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2021 Japanese Guidelines for the Management of Moyamoya Disease: Guidelines from the Research Committee on Moyamoya Disease and Japan Stroke Society

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Introduction

The angiographic characteristics of moyamoya disease (MMD) were first reported in 1957 as hypogenesis of bilateral internal carotid arteries (ICAs).[1)] Then, the concept of MMD was established as an independent disease entity in the 1960s.[2-6)] MMD is characterized by chronic progressive stenosis of the terminal portion of the bilateral ICAs, which leads to the formation of an abnormal vascular network, functioning as a collateral pathway at the base of the brain. The appearance of this vascular network on cerebral angiography was similar to a "puff of smoke," which was described as "moyamoya" in Japanese.[5)] As the steno-occlusive changes of the bilateral ICAs progress, the moyamoya vessels eventually regress, and the entire cerebral hemisphere is perfused by the external carotid artery and the vertebrobasilar artery systems.[2-7)] MMD was designated as an intractable disease in Japan, which was initiated by the Intractable Disease Health Care Act to secure a budget for maintaining medical expense subsidy for patients with intractable diseases and to promote research on clarifying the pathogenesis. Presently, the diagnostic criteria for MMD are defined by the research committee approved by the Ministry of Health, Labor and Welfare of the Japanese government[8)] and then approved by the Japan Neurosurgical Society, the Japan Stroke Society, and the Japanese Society on Surgery for Cerebral Stroke. In this article, we report new guidelines for the management of MMD on the basis of 2021 guidelines from the Japan Stroke Society.[9)]

[1] Surgical Treatment

Recommendations

i. Surgical revascularization is reasonable for MMD manifesting as cerebral ischemic symptoms (Appendix 1, Recommendation Grade B, Level of Evidence: low).
ii. Appropriate blood pressure control may be reasonable for patients with postoperative cerebral hyperperfusion syndrome while considering the concomitant cerebral ischemia (Recommendation Grade C, Level of Evidence: low).

Comments

i. Indication of surgery

Surgical revascularization for MMD patients with cerebral ischemic attacks has been reported to reduce the frequency of transient ischemic attacks (TIAs) and the risk of

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Appendix 1 Classification of evidence levels and recommendation grades

Classification of evidence levels in the Guidelines

Evidence level	Definition
High	Consistent evidence from randomized controlled trials or exceptionally strong evidence from observational studies, which cannot be overturned by future studies.
Middle	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies, which can be overturned by future studies.
Low	Evidence from observational studies, systematically nonorganized clinical studies, or randomized controlled trials with serious flaws.

Classification of recommendation grades in the Guidelines

Recommendation grade	Definition	Comments
A	Strong recommendation	Recommended Should perform
B	Middle recommendation	Reasonable
C	Weak recommendation	May/might be reasonable Undetermined effectiveness
D	Non-beneficial	Not recommended Ineffective
E	Harmful	Recommended not to perform Should not perform

cerebral infarction and to improve the postoperative activities of daily living (ADLs) and long-term prognosis of neurocognitive function.[10-19] Improvement of cerebral hemodynamics and metabolism has been reported after revascularization surgery in patients with hemodynamic impairment on single-photon emission tomography (SPECT) or positron emission tomography (PET).[10,17,20]

ii. Surgical procedures

Revascularization procedures for MMD include direct revascularization, indirect revascularization, or a combination of these two types of surgery. Superficial temporal artery-middle cerebral artery anastomosis represents direct revascularization surgery. Indirect revascularization surgery includes encephalo-arterio-synangiosis, encephalo-duro-synangiosis, encephalo-myo-synangiosis, multiple burr hole surgery, or a combination of these procedures. Both direct and indirect revascularization or a direct/indirect combined revascularization surgery have been reported to improve cerebral hemodynamics, ameliorating the severity and frequency of TIAs, reducing the risk of cerebral infarction, and improving the postoperative ADL and long-term prognosis of neurocognitive function.[10-21] For adult patients, the indirect procedure alone is not sufficient and a direct procedure or combined procedure is necessary.[18,19,21-26] Moreover, a combined procedure supplies a wider territory of the ischemic brain than the direct procedure alone, resulting in better surgical outcomes for adult MMD patients.[25] In pediatric patients, surgical revascularization, regardless of direct or indirect revascularization, has been reported to improve the clinical outcomes.[27,28] Endovascular treatment for the steno-occlusive lesions of MMD is not recommended.[29]

iii. Perioperative management

Sufficient blood pressure control and fluid replacement, maintenance of normocapnia, and as-needed antiplatelet therapy are necessary for the perioperative management to avoid ischemic complications not only on the surgical side but also on the nonsurgical side.[30] Transient neurological deterioration due to cerebral hyperperfusion syndrome or relevant delayed intracranial hemorrhage is of concern after revascularization surgery for MMD, especially in adult patients.[31,32] Hence, it is recommended to assess cerebral hemodynamics in the early postoperative period to differentiate postoperative ischemia from hyperperfusion. Strict blood pressure control is effective for symptomatic hyperperfusion syndrome. Ischemic complications in a remote area or adjacent area of hyperperfusion (watershed shift phenomenon) should be watched for during strict blood pressure control.[31-36] The perioperative administration of minocycline hydrochloride or edaravone may prevent symptomatic hyperperfusion.[37,38]

iv. Postoperative evaluation

The assessment of cerebral hemodynamics and metabo-

lism using PET or SPECT is useful for evaluating the effects of revascularization surgery.[10,17,20] Cerebral angiography and magnetic resonance angiography (MRA) are useful for evaluating bypass development.[39,40]

[2] Medical Treatment

Recommendations

i. Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) may be considered under careful evaluation of the risk of hemorrhagic complication in the hyperacute phase of cerebral ischemia in MMD (Recommendation Grade: C, Level of Evidence: low).
ii. Oral administration of antiplatelet agents may be considered as a medical treatment for ischemic MMD (Recommendation Grade: C, Level of Evidence: low).
iii. Reduction of systolic blood pressure may be reasonable in the acute stage of hemorrhagic MMD, as described for spontaneous intracerebral hemorrhage, considering the development of cerebral ischemia (Recommendation Grade: C, Level of Evidence: low).

Comments

The medical treatment of MMD is roughly classified into treatment for the acute phase of stroke, treatment for preventing recurrence in the chronic phase of stroke, and treatment of asymptomatic MMD.

1. Acute stage

i. Ischemic MMD

The intravenous administration of recombinant tissue-type plasminogen activator (rt-PA) therapy should be carefully considered in the hyperacute phase of ischemic onset MMD based on the "Guidelines of Proper Treatment with Intravenous Thrombolysis (rt-PA), the 3rd version (2019)".[41] In the acute phase of cerebral infarction in adults, edaravone or antiplatelet therapies are considered on the basis of the treatment of atherothrombotic cerebral infarction. For patients with large infarcts causing cerebral edema and intracranial hypertension, the use of glycerol should be considered. Furthermore, supportive treatment, such as antipyretics for fever, anticonvulsants for convulsions, control of blood sugar, oxygen supplementation for maintenance of arterial oxygen saturation, and prophylactic administration of antiulcer agents, is important. Maintenance of normocapnia should be indicated when mechanical ventilatory support is necessary. Regarding blood pressure control, as in the treatment of other cerebral infarctions, the blood pressure should not be reduced during the acute phase.

There is little evidence supporting a treatment strategy for ischemic MMD in children. Antiplatelet therapy with aspirin is generally used in the United States. If the patients exhibit aspirin resistance, low-molecular heparin can be used. Blood transfusion should be considered for patients with MMD associated with sickle cell disease because medical therapy is not effective for these patients.[42] It should be noted that aspirin has a potential risk of Reye's syndrome.

ii. Hemorrhagic MMD

In patients with hemorrhagic MMD, antihypertensive therapy can be considered on the basis of the treatment of hypertensive intracranial hemorrhage. Cerebral ischemic attack due to hypotension is of concern during antihypertensive therapy, although there is no evidence. The discontinuation of antiplatelet or anticoagulant therapies and the use of vitamin K, blood products, or antagonists should be considered.

2. Prevention of recurrence in the chronic stage

The surgical indications for the prevention of recurrent stroke should be primarily considered in patients with ischemic MMD. Medically, oral administration of antiplatelet drugs is the treatment of choice,[43] but long-term administration has a potential risk of hemorrhagic transformation. Regular follow-up by T2*-weighted imaging for the detection of microbleeds may be effective to predict future hemorrhage.[44] When aspirin is not effective to prevent an ischemic attack, clopidogrel or cilostazol can be considered. The safety of clopidogrel for pediatric patients has been validated.[45] Long-term use of multiple antiplatelet agents is considered to have a high risk of hemorrhagic complications, especially in patients with brain atrophy or marked development of fragile moyamoya vessels.[42]

General risk factors for stroke should be managed according to general practice. In terms of lifestyle guidance, hyperventilation often induces symptoms of ischemic attacks; therefore, pediatric patients should avoid hot meals (noodles, soup, etc.); strenuous exercise; playing wind instruments, such as a flute; and blowing balloons. In infants, it is important to avoid crying and dehydration due to vomiting and diarrhea.

3. Medical management of asymptomatic MMD

Asymptomatic MMD patients also have a risk of cerebrovascular events during follow-up.[46] Management of risk factors and lifestyle guidance should be implemented according to the prevention of stroke recurrence in symptomatic MMD. The use of antiplatelet agents requires caution in adult patients while considering the potential risk for a hemorrhagic event in adult MMD.

4. Management in the perinatal period

Pregnancy and parturition are acceptable in female patients with MMD.[47-49] Close cooperation with obstetricians and pediatricians is reasonable in the management of MMD patients in the perinatal period because we might not rule out the possibility of the increased risk of stroke

during pregnancy, delivery, and postpartum period.

[3] Management of Hemorrhagic MMD

Recommendations

Revascularization surgery is reasonable for hemorrhagic MMD, especially posterior hemorrhage, to prevent recurrent hemorrhage (Recommendation Grade: B, Level of Evidence: middle).

Comments

Intracranial hemorrhage is the most detrimental factor for the clinical prognosis of MMD.[50] In the acute stage after intracranial hemorrhage, appropriate control of blood pressure and intracranial pressure by prompt medication and/or intraventricular drainage might be reasonable while considering the potential risk for concomitant cerebral ischemia in MMD. Disruption of the dilated collateral vessels (moyamoya vessels) due to hemodynamic stress or rupture of the peripheral aneurysms formed on the collateral vessels are possible sources of bleeding. Revascularization surgery is considered effective to reduce recurrent hemorrhage, considering that the postoperative angiography demonstrated regression of these collateral vessels or peripheral aneurysms after revascularization surgery.[51,52] Furthermore, revascularization surgery is effective for patients with hemorrhagic MMD manifesting ischemic symptoms.[53]

In Japan, a prospective randomized trial of extracranial-intracranial bypass surgery, Japan Adult Moyamoya (JAM) Trial, was conducted to investigate the efficacy of bypass surgery to prevent recurrent hemorrhage.[54,55] In this trial, patients with hemorrhagic MMD were randomly assigned to two of the following groups: bilateral direct bypass surgery group and medical treatment alone group. The incidence of primary endpoints (all medical adverse events including rebleeding attacks) over 5 years was significantly lower in the surgical treatment group. Although the results were borderline significant, the efficacy of direct revascularization surgery to prevent recurrent bleeding was confirmed.

In the JAM Trial, the site of hemorrhage was classified as either anterior or posterior before assignment, and the clinical outcome and effects of surgery were compared between the two groups.[56] Consequently, the annual rebleeding rate in the nonsurgical group was as high as 17.1% in the posterior hemorrhage group. Moreover, the preventive effects of surgery on rebleeding were significantly higher in the posterior hemorrhage group. Subgroup analysis demonstrated posterior cerebral artery stenosis and choroidal anastomosis to be relevant factors for posterior hemorrhage. The risk of hemorrhage was higher in the hemisphere with advanced choroidal anastomosis, which was a key angiographical prognostic factor.[57,58] Furthermore, hemodynamic failure is an independent risk factor for subsequent hemorrhage in hemorrhagic MMD.[59] Thus, along with the development of choroidal anastomosis, hemodynamic failure is an additional important factor to determine surgical indications.

Conflicts of Interest Disclosure

All authors have no conflicts of interest to declare. All authors who are members of The Japan Neurosurgical Society (JNS) have completed the Self-reported COI Disclosure Statement forms available at the website for JNS members.

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