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Imaging of Moyamoya Disease and Moyamoya Syndrome: Current Status

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Abstract: Moyamoya disease (MMD) and Moyamoya syndrome (MMS) are referring to a progressive steno-occlusive vasculopathy at terminal portions of the bilateral internal carotid arteries and their proximal branches with prominent collateral artery formation. They can be found throughout the world and cause irreversible damage to the cerebral hemodynamics due to the progressive nature. Prompt diagnosis and accurate assessment could significantly improve the prognosis of MMD and MMS. Some imaging modalities could be used for diagnosis and nonquantitative evaluation of MMD and MMS, such as conventional computed tomography (CT) and magnetic resonance imaging (MRI), digital subtraction angiography, CT angiography (CTA), and magnetic resonance angiography. Some could quantitatively evaluate the cerebral hemodynamics of MMD and MMS, such as single-photon emission CT, positron emission tomography, xenon-enhanced CT, perfusion CT, dynamic susceptibility contrast MRI, arterial spin labeling MRI, and the hemodynamic parameters measured by those imaging methods could guide treatment of MMD and MMS. All the imaging modalities have their merits and demerits, and they can play a part in certain situation. We need establish standardized protocols for preoperative and postoperative evaluation with different imaging techniques in the further science for MMD and MMS.

Key Words: Moyamoya, imaging modality, cerebral hemodynamics

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Moyamoya disease (MMD) was first described by Takeuchi and Shimizu in 1957 and then termed by Suzuki and Takaku's in 1969.¹ It is a progressive steno-occlusive disease at terminal portions of the bilateral internal carotid arteries and their proximal branches with prominent collateral artery formation. Although MMD is more common in Asian populations, it can be found throughout the world. Two peak incidences of MMD are the ages of 5 and 40 years. Moyamoya syndrome (MMS) is refer to the Moyamoya-like vasculopathy with associated risk factors, such as neurofibromatosis type, down syndrome, thyroid disease, cranial irradiation, sickle cell anemia, and so on.^{2,3} The clinical manifestations of MMD and MMS could be subdivided into two

types: ischemic type and hemorrhagic type. In Asian populations, the former is common in children, whereas the latter is common in adult.⁴ However, some authors argue that the most common clinical presentation among adult patients is ischemic stroke and/or transient ischemic attacks in some other countries.⁵ Because of the progressive nature of MMD and MMS, prompt diagnosis and appropriate management are crucial to improve the long-term prognosis of patients.⁶

Imaging of MMD and MMS

To this day, different imaging modalities has been used for diagnosis of MMD or MMS, including digital subtraction angiography (DSA), computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission CT (SPECT), and positron emission tomography (PET). Some imaging modalities are quantitative, whereas the others are nonquantitative. All of them are useful in certain situation. Each of these imaging techniques has its advantages and disadvantages.

Nonquantitative Imaging

Nonquantitative imaging techniques include different basically angiographies, such as angiography: DSA, CT angiography (CTA), and magnetic resonance angiography (MRA).

Digital subtraction angiography is currently considered to be the criterion standard for diagnosis and assessment of MMD and MMS. Then, the “Moyamoya” was originally used to describe the DSA manifestation of MMD. Moyamoya disease had been subdivided into 6 stages by Suzuki and Takaku (Table 1).¹ This staging system has been well accepted so far. However, the disadvantage of this staging system is that it cannot really reflect the hemodynamic status of the brain parenchyma and is insensitive to longitudinal follow-up.^{7–9} Digital subtraction angiography can be also used for assessment of the postoperation changes, especially extracranial-intracranial (EC-IC) bypass surgery. However, DSA is still an invasive surgery with associated risks, such as groin hematoma, transitory neurological symptoms, and so on¹⁰ (Fig. 1).

Recently, CTA and MRA have been widely accepted for diagnosis and evaluation of MMD and MMS.¹¹ Computed tomography angiography is especially helpful in patients who are presented to the emergency department with suspected complications due to vascular abnormalities.¹² Compared with the DSA, both of CTA and MRA are less time-consuming and safer, although the CTA still accompanies with radiation exposure and the MRA is relatively time-consuming and limited in critically ill patients.¹³ Sugino et al¹¹ reported that CTA was superior to MRA in identification of very small stenotic lesions in the internal carotid artery (ICA), middle cerebral artery (MCA), and posterior cerebral artery, whereas MRA tends to underestimate the presence of such lesions. Magnetic resonance angiography is widely accepted for it is a completely noninvasive examination with no requirement of contrast medium and radiation exposure. Early report revealed that MRA may overestimate stenotic lesions and underestimate the Moyamoya vessels.¹⁴

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The authors declare no conflict of interest.

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TABLE 1. Angiographic Suzuki Grading System of MMD

Stage	Manifestation
Stage I	Narrowing of the carotid Fork
Stage II	Initiation of the Moyamoya with dilatation of the intracerebral main arteries
Stage III	Intensification of the Moyamoya with partial disappearance of the intracerebral main arteries
Stage IV	Minimization of the Moyamoya., advanced steno-occlusive ICA, ACA and MCA with gradually enlarged collateral from the extracranial area
Stage V	Reduction of the Moyamoya, disappearance of ACA and MCA with increased collateral from the external carotid artery
Stage VI	Disappearance of the Moyamoya with cerebral circulation maintained only by the external carotid artery or the vertebral artery.

With the advances of technology, these drawbacks may be overcome to some degree. 3.0-Tesla MRA was better than 1.5-Tesla MRA in depiction of small vessel segments due to the improvement of the contrast-to-noise ratio.^{15,16} According to the results of this study, 3-Tesla time-of-flight MRA and CTA did better in depiction of intracranial segment of bypass and the trepanation segment, respectively, and there was no difference in assessing the stenosis degree of bypass of the extracranial superficial temporal artery segment between the 2 imaging modalities (Figs. 2A, B).

Conventional CT and MRI

Although conventional CT and nonquantitative MRI play a limited role in diagnosis and evaluation of the vasculopathy of MMD and MMS, some authors have attempted to improve the usefulness of these basic imaging modalities. These modalities, which are commonly available, can at least provide clues to make preliminary diagnosis and evaluation and offer the possibility for us to obtain the early diagnosis, especially in those asymptomatic MMD and MMS patients (Figs. 3A, B).

Application in Disease Diagnosis

Yamada et al¹⁷ reported that combined utilization of T1-weighted imaging (T1WI) and T2-weighted imaging of MRI can successfully demonstrate occlusive disease in the basal portions of the ICA, anterior cerebral artery (ACA), MCA, and posterior cerebral artery, as well as collateral vessels of MMD patients. Hu et al¹⁸ retrospectively analyzed the conventional CT and axial T2-weighted imaging of MMD and MMS patients. They found that these two imaging modalities are not only convenient, cost-effective, and commonly available in different clinical practices but also useful in identifying steno-occlusive changes of horizontal segments of the MCAs.¹⁸ Yuan et al^{19,20} found that some findings, such as smaller outer diameter and wall thickness, concentric stenosis, homogeneous signal intensity, and collateral vascular structures in high-resolution MRI, might be the characteristics of MMDs, whereas pathological shrinkage of MCA was an important phenomenon of progression.

Specific Manifestations

The ivy sign was first reported by Ohta et al²¹ in 1995, which was used to describe a diffuse leptomeningeal enhancement on postcontrast MRIs of MMDs. Later, the ivy sign was used to depict linear high signal intensity along the cortical sulci or brain surface in the cerebral hemisphere on unenhanced fluid-attenuated inversion recovery (FLAIR) MRIs. It is reported that ivy sign on FLAIR can be seen in approximately half of involved hemispheres and in nearly one third of asymptomatic MMD patients. It may be caused by slow retrograde flow of engorged pial arteries via leptomeningeal anastomosis, maximally dilated pial vasculature compensating for decreased perfusion pressure, and congestive thickening of the leptomeninges.²² Thus, the ivy sign can be used

to indicate the hemodynamic status of the leptomeningeal collateral pathways in MMD, which is more prominent in hemispheres with poorer visualization of the cortical branches of the MCA on MRA.^{23,24} In the study of Mori et al,²⁵ the degree of the ivy sign was classified into 3 grades and the results was compared with the finding of ¹²³I-IMP SPECT. Their findings showed that the degree of the ivy sign on FLAIR images demonstrated a negative relationship with the resting cerebral blood flow (CBF) and a more prominent negative relationship with the cerebral vascular reserve (CVR).²⁵ The same grading was used by Kaku et al²⁶ to correlate it with the results of ¹⁵O gas PET. It turned out that the ivy sign was associated with both dilated pial vasculature and the slow flow of developed leptomeningeal collaterals in MMDs²⁶ (Figs. 4A, B).

Susceptibility-weighted MRI (SWI), which is available to evaluate deep venous flow in ischemia and to demonstrate increased oxygen extraction in focal cerebral ischemia, can be also used to assess the severity of the hemodynamics in MMDs.²⁷ Horie et al²⁸ used SWI to evaluate the deep medullary vein and found that the SWI stage correlated with hemodynamics on SPECT, especially CVR.

Quantitative Imaging

Once the diagnosis of MMD or MMS is made, how to select the therapeutic schemes may be the next key step for the prognosis. Although medical therapies are not effective for MMD and surgical revascularization become more acceptable,^{6,29} medical treatments still are the first choice in the asymptomatic MMD



FIGURE 1. Internal carotid artery angiography shows smog-like vessels. Figure 1 can be viewed online in color at www.jcat.org.

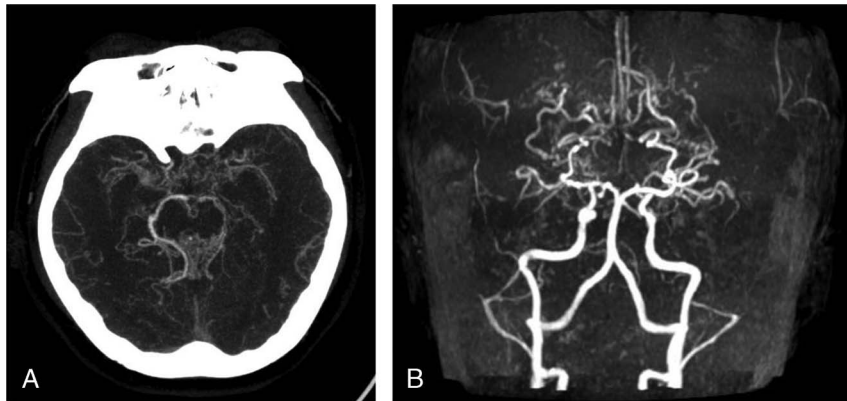


FIGURE 2. Maximal intensity projection images of CTA and bilateral ICA occlusion of the bed segment occlusion. A, Maximal intensity projection images of CTA showed bilateral ICA bed segment occlusion. There was no development of bilateral anterior and middle cerebral arteries, as well as multiple abnormal vascular network at basis crania. B, Magnetic resonance angiography images of bilateral ICA occlusion of the bed segment occlusion. Bilateral middle cerebral artery showed no development. Multiple abnormal vascular network at basis crania.

patients.³⁰ It is noteworthy that cerebral hemodynamic status has no correlation with the angiographic stage according to the Suzuki and Takaku's classification.³¹ To this day, there is no established standard of the best time to choose the surgical treatment. However, it is recognized that the cerebral hemodynamic status should be carefully evaluated before and after surgical revascularization.

Hemodynamic Characteristics of MMD and MMS

Reported mechanism (Fig. 5) of MMD and MMS demonstrate that progressive nature of MMD and MMS leads to sustained reduction of cerebral perfusion pressure (CPP). Decreased CPP could cause the reduction of CBF. Fortunately, CBF can be still within the normal range due to the autoregulation, which is referring to the vasodilation of resistance arterioles, and this ability to maintain CBF is termed CVR. When the autoregulation cannot offset the effect of decreased CPP, CBF will decrease as well. To maintain normal oxygen metabolism, compensatory increases in oxygen extraction fraction (OEF) could work temporarily and this phenomenon is named misery perfusion. Ischemic symptom will come up if the reduction of CPP beyond the limit of compensatory increases of OEF. Cerebral blood volume (CBV) comprises arterial, capillary, venous, parenchyma, and pial components. It may increase because of autoregulation when the CPP decreases; however, the results could be variable in different studies. Other hemodynamics parameters, such as mean transit time (MTT) and time

to peak (TTP), could also be used to reflect the cerebral hemodynamic changes of MMDs. Among these hemodynamic parameters, CVR may be the most valuable indicator for choosing therapeutic regimen. To figure out the CVR, resting CBF and activated CBF should be measured respectively. Acetazolamide or CO₂ is often used as the vasodilator. Sometimes, the blood may flow into areas where the autoregulation can still work from areas where vasodilation is at its maximum. When treated with surgical revascularization, elevated CBF may cause hyperperfusion syndrome, some of which could lead to transient or permanent neurological deficits.

Quantitative Modalities of MMD and MMS

Single-photon emission CT, PET, xenon-enhanced computed tomography (Xe-CT), perfusion CT, dynamic susceptibility contrast (DSC), and arterial spin labeling (ASL) MRI, quantitative DSA (QDSA), as well as other modalities could be used in evaluation of cerebral hemodynamic status in MMD and MMS. Each of them has its merit and demerit. Single-photon emission CT, PET, and Xe-CT may be the top-quality methods on account of their good quantitative accuracy, and they are often used as the reference standard. However, they are expensive and have risks of radiation damage. In addition, PET and Xe-CT are not always available, especially the Xe-CT for the Xenon gas, and the hardware of Xe-CT can be only found in few institutions of some

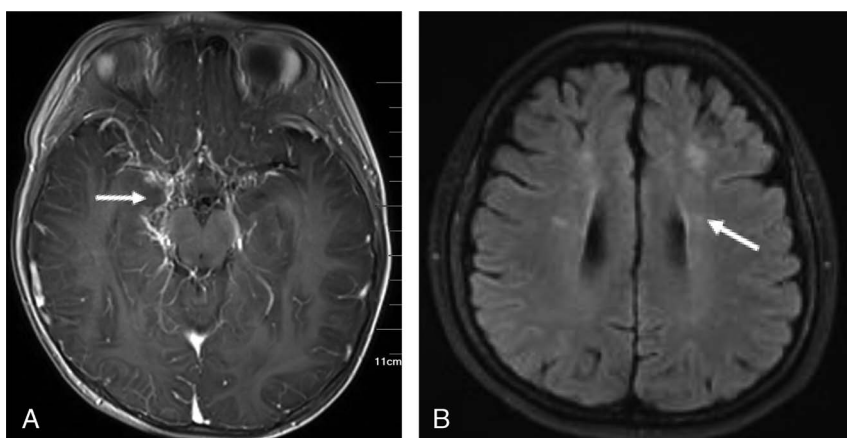


FIGURE 3. T1-weighted imaging-enhanced scan and FLAIR sequence at basis crania. A, T1-weighted imaging-enhanced display of multiple abnormally enhanced vascular network at basis crania. B, FLAIR sequence bilateral radial coronary region multiple cerebral infarction.

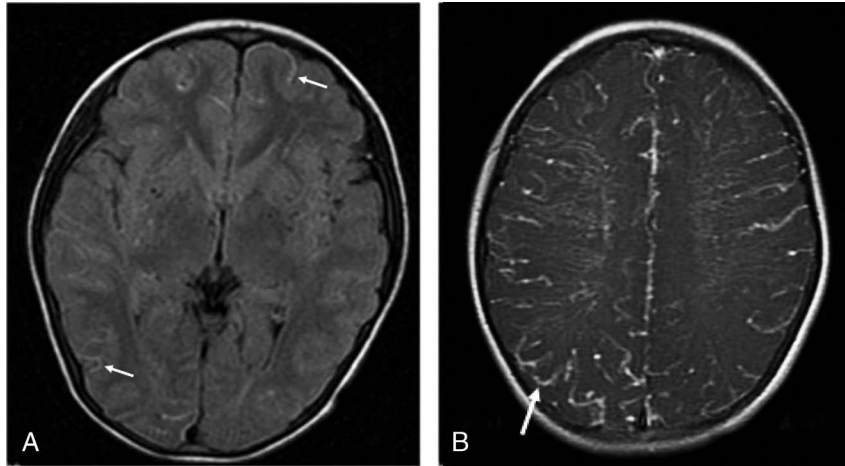


FIGURE 4. FLAIR sequence and T1WI-enhanced scan. A, FLAIR sequence showed multiple dots and bars of high signals (arrows) along the soft meninges distributed in the cerebral cortex of both hemispheres, ivy-like. B, T1-weighted imaging–enhanced scan was performed on both hemispheres of the brain with abnormal enhancement of blood vessels, ivy-like.

countries.^{5,32} On the contrary, perfusion CT, DSC and ASL-MRI, and Doppler are easier to go with. Recently, ASL-MR has been widely used for assessment of MMD because of its repeatability and lack of radiation and no need of intravenous contrast.^{33–36} Doppler may be the most convenient method in this situation; however, it is an indirect method for evaluating cerebral hemodynamic status and operator dependent. quantitative digital subtraction angiography is another approach to reflect the cerebral hemodynamic status in MMD, and its results may be affected by the injection rate, total amount of the contrast media catheter tip, and the patient's cardiac function.^{37,38} A number of articles had focused on assessment of preoperative and postoperative cerebral hemodynamic status of MMD and MMS with different modalities.

Assessment of Preoperative and Postoperative Hemodynamics and Cerebral Oxygen Metabolism of MMD and MMS

Single-Photon Emission CT

Single-photon emission CT can use the ¹³³Xe, ^{99m}Tc-HMPAO, ^{99m}Tc-ECD, and ¹²³I-IMP as the blood tracer to evaluate the regional CBF and CVR in MMD. A study of Honda et al³⁹ by using Split-dose ¹²³I-IMP SPECT reported that resting regional CBF increased significantly in treated hemispheres and the frontal

lobe of unaffected hemispheres, whereas only the CVR in the frontal lobe of treated hemispheres increased significantly in MMD patients after surgery. Marushima et al⁴⁰ found that regional CBF and CVR obtained from ^{99m}Tc-ECD SPECT during conservative therapy or before and after revascularization surgery were useful to assess clinical status in MMD patients. In their study, CBF of hemispheres with a hemodynamic disorder was significantly lower than that of normal contrast and increased significantly after surgery. The follow-up CVR decreased significantly if no revascularization was performed. The results of Fujimura et al⁴¹ showed that 21.5% of hemispheres of MMD patients who received EC-IC bypass could develop symptomatic hyperperfusion evaluated by ¹²³I-IMP SPECT. They declared that MMD patients tend to develop symptomatic hyperperfusion after EC-IC bypass compared with the other occlusive cerebrovascular diseases.⁴¹

Positron Emission Tomography

Positron emission tomography may be one of the most reliable quantitative assessment modalities for MMD and MMS, and it could be used to evaluate the CBF, CBV, OEF, and cerebral metabolic rate of oxygen (CMRO₂). In this technique, some tracers, such as H₂¹⁵O, C¹⁵O₂, and ¹⁵O₂, are often used.⁴² The findings may vary among different researches. Kuhn et al⁴³ retrospectively analyzed preoperation and postoperation CBF and CVR measured

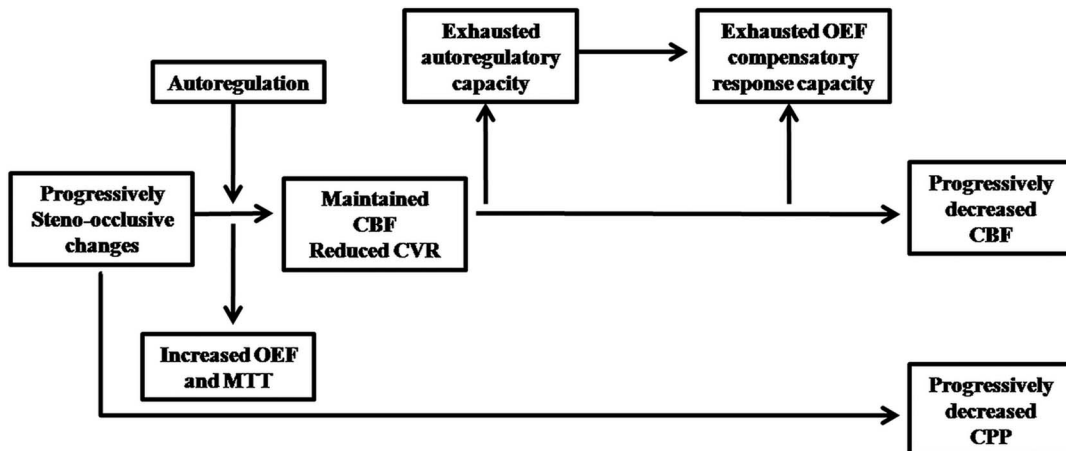


FIGURE 5. Basic changes of cerebral hemodynamics in MMD and MMS. Abbreviation: MTT, mean transit time.

by $H_2^{15}O$ PET of 14 pediatric MMD patients. The results of their study showed that the preoperation deficits of resting CBF, activated CBF, and CVR were more prominent in cortical rather than that of subcortical regions or cerebellum, and these deficits were most evident in MCA and ACA regions. Significant improvement of resting CBF and activated CBF could be found in postoperation measurements. However, no significant differences can be seen in CVR. The authors also thought that it might be caused by small sample size, steal phenomenon, and relatively short interval between preoperation and postoperation follow-up PET, which was not long enough for recovery of brain tissues. Kuroda et al⁴⁴ reported that approximately 80% of adult and pediatric MMD patients with lesions involved hemispheres had significant depression of $CMRO_2$ measured by $^{15}O_2$ gas PET, and significant improvement of $CMRO_2$ could be found after revascularization in pediatric or younger adult patients without parenchymal lesions, even though the underlying mechanisms are still unclear.

Xe-CT

Xe-CT has been a reliable method to quantitatively measure CBF for a long-term following-up. Cerebral vascular reserve can be calculated as well if the vasodilator is used with Xe-CT. Several earlier studies had investigated its usefulness for evaluation of MMD.^{45,46} McAuley et al⁴⁷ suggested that Xe-CT could be used to assess the stroke risk in pediatric MMD patient population and predict surgical outcome earlier than DSA.

Perfusion CT

The acquisition time of perfusion CT, which has satisfactory temporal resolution and spatial resolution, is relatively short. With the progress of CT hardware, whole-brain hemodynamics can be also obtained by perfusion CT. Thus, perfusion CT can be used in evaluation of cerebral hemodynamic parameters, such as CBF, CBV, MTT, and TTP. Zhang et al⁴⁸ analyzed the preoperation and postoperation whole-brain perfusion CT values of 39 MMD patients using 256-slice CT. The results showed that postoperative CBF, relative CBF, and relative CBV values of surgical sites were significantly increased, whereas the postoperative MTT, TTP, relative MTT, and relative TTP (rTTP) were significantly decreased in the region of MCA compared with those of preoperation.⁴⁸ Dai et al⁴⁹ used the perfusion CT to evaluate the effects of multiple burr hole surgery on adult ischemic MMD. The cerebral hemodynamic changes of 6-month follow-up were the same as those of Zhang et al,⁴⁸ and they also suggested that CBF and TTP, especially the rTTP, were sensitive to the presence of early altered cerebral hemodynamics after indirect revascularization. Acetazolamide can be also used in perfusion CT to assess the CVR. Kang et al⁵⁰ reported that the quantitative CVR obtained from perfusion CT was comparable with that of PET or SPECT.⁵⁰

Dynamic Susceptibility Contrast and ASL-MRI

Both of the 2 imaging modalities are noninvasive and do not expose the patients to ionizing radiation. Dynamic susceptibility contrast MRI can be easy to assess and performed on children. However, its application needs injection of contrast media and the signal intensity is affected by several factors, for instance, bolus delay and nonlinear contrast relaxivity. Thus, CBF measured by DSC is relatively reliable. In addition, the interpretation of DSC may be difficult and lack standardization. Tanaka et al⁵¹ found that CBV and MTT measured by DSC were valuable in MMD patients when compared with PET, and prolonged MTT may suggest the presence of misery perfusion. Arterial spin labeling MRI may be a more acceptable method because it is completely noninvasive and uses endogenous water as a tracer. However, extensive collaterals of MMDs can prolong arterial transit delays and thereby result in

inaccurate assessment of perfusion. Goetti et al³⁶ demonstrate the possibility of using ASL-MRI to evaluate DSC for detection of reduced perfusion per vascular territory in pediatric MMD patients. Wang et al⁵² suggested that perfusion data from multidelay ASL-MRI are accurate as that from CT perfusion. Goetti et al⁵³ reported that ASL-MRI had a good correlation with $H_2^{15}O$ PET in quantitative evaluation of CBF in children and young adult MMD patients. Noguchi et al⁵⁴ used a standard ASL-MRI sequences and pulse-wave-synchronized ASL to obtain the CVR of MMD patients. They found similar results compared with those determined by ^{123}I -IMP SPECT.⁵⁴

Quantitative DSA

Although the conventional DSA is still the criterion standard for evaluating the severity of MMD, it is frustrating that the imaging finding of conventional DSA cannot reflect the hemodynamic changes of MMD. As an alternative, QDSA may offset this drawback. Using QDSA, Hung et al³⁸ measured the delay time of maximal opacification between ICA and MCA in MMD patients without bypass surgery. They found that delay time of maximal opacification significantly correlated with the Suzuki staging and closer correlation with prolonged rTTP measured by DSC.³⁸ However, standardizing the DSA procedures is required to minimize the affection of the injection rate and the total amount of the contrast medium.³⁷

Doppler

Doppler is a completely noninvasive, real-time, easily repeatable, readily available, and economical method for evaluation of hemodynamics of MMD.⁵⁵ It offers information about quantitative flow characteristics, including ratio between systolic and end-diastolic velocity, flow resistance, and vessel pulsatility. This technique has been used to measure blood flow volume in the ICA as a correlate for CBF in the corresponding hemispheres.^{12,45} Thus, Doppler can be used to assess the preoperative and postoperative changes of MMD and MMS. Ruan et al⁵⁶ reported that transcranial color Doppler and power Doppler can be used to display the stenocclusive changes of intracranial arteries and Moyamoya vessels, which could be used to make diagnosis of MMD when combined with the symptoms and hemodynamic changes of extracranial arteries. Some authors suggested that duplex ultrasonography is a reliable method to evaluate the postoperative changes of MMD.^{57,58}

CONCLUSIONS

To this day, different imaging modalities have been used for diagnosis of MMD and MMS and for evaluation of the prognosis after various treatments of MMD and MMS. Each of these imaging techniques has its strengths and weaknesses, and each of them can be performed for different purposes in management of MMD and MMS. Apparently, the most valuable and acceptable imaging modality is based on the facts that it should have less injury to the human body, need less or no injection of contrast media, as well as be technically stable and convenient. Quantitative MRI-based methods and Doppler may become promising tools for accurate diagnosis of MMD and MMS, whereas establishment of standardized protocols for preoperative and postoperative evaluation with different imaging techniques is warranted in the further science for MMD and MMS.

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