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Practice guidelines

French clinical practice guidelines for Moyamoya angiopathy

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https://doi.org/10.1016/j.neurol.2017.12.002

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INFO ARTICLE

Article history:
Received 9 October 2017
Accepted 11 December 2017
Available online xxx

1. Preamble

1.1. Requesting body

These guidelines were drawn up within the framework of the French reference center for rare vascular diseases of the brain and eye (CERVCO) tasks, as defined by the French ministry of health, and with the collaboration of the French center for pediatric stroke.

1.2. Topic

These guidelines concern management practices for patients with Moyamoya angiopathy. Three clinical aspects were considered separately: diagnosis and initial assessment, therapeutic management and follow-up.

1.3. Patients concerned

These guidelines are directed to pediatric and adult patients.

1.4. Professional concerned

These guidelines are written for healthcare professionals involved in the management of patients with Moyamoya angiopathy including general practitioners.

1.5. Methods

The proposed guidelines stem from a work coordinated by a steering group according to the good practice recommendations designed by the French National Authority for Health [1]. A writing group (5 members) analyzed the literature and elaborated proposals for guidelines which were submitted to an independent multidisciplinary working group (17 members). The final manuscript was published on the website of the French National Authority for Health (HAS) in August 2017 (Appendix A).

The analysis of the literature was conducted using the keyword "moyamoya" in the Medline database during the search period from 01/01/1950 to 04/11/2016. Among 3161 abstracts, 733 were retained after applying several selection criteria. Only publications with abstract written in English and containing original data were selected. Case-reports including 1 or 2 cases and studies leading to previously published and/or validated results were excluded.

1.6. Guideline grades

Unless mentioned otherwise, the guidelines proposed are based on expert agreement among members of the multidisciplinary working group. The grade recommendations and the levels of evidence used, when possible, are detailed in appendix B.

2. Introduction

Moyamoya disease and Moyamoya syndrome refer to a rare form of intracranial angiopathy characterized by a progressive stenosis of the termination of the internal carotid arteries and the origin of their terminal branches, followed by the development of fragile neovessels at the base of the skull [2]. This abnormal vascular network may initially develop to compensate the reduction of blood flow downstream of intracranial arterial stenosis. The aspect of this network on cerebral angiography, called "puff of smoke" ("moya" in Japanese) explained the name of the disorder. The term Moyamoya disease (MMD) refers to this type of angiopathy when it is isolated and of undetermined etiology. Otherwise, the term Moyamoya syndrome (MMS) is used. The use of the term Moyamoya angiopathy (MMA) refers to the radiological criteria of the angiopathy without referring to the underlying cause [3,4]. MMA may concern children and adults of any age. It is strongly predominant among women (ratio f/m: 1.4 in Europe) [5]. In mainland France, in a survey including hospital child neurologists, the prevalence of MMA was estimated at 0.4/100,000 in children which is 20 times less than in Japan, where the disease is the most frequent [6]. MMA may concern few hundreds individuals on the national territory. However,

Please cite this article in press as: Hervé D, et al. French clinical practice guidelines for Moyamoya angiopathy. Revue neurologique (2018), https://doi.org/10.1016/j.neurol.2017.12.002

the epidemiology of MMA remains largely unknown. The pathophysiology of the disease is not well known. The thickening of the wall of the intracranial arteries is related to the presence, within the intima, of cells expressing smooth muscle cell markers, without inflammation or associated atherosclerotic lesions [7]. The identification of familial forms in 7.5% of MMD cases suggests the implication of genetic factors but no monogenic form of MMD has been identified so far [8]. Moyamoya syndromes are encountered in a variety of diseases such as sickle-cell anemia, neurofibromatosis type 1 or Down's syndrome. MMS can also appear after cerebral irradiation. Other rarer genetic or non-genetic causes are also reported with Moyamoya syndrome (Appendix C) [9]. The natural history and factors influencing the prognosis of the disease are not well known [10–16]. The clinical presentation appears highly variable, especially in adults. It can be severe and characterized by the occurrence of infarction and/or cerebral hemorrhage, or may be paucisymptomatic, or even asymptomatic.

3. Diagnosis and initial evaluation

3.1. *Circumstances of discovery*

The clinical expression of MMA considerably varies from one patient to another. The main circumstances of discovery are the following:

- transient ischemic attacks (TIA): TIAs frequently reveal the disease. Fourty percent to 60% of patients have had at least one TIA at their initial evaluation [17,18]. Hemodynamic triggers such as hyperventilation (crying, exercising, using wind instrument, stress) or fall in blood pressure (orthostatic arterial hypotension, recent introduction of a hypotensive drug, general anesthesia) are sometimes identified [3];
- cerebral infarction: 40 to 60% of patients have had a cerebral infarction at the time of diagnosis [3,17,18]. Symptoms related to ischemic lesions are variable and mainly depend on their location (unilateral or bilateral sensory or motor deficit, language impairment, spatial neglect, visual field defect, swallowing difficulties). Cerebral infarcts most often involve the anterior circulation and are frequently bilateral and asymmetrical. Silent ischemic lesions are sometimes discovered with cerebral imaging;
- intracerebral hemorrhage: 10 to 40% of adult patients have had intracerebral hemorrhage at time of diagnosis [3,17]. These may include parenchymal, subarachnoid, or intraventricular hemorrhage. Symptoms associated with parenchymal hemorrhage mainly depend on its volume and location. In the case of subarachnoid hemorrhage, the meningeal syndrome is in the foreground, sometimes accompanied by an altered level of consciousness. Such a complication appears much less frequently in children (< 10%) [18];
- cognitive impairment is detected in 2/3 of patients using detailed neuropsychological tests [19]. These cognitive disorders can be explained by ischemic or hemorrhagic brain lesions and/or by chronic cerebral hypoperfusion [20]. In children, fatigability, sometimes associated with a reduction of academic performances, may be a warning sign;
- movement disturbances: they are usually choreic and of sudden onset, and are sometimes triggered by hemodynamic factors (see TIA) with or without parenchymal lesion on MRI [21,22];
- headaches: recurrent headaches, sometimes suggestive of migraine with or without aura, can lead to MRI and to the diagnosis of MMA;
- seizures: an epileptic seizure, especially with focal onset, can lead to the diagnosis of MMA;
- unexpected findings during brain imaging: the diagnosis of moyamoya is sometimes established in the absence of symptomatology suggestive of the disease;
- screening in an asymptomatic relative;
- brain imaging during a systemic disease at risk of MMA.

These different presentations are not mutually exclusive.

3.2. *Confirmation of diagnosis/differential diagnosis*

3.2.1. *Confirmation of diagnosis*

The diagnosis of MMA is radiological and is based on the combination of the following two criteria [2]:

- presence of stenosis and/or occlusion of the distal portion of the ICA and/or of the origin of the MCA and/or of the origin of the ACA;
- presence of an abnormal arteriolar network in the vicinity of the steno-occlusive lesions.

Bilateral involvement is necessary for the diagnosis of moyamoya disease.

These arterial abnormalities can be observed on any type of cerebral vascular imaging. The positive diagnosis has been validated in the literature with 3D-TOF MRA and cerebral conventional angiography [2,23]. Because MRA is less invasive than conventional angiography, MRA is recommended at first, especially in children. Brain MRI also provides crucial information particularly at tissue level (see 2.4.1).

3.2.2. *Differential diagnosis*

Steno-occlusive lesions of the bifurcation of carotid terminations are sometimes observed without any associated neovascular network. A differential diagnosis should be considered in this situation, in particular:

- transient cerebral angiopathy (or focal cerebral arteriopathy) in children;
- primary or systemic cerebral angeitis (in this situation superficial temporal artery (STA) biopsy for pathological examination should be avoid, whenever possible, to preserve potential donor vessels for IC-EC bypass);
- reversible cerebral vasoconstriction syndrome;
- intracranial atherosclerosis;
- intracranial dissection.

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3.3. *Search for comorbidities*

MMS associated conditions should be carefully considered during the initial assessment [24].

- medical history:
- cranial irradiation [25,26],
- hypertension or other vascular risk factors,
- antiphospholipid syndrome,
- dysthyroidism,
- sickle cell anemia or ethnicity at risk of sickle cell anemia (African, Caribbean or Mediterranean) [27],
- Down's syndrome [28],
- medical history suggestive of a genetic condition;
- suggestive clinical signs:
- cutaneous lesions suggestive of neurofibromatosis type 1 (*café au lait* patches, neurofibromas) or other skin abnormalities [29];
- height or weight retardation, microcephaly;
- high blood pressure, abnormal cardiovascular examination;
- facial dysmorphism;
- intellectual disability or cognitive impairment;
- cryptorchidism, delayed puberty onset, sterility;
- digestive disorders (esophageal achalasia);
- ophthalmological abnormalities: retinal vascular anomalies, coloboma, posterior embryotoxon, cataract.

A clinical genetics consultation should be proposed when a genetic MMS is suspected especially when symptoms are not typical of a specific condition (e.g. possible slight dysmorphism).

The biological assessment must include:

- hemoglobin electrophoresis in case of any clinical argument in favor of sickle cell anemia;
- CSF study (pleiocytosis in favor of angeitis) in the absence of any identified cause;
- inflammatory and autoimmune assessment;
- screening for thrombophilia (including homocysteinemia) and antiphospholipid syndrome;
- screening for dysthyroidism in adults;
- liver and kidney function;
- DNA analysis in case of symptoms suggestive of a genetic disorder.

The imaging assessment shall include at least:

- an echocardiography;
- an imaging of the cervical arteries, the aorta and its branches (in particular renal arteries).

3.4. *Assessment of severity and prognosis*

An assessment of the severity of the disease and prognosis is necessary during the initial assessment.

3.4.1. *Assessment of severity*

The assessment of severity is primarily based on clinical and radiological data.

At the clinical level, a complete neurological examination allows to assess the presence of a motor, cognitive or sensory impairment. A detailed cognitive assessment (neuropsychological assessment, speech assessment, impact in daily life, quality of life) is recommended at baseline.

Imaging work-up must include brain parenchyma, intracranial vessels and cerebral perfusion imaging.

MRI of the cerebral parenchyma includes diffusion-weighted, FLAIR, gradient echo (T2 *), T1 and T2 sequences. These sequences allow evaluating the number, the location and the volume of recent or old brain ischemic and hemorrhagic lesions. The deep neovascular network can be visualized on T1, T2 and FLAIR sequences when it is sufficiently developed. Hyperintense vessels on FLAIR images sometimes suggest a cerebral hemodynamic impairment.

When the diagnosis of MMA is suspected or established by non-invasive imaging, a conventional angiography allows to specify the collateral circulation and to grade the angiopathy (Suzuki grading). Conventional angiography also allows evaluation of the size of superficial temporal arteries when surgical revascularization is considered (cf. 3.2.1).

The aim of perfusion imaging is to evaluate the cerebral hemodynamic status. Several imaging techniques can be used. Cerebral perfusion imaging with single-photon emission tomography (TEMP or SPECT) allows assessment of the vascular reserve when coupled to an acetazolamide assay. Positron emission tomography (PET) provides quantitative measurements of cerebral blood flow (oxygen extraction fraction). However, its accessibility is more limited. More recent MRI techniques such as ASL (arterial spin labelling) have the advantage of being less invasive and more accessible. The performance of ASL in evaluating cerebral perfusion in MMA appears to be comparable to that of SPECT [30,31]. In children, these examinations must be carried out in a specialized center as they usually require sedation, which can lead to complications (see 3.3).

3.4.2. *Prognostic evaluation*

Prognostic evaluation at the individual level is difficult because of limited knowledge on the natural history of the disease and on the predictive factors of clinical worsening. Young age (< 3 years) and/or the occurrence of a recent stroke might be pejorative [13,32–35]. The prognosis may be altered by the presence of comorbidities, particularly in patients with a MMS (cardiopathy, etc.). These comorbidities should be investigated and taken into account [36].

The presence of ischemic or hemorrhagic cerebral parenchymal lesions on MRI may have a pejorative value. Cerebral arteriography including the opacification of both ICAs, ECAs, and vertebral arteries shows the possible involvement of the posterior circulation, the quality of the supplemental pathways (leptomeningeal anastomoses, moyamoya neovascular network, transdural anastomoses) and the presence of potentially associated arterial aneurysm at risk of rupture.

The presence of cerebral hemodynamic impairment is often considered as a potential predictor of worsening. However, in non-operated patients, no hemodynamic prognosis marker has been previously confirmed in longitudinal studies. In patients treated with surgical revascularization, identification of a pre-operative vascular reserve decrease is a favorable prognostic factor [18].

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3.5. *Announcement of diagnosis and patient information*

This announcement should be done during a dedicated consultation. It includes detailed information about diagnosis, modalities of follow-up, treatment planning, and on research prospects. The corresponding physician or child neurologist should be informed of the diagnosis (see 3.3 and 3.6). The presentation of the national patient organization (association Tanguy Moyamoya) can be made on this occasion. An information leaflet, such as a ''patient medical card'' or Emergency Orphanet® card, can be provided.

3.6. *Search for contraindications to treatment*

There is no absolute contraindication to surgical treatment. The identification of associated severe comorbidities will be sought within the framework of preoperative assessments. If antiplatelet therapy is considered, contraindications should be considered:

- drug allergy;
- major coagulation abnormality;
- history of intracranial hemorrhage;
- severe peripheral hemorrhage.

3.7. *Genetic counseling*

When MMS is secondary to an already known genetic disorder, a genetic counseling consultation will be proposed to the proband or his/her two parents (in case of a child proband) to precise the following points:

- the risk for relatives;
- the potential for prenatal or preimplantation genetic diagnosis;
- the possibility of genetic testing in asymptomatic relatives.

A consultation for at risk relatives may also be proposed, either in the reference center for this condition (neurofibromatosis type 1, sickle cell disease, CERVCO) or with a geneticist.

When dealing with a MMA or an MMS in which a genetic etiology is suspected, brain imaging or genetic testing (such as whole exome sequencing) should not be performed in an asymptomatic at risk family member unless he/she has benefitted of a genetic consultation and he/she has been informed on the clinical manifestations of the disease.

4. Therapeutic management

4.1. *Pharmacological treatments*

4.1.1. *Preventive pharmacological treatments*

No specific drug treatment was shown to be effective. Antiplatelet therapy (aspirin in first intention) is initiated after cerebral ischemic manifestations and in the absence of cerebral hemorrhage [37]. Vascular risk factors (diabetes, dyslipidemia, smoking, high blood pressure) can be treated [2].

4.1.2. *Symptomatic treatments*

Symptomatic treatments have to be discussed in the following circumstances:

- headache: the treatment of migraine attacks and non-migraine headaches is based on the use of usual analgesics with the exception of vasoconstrictor drugs;
- epilepsy: an anti-epileptic treatment should be adapted to the type of crises and epileptic syndrome;
- depression: mood disturbances that can occur during the course of the disease are managed according to usual recommendations [38];
- pain: pain symptoms secondary to musculo-tendinous retractions or pressure points (in the case of immobility) sometimes need physiotherapy and occupational therapy. Analgesic molecules that can be used are not specific. They are based on good practice recommendations in the management of chronic pain. In presence of pharmacoresistant pain, referring to a pain management center must be privileged;
- spasticity: in presence of hypertonia of pyramidal origin, antispastics (dantrolene, baclofen) can be used. There is no contraindication for using botulinum toxin.

4.2. *Surgical treatment*

4.2.1. *Principle of surgical revascularization techniques*

The main objective of surgical revascularization is to reduce the risk of ischemic events by increasing cerebral blood flow within hypoperfused brain regions [39]. Prevention of hemorrhagic events is presumably obtained with a reduction of the neovascular network and of associated hemodynamic stress [40]. The surgical procedures are direct revascularization and indirect revascularization. These two techniques can be used separately or in combination. The principle of surgery is to supplant the failing internal carotid system by obtaining a direct anastomosis, or by promoting the progressive development of indirect anastomoses from the spared external carotid system [3].

Direct anastomosis is an extra-intracranial anastomosis most often performed between the STA and a cortical branch of the middle cerebral artery. It allows only one hemisphere to be treated at a given time and needs to be performed under antiplatelet treatment.

Indirect revascularization consists of laying a tissue vascularized by branches of the external carotid artery (dura mater, galea, temporal muscle, ECA branches) in contact with the brain in order to promote the development of neovascularization in hypoperfused areas (encephalosynangiogesis). Indirect revascularization techniques can be performed by a craniotomy (bone flap) or through multiple holes. These techniques of direct and indirect revascularization can be used separately or in combination.

The choice of the best technique depends on many factors including:

- the age of the patient;
- the size of the donor vessels (in particular the STA);
- the existence of pre-existing collaterality involving the ECA. In this case, these vessels cannot be taken as a donor for

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direct anastomosis due to the risk of sacrificing the territory they are already revascularizing;
- the course of the disease: direct revascularization allows an immediate improvement of the cerebral blood flow in the concerned territory.

In children, indirect revascularization techniques are preferred because of the smaller size of STA (often less than 0.7 mm).

In adults, the choice of the best technique depends on many factors including the age of the patient, the size of the vessels (in particular the STA), the presence of pre-existing anastomoses involving the ACE, disease course (direct revascularization has an immediate effect on cerebral blood flow) and the habits of each center.

4.2.2. *Perioperative complications*

Perioperative complications associated with MMA surgical revascularization are mainly related to the occurrence of infarction or cerebral hemorrhage with a frequency varying between 3 and 16% depending on the studies [18,41–46]. These complications also include the occurrence of epileptic seizures, subcutaneous or epidural hemorrhage, infection or cutaneous complication (necrosis). Direct revascularization techniques also expose the patient to the risk of reperfusion syndrome [47].

4.2.3. *Surgical indications*

4.2.3.1. Data from the literature *4.2.3.1.1. Ischemic presentation*. Japanese recommendations for adult and child with MMA recommend surgical revascularization in cases of ischemic cerebral manifestations (Table 1) [2]. The American Heart Association also issued recommendations in 2008 on the management of stroke in children and advocated surgical revascularization in pediatric forms of MMA in presence of progressive ischemic symptoms, or evidence of inadequate blood flow, or a significant reduction of the cerebral perfusion reserve [48]. However, no randomized study has been published for ischemic forms of MMA. Only few comparative, non-randomized and mostly retrospective studies with a limited number of patients are available. These studies do not provide an answer about the superiority of surgical treatment [10–16,41,42,49]. Several series on a large number of operated patients demonstrate a significant reduction of ischemic cerebral events after direct or indirect surgical revascularization in the adult and pediatric forms of MMA suggesting some efficacy of this treatment [17,18,41–46,49]. In the absence of solid data about the natural history of the disease, the interpretation of these non-comparative studies should remain cautious. Finally, in a systematic review of the literature from 2005, the effectiveness of surgical revascularization for treating MMA was evaluated in 57 studies including 1448 selected patients (Table 2). This study resulted in a grade D recommendation (scales from A to D) based on a level of class 3 evidence (scale from 1 to 4) [50]. Indications for revascularization surgery in MMA are thus based more on a consensus of experts than on a high level of evidence.

4.2.3.1.2. Hemorrhagic presentation. In a randomized study, assessing the efficacy of surgical revascularization in adults with hemorrhagic MMA (Table 3), [51] direct revascularization ($n = 42$) was compared with conservative ($n = 38$) treatment. Patients were followed for 5 years. The primary endpoint was the occurrence of cerebral hemorrhage, disabling stroke (modified Rankin score < 3), disabling morbidity of other origin, death, or the need for surgical revascularization for patients in the conservative treatment group. The occurrence of events was 14.3% in the surgical group and 34.2% in the conservative group. This difference was significant using the Kaplan Meyer's cumulative curve analysis for the main criterion ($P = 0.048$) but not with using the Cox regression model.

4.2.3.2. Recommendations. Indication of surgical revascularization should be discussed on a case-by-case basis using a multidisciplinary approach (with a dedicated meeting), at less involving neurologists, child neurologists, neurosurgeons and anesthesiologists. The occurrence of ischemic or cerebral hemorrhagic events, progression of angiopathy on imaging, efficacy of collateral pathways, level of intracerebral hemodynamic impairment, and functional status are taken into account for discussing the indication of a surgical procedure

Table 1 – Recommendations for good practice.

Authors	Research committee on the pathology and treatment of spontaneous occlusion of the circle of willis. 2012. Japan	Roach et al., 2008, USA
Objective	Japanese recommendations for the diagnosis and treatment of moyamoya disease	Recommendations of the American Stroke Association (AHA) for the management of stroke in children
Expert panel composition	Research Committee on the physiopathology and treatment of MMA including 11 neurosurgeons, 4 neurologists, 1 internist and 1 researcher in health sciences and environment	Working group formed by the AHA and including 4 neuropediatricians, 4 neurosurgeons, 1 pediatrician, 1 neuroradiologist, 3 neurologists
Population	MMD, adult and child	Pediatric stroke
Results (with grade of recommendations)	Surgical revascularization was recommended in case of cerebral ischemic manifestations. Level of proof of class IIb (IIb = well designed quasi-experimental studies, scale from I to IV). Grade B recommendation (B = recommended, scale from A to D)	Surgical revascularization was recommended in case of persistent cerebral ischemic manifestations and/or alteration of cerebral hemodynamics. Level of evidence of grade B (B = single randomized trial or non-randomized studies, on a scale from A to C), Class I recommendation (I = evidence and/or general agreement that the procedure or treatment is useful and effective, on a scale from I to III)

Table 2 – Systematic review of the literature.

Author	Fung et al, 2005, UK
Objective	To evaluate the effectiveness of surgical revascularization for the treatment of MMA
Bibliographic search strategy	Yes
Selection criteria of the studies	A/English publications B/Studies evaluating the surgical treatment of Moyamoya C/Patients under 21 years of age D/Studies involving at least 5 patients E/Follow-up data available
Population	Pediatric population with MMA
Results	57 studies including 1448 patients were selected. The superiority of surgical treatment vs medical treatment was based on data having a level of proof of class 3 (3: non-analytic studies, e.g. case reports, case series. on a scale from 1 to 4). Grade D recommendation (on a scale from A to D)

Table 3 – Randomized Control Trial.

Authors	Miyamoto et al., 2014, Japan
Objective	To evaluate the effect of extra-intracranial surgical revascularization on the risk of hemorrhagic recurrence and prognosis of patients
Methods	Controlled, prospective, randomized, multicentric study
Population	80 adult patients with MMD complicated by cerebral hemorrhage
Type of revascularisation	Direct surgical revascularization
Endpoints	Recurrent bleeding, completed stroke causing significant morbidity, significant morbidity and mortality from other medical cause, requirement for extracranial-intracranial bypass for a non surgical patient because of progressive ischemic stroke or crescendo TIAs
Results and significance	Reduction of the risk of events in the surgical group: non-significant trend using regression statistical analysis (cox proportional hazard model); significant difference was found ($P = 0.04$) using Kaplan-Meier analysis

and for guiding the modalities of the intervention. The age of the patients should also be taken into account, because of the more severe prognosis of MMA in infants [32–35].

4.2.3.2.1. *Ischemic presentation*. In children with MMA, surgical revascularization should be discussed after TIA or cerebral infarct. Impaired cerebral perfusion should also be considered for choosing a surgical procedure (grade 4 evidence, grade C recommendation). A delay of a few weeks should be observed before the surgical revascularization in case of recent cerebral infarct.

In adults with MMA, surgical revascularization must be discussed in case of TIA or cerebral infarct when they are recurrent and/or associated with a significant impaired cerebral perfusion (grade 4 evidence, grade C recommendation). A delay of a few weeks should be observed before the surgical revascularization in case of recent cerebral infarct.

4.2.3.2.2. *Hemorrhagic presentation*. The first step is to look for a possible arterial aneurysm on conventional angiography and to discuss all possible treatment modalities. Surgical revascularization will be considered in a second step to reduce the risk of new cerebral hemorrhage or ischemic event (Grade 2 evidence, grade B recommendation).

4.2.4. *Perioperative management*

The surgical revascularization procedure must be carried out by surgical and anesthetic teams in highly specialized centers in order to limit the risk of perioperative complications. General anesthesia should follow a dedicated protocol including adequate measures to correct pain, prevent hypotension, hypovolemia, hypercapnia, hypocapnia, or any other metabolic disturbance [52]. Blood pressure monitoring should be permanent to limit variations of mean arterial pressure (MAP), and to preserve cerebral perfusion pressure. Continuous blood pressure measurement and continuous carbon dioxide monitoring should be ensured for any performed action (sedation, anesthesia, post-operative monitoring). Indeed, cerebral vasomotor reactivity can be severely compromised in MMA patients, with consequent increased risk of cerebral ischemic complications [53].

Direct revascularization techniques imply clamping of a cortical artery for 30 to 45 minutes. A 10% increase in MAP compared to the initial measurement can be achieved during this period. The prevention of reperfusion syndrome, on the other hand, requires very strict control of the blood pressure once clamping of the cortical artery is lifted [54].

Indirect revascularization techniques, in particular in children, expose them to significant hemorrhage which should be evaluated and, eventually, corrected by transfusions.

4.3. *Drug treatments to avoid or to use with caution, and anesthetic precautions*

Treatment intensification for hypertension should be cautious and discussed with the referral team due to the risk of worsening cerebral hypoperfusion and ischemic complications. Anticoagulants are not indicated for the prevention of ischemic cerebral events because they demonstrated no efficacy in MMA and an increased risk of cerebral hemorrhage. They should be prescribed only in case of a formal indication (peripheral thromboembolic complications,

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complete arrhythmia by atrial fibrillation, etc.). No recommendation can be made regarding IV thrombolysis and endovascular treatment of acute ischemic stroke in the context of MMA. Preventive endovascular revascularization techniques should not be used because of their ineffectiveness and the risk of complications [55]. In cases with migraine (frequent in MMA patients, especially in children), vasoconstrictors, especially triptans and ergot derivatives, should be avoided because of the risk of worsening cerebral hypoperfusion. ''Hidden'' vasoconstrictors (e.g. nasal vasoconstrictors) should be also avoided [56]. Finally, any general anesthesia must comply with the precautions mentioned in chapter 4.2.4. The perioperative control of pain is essential because of the risk of vasoconstriction secondary to the hypocapnia it can cause. Contact with the patient's referral team is recommended prior to any anesthesia. Regional anesthesia techniques should be favored whenever possible with the same precautions concerning, in particular, the monitoring of blood pressure [37,57–59].

4.4. *Pregnancy*

In cases of planned pregnancy (or a current pregnancy), it is recommended that the patient consults her neurologist. The risk of complication related to MMA during pregnancy and peripartum is not well known. Until delivery, cerebrovascular complications do not appear to be significantly increased [60,61]. In peripartum, reported complications (cerebral hemorrhage and TIA) mainly concern patients whose diagnosis of MMA was unknown until then [62]. A multidisciplinary discussion between the patient's referral team, gynecologists and anesthesiologists is desirable at the time of the third trimester anesthesia consultation.

Recent studies suggest that the choice of vaginal delivery, under locoregional anesthesia, may be considered because it is not associated with an over-risk of cerebrovascular complications [63,64]. If general anesthesia is required, it should be prepared because induced hemodynamic changes may favor the occurrence of cerebral infarct (see chapter 4.2.4).

When oral contraception is considered, progestogen-only pills may be used. In case of ischemic complications, pills containing estrogen are contraindicated.

4.5. *Rehabilitation, psychotherapy, academic and occupational inclusion*

Multidisciplinary care (speech and language therapy, physiotherapy, neuropsychology, occupational therapy, etc.) is often necessary.

4.5.1. *Physiotherapy*

Physiotherapy should be started early, as soon as motor impairments appear, in order to limit the deleterious effects of decubitus and immobility. Physiotherapy should prevent bronchial congestion, ensure ventilatory functions, and promote recovery of sensori-motor functions. Care can be provided at home, in a private practice, or in specialized centers, depending on the individual situation. The patient is encouraged to prolong rehabilitation during the day by implementing a self-rehabilitation program involving caregivers.

4.5.2. *Speech and language therapy and cognitive rehabilitation*

The rehabilitation of cognitive deficits (language disorders, memory, attentional and executive functions deficits, unilateral spatial neglect) must be initiated early after a detailed evaluation (neuropsychological assessment, speech-language assessment, assessment of impact of those deficits on everyday life, quality of life). Dysarthria and swallowing difficulties should also be managed when needed.

4.5.3. *Occupational therapy*

Occupational therapy is organized when functional disability occurs and as soon as an impact of neurological deficits becomes evident in basic and/or instrumental activities of daily living (washing, dressing, dressing, food, shopping, administrative procedures, transportation, and finance). It is also useful to implement technical aids (appliances, use of a computer keyboard, etc.) to assess difficulties accessing one's home/bathroom, etc., to secure the environment and to propose adapted facilities.

4.5.4. *Psychomotor therapy*

Psychomotor therapy can reduce the consequences of neurological disorders: motor coordination, communication, and behavioral disturbances. Through interventions with strong body mediation, it aims to reconcile the patient with his body, to give him some gestural ease, and to increase the sensation of physical well-being. This approach can alleviate painful or anxious feelings.

4.5.5. *Psychotherapy*

Psychological support should be offered to the patient and his family. Such a support can reduce the psychological consequences of the disease as well as the personal, professional, and family difficulties.

4.5.6. *Dietary/nutritional management*

The occurrence of swallowing disturbances may require specific management by a physiotherapist or a speech therapist, and justify the use of gelled water and thickeners. These swallowing disorders may require a gastrostomy associated with enteral nutrition. Hyperprotein and hypercaloric dietary foods (beverages, creams, cereals, mixed meals, etc.) are sometimes needed. For all these reasons, a specific intervention from a dietician may be necessary.

4.5.7. *Medical and social care*

The role of the social worker is essential, particularly for helping with administrative procedures, for linking with administrative and social services, for information on legislation related to disability and on all potential help to be implemented at home, for advice on funding accommodation in specialized center. Caregivers should be informed of these different options for assistance.

4.5.8. *Medical devices*

Medical devices can be considered in case of motor deficiencies. Different technical aids are available for compensating moving or grip difficulties (sticks, crutches, orthoses, walking frames, shower armchair, wheelchair, adapted cutleries, etc.).

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In presence of functional impairment requiring human assistance, the use of medical lifts, equipment to assist transfers, and/or medical beds will be considered.

4.5.9. *School and occupational inclusion*

In young children, school inclusion may justify adjustments in presence of specific learning disabilities, disabling motor deficits, or fatigue. Extra time for assignments and examinations may be justified and should be assessed on a case-by-case basis. A personalized academic project can be proposed in collaboration with the family, the attending physician, the referring teacher, the school doctor, and the national or local disability services. In the event of major learning disabilities, referral to a specialized academic structure will be discussed with the parents, the teaching staff, the referring teacher, and other stakeholders. In adults, a socio-professional adaptation must sometimes be put in place, and the patient may require care from vocational services or other structures dedicated to acquired brain injury and/or disability.

4.6. *Therapeutic education and lifestyle adaptation*

Some activities can worsen cerebral hypoperfusion. Any activity inducing significant hyperventilation, dehydration, or altitude-related hypoxia (air travel, mountain stay) should be discussed on a case-by-case basis with the referring specialist and assessed repeatedly over time. Some activities, such as sports with competitions or the practice of a wind instrument, can however be maintained if they are well tolerated. Recreational sport should be preferred to competition. A medical certificate may be drafted along these lines. After revascularization surgery, it is recommended, at least temporarily, to avoid all sports exposing to head trauma (combat sports, rugby...).

4.7. *Patient associations*

Health professionals, patients, and caregivers should be informed about the potential support from a patient association. These associations (in France: http://www.tanguy-moya-moya.org/) can participate in the overall management of the disease by promoting cooperation between patients, caregivers and caregivers, and by disseminating documents such as a personal medical card.

5. Follow-up

5.1. *Timing and content of follow-up consultations*

Regular follow-up is required. Its frequency should be adapted on a case-by-case basis and maintained throughout life even long after the diagnosis, and even in the absence of clinico-radiological changes.

The aims of follow-up consultations are:

- to identify neurological symptoms suggestive of TIA or stroke, headache, movement disturbances, epileptic seizures, cognitive problems;
- to monitor the occurrence of any extra-neurological clinical sign suggestive of MMS;
- to monitor the occurrence of any additional vascular risk factors (in particular hypertension), taking into account the above-mentioned precautions (see 3.3);
- to evaluate the tolerance and indication of each treatment (specially antiplatelet and hypotensive drugs);
- to assess the cognitive and motor status; for this purpose a consultation with a specialist of Physical Medicine and Rehabilitation may be proposed;
- to evaluate the psychological and medico-social burden, the educational and/or professional adaptations put in place or necessary.

In case of revascularization surgery:

- a clinical evaluation 6 to 8 weeks after the intervention is needed to check the absence of symptoms suggestive of any additional cerebrovascular event or of any other complication likely to occur after the surgery (infection, subdural hematoma...);
- a neurological evaluation including a detailed cognitive assessment will also be organized between 6 months and one year after the surgical procedure.

5.2. *Imaging and biological follow-up*

The following imaging and biological investigations have to be considered during the follow-up:

- cerebrovascular imaging: The frequency of MRI and MRA follow-up is adapted on a case-by-case basis according to the clinical and radiological evolution of the patient (at least once a year during the first years). The realization of a cerebral conventional angiography during follow-up is discussed when a surgical procedure is envisaged, or after a cerebral hemorrhage. In case of surgical revascularization, a postoperative evaluation by MRI and MRA is organized during the first days after the procedure to evaluate the occurrence of any new ischemic lesion. Another cerebral MRI and MRA will be done one year after the revascularization;
- cerebral perfusion imaging is recommended at the time of diagnosis. It must be performed to assess the benefit/risk balance of surgical revascularization, and/or any other therapeutic intervention bearing a potential risk (hypotensive drugs, anesthesia, etc.). It may also be considered after a revascularization procedure to evaluate the possible improvement of cerebral perfusion [65];
- biological assessment of vascular risk factors.

5.3. *Role of the attending general practitioner*

The role of the attending physician is:

- to coordinate care with the referring specialist;
- to detect neurological complications arising during the disease (stroke, TIA, recurrent headaches, epilepsy, disability-related complications);
- to prevent and manage vascular risk factors;

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- to ensure that the patient is aware of the precautions associated with the disease, and that drugs at risk are avoided or used with caution (see 3.3);
- to participate in the setting up and coordination of home care, to participate in the drafting of various medical certificates.

The vaccination schedule can be followed normally.

5.4. *Monitoring and support for caregivers*

The role of caregivers is essential to support the patient in his/her daily activities. It is necessary to prevent, identify, and manage the difficulties associated with this support among caregivers.

Patient follow-up should be an opportunity:

- to identify the patient's main caregiver(s);
- to detect a possible degradation of the psychic and physical status of caregivers;
- to estimate the needs of caregivers to ensure that they are in line with the means put in place to support them (medical, social and financial aid).

When appropriate, to guide the caregiver towards:

- a psychologist, a social worker;
- the patient association;
- the community-based or home-based care facilities in order to obtain specific support.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurol.2017.12.002.

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