85] Interestingly, HLA expression is involved in autoimmunity and several studies reported an increased prevalence of autoimmune diseases – such as diabetes mellitus and thyroid disease – in patients with MMD.[86–88] These observations support the hypothesis of a role for autoimmunity in moyamoya pathophysiology.

In 2011, two research teams using different approaches identified ring finger protein 213 (RNF213), located in chromosome 17q25.3, as the first MMD susceptibility gene in Japanese moyamoya patients.[74,89] A GWAS study detected a strong association between MMD and a single base substitution leading to an amino acid change p.R4810K (rs112735431 or ss179362673 corresponding to c.14429G>A on the basis of the National Center for Biotechnology Information NCBI Reference sequence NM_001256071.1, also corresponding to p.R4859K, c.14576G>A on the basis of NCBI reference sequence NM_020914.4) in both sporadic and familial cases.[89] This variant conferred an odds ratio (OR) >190 and was located in a founder haplotype shared by patients from Japan. Genome-wide linkage combined with whole exome sequencing conducted in eight multigenerational families identified this variant in all probands.[74] This variant was then shown to be strongly associated with MMD in both Japanese (maximum OR =339) and Korean patients and, to a lesser degree, Chinese patients. It was absent in Caucasians. The presence of this variant in 1.4%–2.4% of Asian controls strongly suggested that it is a susceptibility factor to MMD, with a probable involvement of other genes or environmental factors in the moyamoya phenotype. Neither this variant nor the founder haplotype was present in Caucasian patients.[90] Additional RNF213 variants have also been detected at a lower frequency.[74,89] These data have been confirmed in additional studies.[91–94] In addition, patients homozygous for the p.R4810K variant have been shown to have an earlier age at onset and a more severe evolution (Table 4).[91,95,96]

The mechanisms leading from RNF213 to moyamoya vascular lesions are unknown so far. RNF213 gene encodes for a 591 kDa cytosolic protein that possesses a ring finger domain (suggesting an ubiquitine-ligase activity) and a pair of 2 AAA+ ATPase modules.[97] To date, we do not know if p.R4810K polymorphism leads to gain or loss of function of RNF213. An in vitro functional study revealed that this mutation affected neither the transcription level nor the ubiquitin ligase activity of the protein.[74] Zebrafish in which RNF213 has been knocked down had abnormalities in vascular development with irregular wall formation in trunk arteries and abnormal sprouting vessels.[74] However, anatomical and histopathological studies of RNF213-deficient mice revealed no alteration in brain vasculature under physiological conditions.[98,99] The development of mice harboring the R4810K mutations would be an important tool to investigate the role of this mutation in the cerebral vessel homeostasis. Recent experimental in vitro studies suggest that endothelial cells derived from induced pluripotent stem cells of R4810K mutated patients have a reduced angiogenic activity.[100] In addition, genomic instability in fibroblasts and induced pluripotent stem cells derived from R4810K mutated patients was also observed.[101] Interestingly, several genes involved in genome stability maintenance are associated with different MMS (see the "Moyamoya syndromes" section). How this genomic instability might relate to moyamoya mechanisms will benefit from further investigations.

In a Caucasian population, no locus or gene has been formally identified as being associated with MMD to date (Table 4). Studies conducted in MMD patients originated from central Europe found significant associations with polymorphisms located in PDGF receptor B and transforming growth factor beta 1 genes[62] and with a polymorphism located in PSRC-1, a gene known to be associated with coronary heart disease.[102] As previously mentioned, a study showed an association between several HLA markers and MMD in Caucasians, but these results have not been replicated.[85] A recent GWAS conducted among 38 European patients failed to identify any major founder variant associated with MMD.[90] In Caucasian MMD patients, no association was found between MMD and the p.R4810K variant in RNF213.[74,90] However, few data suggest a potential role of RNF213 in susceptibility to develop MMD in a Caucasian population. First, sequencing of RNF213 among 50 Caucasian MMD patients revealed four additional variants in four distinct patients which were absent among controls.[74] Second, clusters of variants located in the RNF213 region were weakly associated with Caucasian MMD in GWAS.[90] Additional work on a larger number of patients and controls would be needed to clarify this point.

Moyamoya syndromes

MMS refers to a moyamoya angiopathy associated with other neurological and/or extra-neurological symptoms, or due to a well identified acquired (see Table 2) or inherited cause (see Table 3).

Cerebral angiopathy in MMS affects the anterior circulation, unilaterally or bilaterally, and can also involve the posterior circulation.

MMS have been described in several chromosomal disorders and Mendelian diseases some of whose causative genes have already been identified. Thus, MMS constitute a highly heterogeneous group regarding clinical presentation and patterns of inheritance. The main inherited MMS known to date are described in Table 3. Penetrance of moyamoya angiopathy among the different inherited MMS is highly variable, from 2.5%–6% in NF1 to quasi-constant in BRCC3 - MTCP1 deletions, a newly discovered Mendelian MMS.

The proportion of MMS seems to be higher in Western countries than in East Asian countries.[27,103] A nationwide survey conducted in Japan in 2006 showed that the prevalence and annual incidence of MMS were 0.34/100,000 and 0.11/100,000 respectively, more than ten times lower than those of MMD but close to those observed in Western countries.[10] The difference may also relate to the epidemiology of underlying conditions. For example, sickle cell disease is a frequent cause of moyamoya in people from African origin, which population is more frequent in the US and Europe than in Asia. Interestingly, moyamoya prevalence in Afro-American and Caucasian people was similar when patients with sickle cell disease were excluded.[5]

In the following section, we will focus on three newly discovered inherited MMS in which the cerebrovascular phenotype is highly penetrant.

Heterozygous missense mutations in the ACTA2 gene coding for the smooth muscle alpha actin, one of the major contractile proteins of SMCs, are involved in a pseudo-moyamoya angiopathy.[104–106] The vasculopathy includes stenosis of the terminal part of ICA that can extend to the proximal segments of the MCA and ACA, dilation of the proximal ICA, an abnormal straight course of intracranial arteries and absence of basal collaterals. The posterior cerebral circulation is often impaired. However, the lack of collateral deep vessels and the coexistence of arterial ectasia and stenosis are features which differ from those observed in classical moyamoya angiopathy.[104]

A new recessive X-linked syndrome due to loss of expression of BRCC3/MTCP1 was recently described.[107,108] In the three reported families, all patients were males and pedigrees showed a maternal inheritance. Bilateral moyamoya angiopathy was quasi-constant with an onset of acute neurological symptoms ranging from 4 to 32 years of age. Other frequent symptoms were short stature, hypergonadotropic hypogonadism, stereotyped facial dysmorphism, and heart involvement (isolated left ventricular enlargement or symptomatic dilated cardiomyopathy). Inconstantly, patients presented with arterial hypertension, premature coronary heart disease, and early onset bilateral cataracts. Developmental delay was reported in one family. The disease is caused by an Xq28 deletion that leads to a complete loss of expression of BRCC3 and MTCP1 genes. BRCC3 encodes for a member of two protein complexes: a nuclear DNA repair complex and a cytoplasmic complex that might have a role in cardiomyocyte protection. Knockdown studies in Zebrafish suggest that BRCC3 plays an important role in angiogenesis. The function of MTCP1 is unknown to date.[108]

Another MMS associated with moyamoya and achalasia was identified recently.[109] It is caused by mutations in GUCY1A3, which encodes the α1 subunit of soluble guanylate cyclase (sGC), the major receptor for nitric oxide (NO). Three consanguineous families including a total of nine affected children (six males and three females) were reported. Early onset moyamoya angiopathy was present in one-third of mutated subjects and was revealed by ischemic events

occurring before 5 years of age. Moyamoya was unilateral or bilateral and the posterior circulation could be affected. One child presented a unilateral long arterial stenosis of MCA and ACA without moyamoya neovessels network. Affected children also had constant and severe achalasia, leading to severe regurgitations beginning in the first few months of life. Other hallmark features were arterial hypertension, present in 50% of mutated subjects, and more rarely, vasomotor dysfunctions such as Raynaud phenomenon or livedo, erectile dysfunction, and low platelet count without history of abnormal bleeding. In each family, a homozygous loss-of-function mutation was identified in affected subjects that led to absence of expression of the sGC protein (one nonsense mutation, one splice-site mutation, and one frameshift deletion).

GUCY1A3 encodes for one subunit of the most abundant isoform of the sGC, an NO-dependent enzyme that regulates the SMCs' relaxation in vascular and extravascular systems, which probably explains why vascular and digestive smooth muscles are both affected in this syndrome.

Translating genetic research into the clinics: future perspectives, potential treatments

Moyamoya angiopathy constitutes a "patchwork" including two main nosological entities: on the one hand, MMD, probably multifactorial and polygenic in most patients and on the other hand, MMS, a very heterogeneous group with various clinical presentations, various modes of inheritance, and a variable penetrance of the cerebrovascular phenotype.

Identification of the genes involved in MMD and several monogenic MMS unraveled different pathways involved in the development of this angiopathy, for example the NO-sGC pathway (with GUCY1A3 mutations), the RAS pathway (with NF1, Noonan, and Costello syndromes) or the NOTCH pathway (with Alagille syndrome), as well as pathways involved in genomic stability (with RNF213, Pericentrin and other genes involved in dwarfism, or BRCC3). Genes encoding additional members of these pathways may themselves be involved in this angiopathy genesis.

Identification of MMS causative mutations has several applications in clinical practice including the development of diagnostic tests and genetic counseling for the patients and their relatives.

Knowledge of the pathways involved in either MMD or MMS also provides valuable clues to investigate the pathophysiology of this disorder, and to identify pharmacological targets that could block the development of arterial lesions. Identification of the genes involved in MMD and highly penetrant MMS would also allow the development of moyamoya animal models, which are essential for pathophysiology investigations and for preclinical trials.

In addition, the use of next-generation sequencing tools will undoubtedly speed up the identification of novel familial MMD/MMS remaining to be discovered.

Disclosure

The authors declare that they have no conflict of interest.

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