Contemporary and emerging magnetic resonance imaging methods for evaluation of moyamoya disease

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Numerous recent technological advances offer the potential to substantially enhance the MRI evaluation of moyamoya disease (MMD). These include high-resolution volumetric imaging, high-resolution vessel wall characterization, improved cerebral angiographic and perfusion techniques, high-field imaging, fast scanning methods, and artificial intelligence. This review discusses the current state-of-the-art MRI applications in these realms, emphasizing key imaging findings, clinical utility, and areas that will benefit from further investigation. Although these techniques may apply to imaging of a wide array of neurovascular or other neurological conditions, consideration of their application to MMD is useful given the comprehensive multidimensional MRI assessment used to evaluate MMD. These MRI techniques span from basic cross-sectional to advanced functional sequences, both qualitative and quantitative.

The aim of this review was to provide a comprehensive summary and analysis of current key relevant literature of advanced MRI techniques for the evaluation of MMD with image-rich case examples. These imaging methods can aid clinical characterization, help direct treatment, assist in the evaluation of treatment response, and potentially improve the understanding of the pathophysiology of MMD.

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NUMEROUS recent and ongoing technical advances of imaging techniques offer the potential for improved characterization of moyamoya disease (MMD). These include higher spatial resolution, reduced acquisition time, characterization of findings on conventional and advanced MRI pulse sequences, use of high-field MRI, and application of artificial intelligence techniques. The cross-sectional, luminal angiographic, vessel wall, perfusion, and functional imaging features of MMD reflect the underlying pathophysiology of the disease. This pathophysiology has been described in more detail previously but remains incompletely understood.^{4,64} Several types of imaging examinations are available to character-

ize each of the major pathologic features, each with pros and cons. Qualities to consider when comparing techniques include the dependence on requisite hardware or software, the need for special expertise for interpretation, quantitative capability, the requirement of intravenous contrast, and exposure to ionizing radiation. This review will focus on recent and emerging advances of knowledge and technique, with an emphasis on MRI.

Cross-Sectional MRI

Although the essential pulse sequences used to assess MMD remain similar to those traditionally employed (e.g.,

ABBREVIATIONS ASL = arterial spin labeling; BOLD = blood oxygen level-dependent; CBF = cerebral blood flow; CBV = cerebral blood volume; CVR = cerebrovascular reactivity; DKI = diffusion kurtosis imaging; DSC = dynamic susceptibility contrast; DTI = diffusion tensor imaging; DWI = diffusion-weighted imaging; ECA = external carotid artery; fMRI = functional MRI; ICA = internal carotid artery; MCA = middle cerebral artery; MIP = maximum intensity projection; MMD = moyamoya disease; MMS = moyamoya syndrome; MTT = mean transit time; OEF = oxygen extraction fraction; PD = proton density; rsfMRI = resting-state fMRI; STA = superficial temporal artery; SWI = susceptibility-weighted imaging; TTP = time to peak; VWI = vessel wall imaging; 3D-TOF = 3D time-of-flight.

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FIG. 1. A and B: Catheter angiograms demonstrating occlusion of the distal right supraclinoid ICA (arrow) with absent flow in the right M₁ segment with a widely patent left ICA and M₁ segment in a 38-year-old woman diagnosed with unilateral MMD. **C and D:** Axial susceptibility-weighted images demonstrating increased prominence of cortical vessels in the right hemisphere (arrows) compared with the left cerebral hemisphere, mildly increased prominence of medullary vessels within the white matter (bracketed by arrowheads), and hemosiderin within a lacunar infarct in the deep right periventricular white matter (asterisk). **E and F:** In contrast, the cortical vessels are not detected on axial 2D T2 FLAIR; associated areas of white matter T2 hyperintensity as well as the lacunar infarct (asterisk) within the right hemispheric white matter are seen. There is also mild volume loss in the right MCA territory with mildly increased prominence of the sulci.

T1 weighting, T2 weighting), technological advancements have ushered in a variety of techniques that improve tissue characterization, speed, and spatial resolution. Recent research continues to offer insight into the utility of various pulse sequences for the assessment of MMD. Examples emphasizing cross-sectional techniques used for the evaluation of MMD are shown in Figs. 1 and 2. An overview of the utility of key imaging techniques presented in this review is presented in Table 1.

First, high-spatial-resolution 3D techniques for many pulse sequence categories are now employed in many clinical practices, particularly with 3T MRI, which allow multiplanar reformatting in any image plane from a single acquisition. These techniques can facilitate advanced analysis such as structural and lesion characterization with automated segmentation and artificial intelligence computer learning algorithms. Three-dimensional imaging is also beneficial for postprocessing such as 3D surface-rendered images for the assessment of regional cortical thickness analysis in MMD.⁵⁵ It is likely that such analyses will serve a role in research and clinical applications for MMD going forward. Additionally, clinicians and radiologists need to be aware that the precise image contrast and ap-

pearance of normal and pathologically deranged anatomy may differ between 2D and 3D techniques.

The utility of the T2 FLAIR sequence for the assessment of MMD has been extensively investigated.^{21,22,28,43,48,63} The “ivy sign,” an indicator of slow or retrograde flow in cortical vessels, can help characterize the origins of collateral supply, correlates with cerebrovascular reactivity (CVR), and can improve in response to revascularization surgery, or it can temporarily worsen after revascularization in the setting of hyperperfusion.^{21,28,48} In the cerebral white matter, linear T2 hyperintense streaks perpendicular to the lateral ventricle, referred to as “medullary streaks,” have been described.⁶³ The pathophysiology of medullary streaks is incompletely understood, but is thought to be associated with ischemia and these may represent collateral vasculature, increased CSF, and edema.⁶³ Additionally, Komatsu et al. reported that T2 FLAIR can demonstrate areas of parenchymal white matter T2 hyperintensity that variably reverse after revascularization.³⁵

The appearance of T2 FLAIR images depends on the precise technique. For example, the ivy sign was shown to be less well depicted with 3D FLAIR than with 2D FLAIR in MMD in a study by Kakeda et al.²⁶ Further-

FIG. 2. Diffuse hypoperfusion, extensive collateral blood supply with ivy sign, and acute superimposed on chronic parenchymal sequelae in a 14-year-old girl with MMD and no prior surgical intervention. **A:** Three-dimensional TOF MIP MR angiogram demonstrating severe stenosis of the bilateral cavernous ICAs, supraclinoid ICAs, and M₁ segments. The internal maxillary arteries (arrows) are enlarged, providing collateral flow via the ophthalmic arteries, with prominent collaterals within the bilateral cavernous sinus regions but a lack of identifiable ICAs (arrowheads). Prominent thalamoperforator and lenticulostriate collateral vessels are present centrally. The anterior cerebral artery (ACA) and MCA are widely patent beginning at the second-order branches. **B:** Diffusion-weighted image demonstrating a small acute infarct in the left subinsular white matter (arrow). **C:** Axial 2D T2 FLAIR image demonstrating a small chronic infarct in the right lateral frontal lobe (arrow) and additional areas of confluent bilateral white matter with T2 hyperintensity. **D:** Axial 2D T2 FLAIR image further demonstrating the ivy sign, which is most marked in the occipital regions (arrows), greater on the right than the left. **E:** Axial reformatted image from a high-resolution volumetric T1-weighted variable flip angle sequence with gadolinium demonstrating small vessels and small areas of enhancement with greater detail than typically seen with traditional spin echo techniques. **F:** Color CBF image derived from ASL perfusion without intravenous contrast, demonstrating diffuse cortical hypoperfusion (diffuse blue) with mild sparing of the medial left occipital region (arrow) and sparing of the thalami.

more, the signal within the subarachnoid space can be affected by recent gadolinium administration or other leptomeningeal pathology. T2-weighted FLAIR images derived from synthetic imaging, a fast imaging method discussed later, can demonstrate flow and noise artifact.⁶⁵

Susceptibility-weighted imaging (SWI) is a technique that utilizes both the phase and magnitude of signal arising from imaged tissue, whereas most traditional techniques completely discard the phase information. Haacke et al. provided a comprehensive technical review of SWI,¹⁹ but, in brief, it can be useful for the assessment of hemorrhage and blood vessels in MMD. The sequence is exquisitely sensitive to areas of chronic microhemorrhage, which are seen with an increased incidence in MMD and may be associated with increased risk of intracranial hemorrhage.^{29,56,72} The brush sign of prominent deep medullary veins on SWI may be associated with likelihood of

infarct, low cerebral blood flow (CBF), and low CVR.²² Asymmetrically prominent superficial cortical vessels on SWI are associated with elevated deoxyhemoglobin content with increased oxygenation extraction; with revascularization, this finding may reverse and may predict potential to improve CBF.⁷¹

Advanced techniques have been developed to evaluate the microstructure of the brain by measuring the degree and orientation of water diffusion. Methods of assessment include diffusion tensor imaging (DTI) with fractional anisotropy determination, and diffusion kurtosis imaging (DKI), which is a more advanced technique that typically requires a longer scanning time and is less widely available. DKI may provide complementary information to DTI and may be more sensitive to white matter alterations in MMD.³⁰ These techniques have been used to characterize structural white matter change of connectivity and

TABLE 1. Key MRI techniques for evaluation of moyamoya disease

Technique	Utility
Cross-sectional MRI	
Volumetric techniques	Allow high-resolution imaging & multiplanar reformatting. Facilitate creation of 3D images & advanced image processing such as cortical thickness determination.
T2 FLAIR	Demonstrates the leptomeningeal “ivy sign” & medullary streaks. Allows assessment of regions of white matter T2 hyperintensity. Image appearance depends on technique (2D, 3D, recent Gd administration, synthetic MRI).
SWI	High sensitivity for most states of blood product, including chronic microbleeds. Can demonstrate prominent cortical & periventricular vasculature w/ increased deoxy-hemoglobin & oxygen extraction.
Contrast-enhanced T1-weighted MRI	Demonstrates vascular enhancement corresponding to collateral arteries. Can demonstrate enhancing subacute infarcts.
DWI	High sensitivity for acute infarcts.
DTI & DKI	Allow assessment of anatomic connectivity btwn brain regions & can serve as an indicator of white matter integrity.
rsfMRI	Demonstrates the degree of functional connectivity btwn brain regions.
MRA	
3D-TOF	Delineates the lumen of major ICA & ECA branches w/o the need for intravenous contrast.
2D phase contrast	Allows assessment of direction of blood flow & approximation of flow velocity.
Time-resolved contrast enhanced	Can demonstrate arterial stenosis & progressive filling of collateral arteries.
Techniques to assess perfusion & CVR	
DSC	Can assess multiple perfusion parameters using a bolus of intravenous Gd. Interpretation can be quantitative or qualitative.
ASL	Facilitates assessment of CBF w/o the need for intravenous contrast. Interpretation can be quantitative or qualitative.
BOLD	Indirect representation of perfusion parameters w/o need of intravenous contrast. Interpretation is qualitative.
VWI	
A wide variety of techniques w/ high spatial resolution & suppression of signal from flowing blood	Differentiate btwn different causes of arterial stenosis. May serve as an indicator of MMD activity. Adjunct for assessment of the lumen.

microstructure in MMD that cannot be visibly assessed in so-called normal-appearing white matter.^{24,30,31} Such changes have been correlated to clinical status, such as cognitive measures with frontal lobe white matter involvement; there is evidence that these imaging and clinical changes can improve after revascularization.³¹

Functional Connectivity

Resting-state functional MRI (rsfMRI) techniques are being applied to study functional connectivity patterns and alterations in MMD by assessment of low-frequency oscillations of blood oxygen level-dependent (BOLD) activity in a task-negative state. Initial data from rsfMRI suggest that patients with MMD have alterations in functional connectivity, including that of key networks such as the default mode network.⁶⁰ Recent evidence indicates that this reduced functional connectivity is associated with certain clinical features depending on the anatomical area of involvement and can improve after revascularization,

both ipsilateral and contralateral to the bypass.^{31,60} However, rsfMRI in the setting of MMD may lead to inaccurate results without appropriate expertise and corrections for temporal alterations of blood flow when assessing patterns of spontaneous brain activity;²³ rsfMRI requires hardware and software and specialized data processing and interpretation that is not universally available clinically.

Luminal Angiographic Techniques

Catheter angiography remains the gold standard examination for the evaluation of intracranial vasculature and external carotid artery (ECA) branches with high spatial resolution and dynamic information, but it is invasive, requires contrast, results in radiation exposure, and has a small but definite risk of complications. CTA also involves radiation and contrast exposure and lacks the spatial and temporal resolution of catheter angiography. Intracranial MRA can be accomplished with several techniques. Cross-sectional methods of angiography such as CTA or

MRA are typically acquired with a high-spatial-resolution technique, which permits evaluation in multiple imaging planes. Maximum intensity projection (MIP) images are produced, allowing a more global view of a volume of intracranial vasculature when projected onto a 2D image. A common MRA technique that does not require intravenous contrast utilized clinically is 3D time-of-flight (3D-TOF), which demonstrates signal based on “flow-related enhancement.”

Three-dimensional TOF can depict the lumen of the main cerebral arteries as well as the ECA branches, including superficial temporal artery (STA) assessment after ECA–middle cerebral artery (MCA) bypass procedures.⁷⁵ Recent studies have demonstrated that 3D-TOF is highly suitable for application of compressed sensing to reduce acquisition time, including in the setting of MMD.⁷⁴ Current 3D-TOF technique remains susceptible to artifacts in some cases and can falsely indicate complete occlusion in areas of very high-grade stenosis and focal pseudolesions of trepanation segment bypass.⁹

The reported utility of 3D-TOF continues to expand; for example, comparison of the signal intensity of the lumen upstream and downstream of a stenosis may approximate the fractional flow.¹⁸ However, 3D-TOF does not provide quantitative information and does not indicate the precise direction of blood flow. In distinction, 2D phase-contrast MRA can indicate the direction of flow and approximate flow velocities within the major intracranial arteries.

Numerous established fast methods of MRI data acquisition have enabled dynamic MRA with a reasonable temporal resolution. For example, time-resolved contrast-enhanced MRA can demonstrate internal carotid artery (ICA) stenosis and progressive filling of collateral vessels, although it has not been widely applied due to the relatively low spatial and temporal resolution relative to conventional angiography.⁴² Another technique, 4D pseudo-continuous arterial spin labeling (ASL), can demonstrate fill from leptomeningeal collaterals.⁶⁶

Overall, these luminal techniques can demonstrate the areas of stenosis or occlusion of the basal arteries, collateral vasculature, and ECA-MCA bypass graft status, and can identify associated aneurysms which may occur in either the basal arteries or peripheral arteries such as moyamoya vessels.⁵¹ Therefore, the modified Suzuki stage can potentially be established with these MRA luminal techniques without the need for formal catheter angiography. Examples highlighting methods of luminal MRA are shown in Figs. 3 and 4.

Cerebral Perfusion and Cerebrovascular Reactivity

Standard angiographic and cross-sectional imaging techniques may be used to diagnose MMD, but they lack functional information of cerebral hemodynamic status, which may better guide treatment and prognosis. Cerebral hemodynamics may be assessed with a variety of perfusion imaging techniques, including several nuclear medicine methods, contrast-bolus or xenon CT, and several MRI methods that have been extensively reviewed previously.^{2,37,40,44,73} These vary in both qualitative or quantitative

capability and type of information provided, but in general provide measures of CBF, cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP), and/or relative oxygen extraction.^{2,38,40,44,73} An understanding of the underlying pathophysiology is essential for the application and interpretation of imaging examinations that assess cerebral perfusion and CVR.

Specifically, progressive intracranial arterial stenosis of MMD results in reduction in cerebral perfusion pressure. Mechanisms to maintain CBF in the setting of reduced cerebral perfusion pressure include cerebral autoregulation and recruitment of collateral vessels. Cerebral autoregulation acts to maintain CBF by vasodilation of the downstream arterioles; this ability to maintain CBF is termed “cerebrovascular reserve.”¹¹ If CBF is unable to meet needs for oxygen metabolism, the oxygen extraction fraction (OEF) will increase, and the tissue will be at increased risk for ischemia.⁵⁴ Typical findings on perfusion imaging in patients with MMD are decreased CBF, increased CBV and OEF, prolonged MTT, and impaired CVR.^{15,37} While these findings have been found to be reproducible in the pediatric population, findings in adults have been more heterogeneous.

There are several methods to assess such cerebral perfusion with MRI. A common method is dynamic susceptibility contrast (DSC) MR perfusion. DSC perfusion signal is derived from T2* susceptibility signal loss of gadolinium, allowing assessment of relative CBV, relative CBF, and MTT. ASL is a method that can determine CBF without the need for intravenous contrast through labeling of flowing blood with magnetic saturation techniques and imaging after a predefined “postlabel delay.” Technical parameters such as the postlabel delay time need to be defined to perform ASL.² An understanding of these parameters is particularly critical in the evaluation of stenotic-occlusive disease such as MMD.² Both DSC and ASL techniques may render qualitative or quantitative data. Another newer, but less well-established, method to assess cerebral perfusion without intravenous contrast is intravoxel incoherent motion.^{20,34,53} Intravoxel incoherent motion, a modification of diffusion-weighted imaging (DWI), has been applied to MMD, but it still needs further evaluation before widespread adoption. Christen et al. reported that temporal analysis of the rsfMRI BOLD signal can produce perfusion delay maps similar to those acquired with DSC perfusion, but without the need for intravenous contrast.¹⁰ Finally, combined-modality simultaneous PET/MRI has recently facilitated direct comparison between nuclear medicine and MRI perfusion methods.¹⁶

Furthermore, in cerebrovascular diseases such as MMD, the cerebral vasculature may be maximally dilated at baseline, limiting the ability to compensate in the setting of increased demand and placing patients at risk for ischemia. CVR, defined as the ability to increase CBF with increased demand or application of a stimulus, is therefore an important indicator of stroke risk in MMD and can facilitate treatment planning and assessment to treatment response. Specifically, CVR may be used to monitor patients and determine when cerebrovascular reserve is waning and revascularization would be beneficial.⁴¹ It may also be used to follow patients after revascularization.^{38,41,78}

FIG. 3. Comparison of conventional angiography and MRA studies. **A–C:** Digital subtraction conventional (A) and MR (B) angiograms obtained in a young child with unilateral left-sided MMD, demonstrating occlusion of the ICA at the bifurcation distal to the anterior choroidal artery. Reconstitution of the MCA distal to the occlusion (arrows) by the lenticulostriate collaterals (asterisks) is visualized on both conventional angiography (A) and MRA source (C) images. **D–F:** Digital subtraction conventional (D) and MR (E) angiograms obtained in a middle-aged woman, demonstrating robust collateral arteries between splenic branches of the posterior cerebral artery and the ACA territory (asterisks). Robust moyamoya vessels can be seen on the MRA source image (F, arrow). These cases demonstrate that, although the spatial resolution is lower than with conventional angiography, areas of major occlusion, reconstitution, and collateral flow with small vessels can be approximated with MRA.

In particular, patients with an intermediate disease stage (modified Suzuki stage II or III) have been found to have variable hemodynamics, and evaluation of CVR is of particular use to guide therapy.³⁷ Evaluation of CVR before and after surgical revascularization has shown that reversal of a preoperative CVR impairment corresponds with collateral formation on DSA and successful revascularization.⁷⁰ Furthermore, evaluation of both the degree and extent of reduced CVR is important in clinical evaluation.⁴⁷

To evaluate CVR, perfusion imaging techniques may be performed without and with a vasoactive, isometabolic stimulus, which elicits a change in CBV and CBF without a change in metabolic demand. Vasoactive stimuli include exogenous pharmaceutical agents (acetazolamide) and hypercapnia, both of which cause a decrease in the local pH, vascular smooth muscle relaxation, and vasodilation. The various available vasoactive stimuli used for CVR measurements have been detailed in prior reviews.^{17,25,68} In brief, acetazolamide is the most commonly clinically

implemented pharmaceutical stimulus in part due to its ease of administration. Hypercapnia is commonly achieved with a breath-hold technique, although this can also be accomplished with use of a rebreathing face mask, nonrebreathing face mask, or computer-controlled gas delivery system.¹⁷ In addition to the typical perfusion methods, CVR can also be assessed via the BOLD response on fMRI without the need for gadolinium. Findings on MRI perfusion and CVR examinations are illustrated in Figs. 2, 4, and 5.

High-Resolution Vessel Wall Imaging

Intracranial high-resolution vessel wall imaging (VWI) consists of a variety of MRI techniques with high spatial resolution (typically submillimeter resolution both in-plane and slice thickness) and suppression of signal from flowing blood (“black blood”) to facilitate evaluation of the vessel wall and diminish apparent wall enhancement

FIG. 4. Quantitative and direction blood flow assessment. **A–C:** Images obtained in a 40-year-old woman with bilateral MMD after a bilateral STA-MCA bypass. Axial PD VWI study with gadolinium, demonstrating marked stenosis or occlusion of the proximal right MCA (arrow) and marked stenosis of the proximal left MCA, better seen more inferiorly (A). Quantitative 2D phase-contrast image analysis segments (Nova software package) demonstrating antegrade flow within both bypasses (B). A 20-second breath-hold BOLD examination study, demonstrating decreased CVR throughout the anterior circulation bilaterally (blue) with preserved CVR posteriorly (C, red). **D–F:** Images obtained in a 48-year-old woman. Three-dimensional TOF MRA MIP study showing stenosis of the right supraclinoid ICA and proximal ICA stenosis (D, arrows). Quantitative 2D phase-contrast image analysis indicating reversal of flow within the right A₁ segment (yellow arrow), compatible with collateral flow to the right cerebral hemisphere via the circle of Willis (E). CBF image demonstrating normal to minimally diminished flow to the right cerebral hemisphere. CBV and MTT demonstrated similar findings (not shown), compatible with good collateral blood supply (F). BA = basilar artery; L = left; PCA = posterior cerebral artery; R = right; VA = vertebral artery.

from technical factors and slow-moving blood.⁴⁵ The potential utility of VWI in the evaluation of MMD is both as a diagnostic modality^{1,5,8,39,49,77} and as an indicator of disease activity.^{7,50,57,69}

The basic findings of MMD on VWI include luminal stenosis or occlusion reflective of intimal thickening and decreased diameter of the vessel (negative remodeling).^{8,39} Vessel wall enhancement on T1-weighted or proton density (PD)-weighted images seems to be variable, with reports ranging from absent to marked.^{8,39,49,50,57,58,69} Variable wall enhancement can also be seen within a single patient with simultaneous nonenhancing and enhancing segments. Vessel wall findings are typically circumferentially concentric and less commonly eccentric. In distinction, causes of secondary moyamoya syndrome (MMS), which demonstrate

an angiographic pattern resembling MMD but are associated with another identifiable pathology, tend to have other patterns of vessel wall abnormality reflective of the underlying pathology. For example, atherosclerosis is most often associated with eccentric vessel wall involvement and heterogeneous internal T2 signal with a thin T2 hyperintense cap and can demonstrate positive remodeling.⁴⁹ When VWI is strongly supportive of secondary MMS or idiopathic MMD, the findings can have a substantial effect on immediate medical treatment strategy.

Nonetheless, VWI findings of stenosis due to MMD and other etiologies can overlap in some cases (Fig. 6). Additionally, the criteria used to differentiate MMD from MMS with VWI in some studies have included VWI findings themselves as definitive histopathological confirma-

FIG. 5. Images obtained in an adult female with MMD and a history of right STA bypass. **A–D:** DSC perfusion with gadolinium permits evaluation of numerous parameters, including CBF (A), CBV (B), MTT (C), and TTP (D). There is decreased CBF and CBV (arrows) compatible with a large chronic infarct in the right cerebral parietal lobe. Some vascular perfusion persists with an elevated MTT and TTP (C and D, arrows), compatible with slow delayed flow within nonviable tissue. In the bilateral ACA territory, CBF and CBV are without substantial abnormality, compatible with adequate blood supply. DSC perfusion parameters in the left MCA and left posterior cerebral artery territories are also unremarkable. **E:** CVR was assessed with a 20-second breath-hold BOLD response superimposed on an axial 3D T2-weighted FLAIR image, demonstrating reduced CVR in the right ACA territory as a blue overlay (arrow), compatible with vascular steal. **F:** Three-dimensional TOF MIP image demonstrating focal stenosis of the bilateral distal supraclinoid ICAs. The STA bypass is also visualized with mild signal loss and narrowing near the level of the calvaria (arrows) but is otherwise patent.

tion is typically absent.^{1,49} For example, in some instances, circumferential vessel wall enhancement was defined to indicate presumptive vasculitis.¹ Other reports indicate that such enhancement can be seen with MMD,^{49,57,69} demonstrating a challenge with interpreting study results. Although MMD classically involves the distal ICA segments bilaterally, unilateral isolated M_1 disease with vessel wall findings most suggestive of MMD has been reported.¹

Limited evidence indicates that high-grade vessel wall enhancement is associated with an incidence of territorial infarct and progressive stenosis of that segment on follow-up examination.^{50,57,69} Roder et al. found a pattern of increasing and then decreasing vessel wall enhancement roughly 6–8 months before and after clinical and radiographic disease progression.⁵⁷ That study employed an imaging technique with high in-plane spatial resolution but a relatively large slice thickness up to 2 mm; replication with higher-resolution techniques to confirm these findings may be useful. However, the association of vessel wall enhancement to infarcts and progression is not entirely consistent, even within a given patient (Fig. 7). Additionally, there is limited evidence that vessel wall enhancement of

stenotic M_1 segments can decrease after application of steroids with a presumptive diagnosis of vasculitis,⁷ although correlation of the degree of enhancement to medication administration in MMD and other steno-occlusive disease needs more work.

Although VWI is primarily used to assess the vessel wall, recent studies have demonstrated utility for luminal characterization.^{3,32} For example, Kim et al. found that lumen diameter measurements of the major intracranial arteries with or without stenosis using VWI black blood images are similar to those obtained with 3D-TOF.³² Bai et al. demonstrated similar findings in the MCA using inverted black/white MIP images to highlight the vessels.³ VWI may be useful for lumen assessment in areas of artifact on 3D-TOF and segments of very high-grade stenosis.³¹

In many cases, these VWI studies need confirmation with additional work to show reproducibility and validity in various patient populations if these findings are to be used to heavily influence clinical care. Readers should take into account spatial resolution and type of flow-suppression technique, as these technical factors can impact the appearance of vessel wall¹² and vessel wall enhance-

FIG. 6. VWI appearance of alternative causes of stenosis of the basal arteries with axial PD images demonstrating multiple distinct vessel wall features, although these vessel wall features can overlap in some cases. **A:** Eccentric plaques along the walls of the left M₁ segment (arrows) without negative remodeling are most consistent with atherosclerosis. **B:** In another case with focal short-segment stenosis, moderate associated vessel wall enhancement (arrow), and negative remodeling, the VWI findings are less specific; the favored diagnosis was atherosclerosis given the short segment involvement as seen on conventional angiography (not shown) and clinical presentation. Although atherosclerosis typically demonstrates normal vessel diameter or positive remodeling, it can occasionally demonstrate negative remodeling. **C:** Marked circumferential enhancement of the luminal surface of the right cavernous ICA wall (arrow) in a 75-year-old man with giant cell arteritis. **D:** Image obtained in a 66-year-old woman with primary angiitis of the CNS, demonstrating marked enhancement of the luminal border of the walls of both cavernous (arrows) and supraclinoid (not shown) ICAs with normal vessel diameter. **E:** Image obtained in a 46-year-old woman with a diagnosis of unilateral MMD, demonstrating marked circumferential vessel wall enhancement with negative remodeling (arrow). **F:** Dissection of the right M₁ segment demonstrating a thin linear flap (arrow) along the length of the vessel segment, separating the true lumen anteriorly from the dissected lumen posteriorly.

ment. Additionally, the methods of image interpretation and criteria used to establish the final diagnosis need careful consideration. Histopathological correlation of vessel walls that enhance is lacking. Although some recent evidence has challenged the prevailing notion that MMD is a noninflammatory condition, it remains unclear if vessel wall enhancement represents inflammation, angiogenesis, cell proliferation, or another factor.^{46,76} Finally, VWI sequences are time consuming. While compressed sensing can be applied to decrease scan time, published reports of effect on image quality and diagnostic accuracy are currently lacking.

High-Field MRI

High-field MRI such as 7T has now moved into both the research and clinical practice realms at some institutions. This may have several advantages for the assessment of MMD, including gains in signal-to-noise ratio and contrast-to-noise ratio that facilitate improved visualization of the basal arteries and moyamoya vessels with VWI, 3D-TOF MRA, T1 MPRAGE (magnetization-prepared ra-

diofrequency pulses and rapid gradient echo) MRA,^{13,14,52} improved assessment of BOLD response, and increased sensitivity for areas of microbleed with SWI. There are also limitations, including limited availability of certain pulse sequences, increased incidence of susceptibility artifact near the skull base (and thus cavernous ICA levels), the need to account for differing contrast properties (e.g., the T1 and T2 relaxation times/appearance and BOLD response are field strength dependent), and more stringent patient exclusion criteria. Limited evidence indicates that, compared with 3T, 7T examinations better depict moyamoya vessels within the basal ganglia, but may not be advantageous for determination of the Suzuki stage, ivy sign depiction, or measurement of the intracranial ICA diameter.^{13,14,52} However, true assessment of impact on imaging assessment and patient management needs further investigation.

Emerging Advanced Methods to Decrease MRI Acquisition Time

As briefly introduced in the preceding sections, a num-

FIG. 7. **A:** A 31-year-old woman presented with bilateral border zone infarcts on DWI. **B:** Three-dimensional TOF MR angiogram obtained at presentation, demonstrating moderate stenosis of the bilateral distal supraclinoid ICAs and proximal M₁ segments (arrows). **C:** Axial PD VWI study with gadolinium, demonstrating mild to moderate circumferential vessel wall enhancement of the left supraclinoid segment (arrow) and no appreciable enhancement of the right ICA vessel wall. **D:** Axial PD VWI study with gadolinium obtained at the 8-month follow-up, demonstrating increased enhancement of the stenotic left segment (arrow). **E:** Axial 3D-TOF MR angiogram demonstrating progressive stenosis of both the nonenhancing right and enhancing left stenotic segments (arrows). This case demonstrates that infarcts and progressive stenosis can be associated with either enhancing or nonenhancing segments and that vessel wall enhancement can evolve over time.

ber of emerging techniques show potential to substantially reduce scanning time and facilitate a comprehensive multimodal MRI assessment within a reasonable appointment time. Such methods may be applied to each of the main areas of MRI assessment of MMD, including standard cross-sectional MRI, MRA, MR perfusion, and VWI.

For example, reduced acquisition of redundant imaging data can be accomplished with the compressed sensing technique.⁷⁴ Synthetic MRI can produce multiple sequences from a single acquisition.⁵⁹ MR fingerprinting applies a novel method of image reconstruction of multiple sequences from raw data based on computer pattern matching to an index library of signal patterns from different tissues. Unlike other common MRI techniques, MR fingerprinting also allows for quantitative assessment of tissue signal intensity.^{6,62} Another approach to decrease scan time is the concurrent acquisition of data from multiple slices using simultaneous multislice imaging techniques. While the premise of simultaneous multislice is not new, recent technological advancements have enhanced the capabilities of these techniques and facilitated increasing clinical implementation.

All of these have been most extensively evaluated in

the technical literature, although reports of clinical evaluation in MMD and other conditions are emerging.^{59,62,74} The availability of these techniques currently varies by vendor and software package, and not all techniques are approved by the Food and Drug Administration within the United States. Further evaluation of effect on image quality and diagnostic utility, technique optimization, and practical practice implementation is also needed.

Artificial Intelligence

Artificial intelligence techniques have numerous potential applications to evaluate MMD, including automated image segmentation, image grading, clinical/imaging prediction scoring, and use to improve image quality of advanced fast scanning techniques. For example, one group has described the technical feasibility of an automated method of intracranial VWI segmentation.⁶¹ Machine learning has been utilized for recognition of MMD on the basis of skull plain radiographs.³³ Although to date there are few reports on the application of artificial intelligence algorithms specifically for the evaluation of cross-sectional imaging examinations in MMD, such methods will like-

ly impact evaluation in the future, given the multimodal imaging evaluation required.

Application of Multimodal MRI Findings to Clinical Practice

The multimodal MRI techniques discussed can help determine patient prognosis, direct medical or surgical treatment, and assess treatment response. As the prior sections have demonstrated, there is a wide variety of techniques available, and those used will depend on local resources and expertise. There is no universally standardized imaging protocol for moyamoya patients, standardized methods of imaging assessment are generally lacking, and there is much more to learn. However, some studies have proposed various approaches to help guide clinical management.

Most patients with a diagnosis of MMD undergo regular clinical and imaging surveillance (approximately every 6 months) to monitor disease progression and guide management. Imaging may include DSA and/or MR, including MRA, structural imaging, and perfusion or CVR measurements as discussed above. As these patients are generally young, it is useful to utilize MRI since it lacks radiation and provides multiple facets of information. Some of the proposed methods to evaluate the MR techniques for clinical decision-making are outlined below.

Perfusion and CVR may be used to assess clinical status and timing of revascularization, guide perioperative management, and assess success of revascularization. In general, a decrease in CBF, increase in MTT, and decrease in CVR indicate increased risk of ischemia and may be used as an indicator for revascularization. In perioperative patient management, there is evidence that increased CBV or reduced OEF is associated with an increased risk of perioperative cerebral hyperperfusion.^{27,67} Assessment of these findings could be useful to prompt heightened vigilance and monitoring. Finally, perfusion and CVR have been applied to monitor success of revascularization.⁷⁰

Methods of systematic analysis of perfusion parameters have been proposed by Lin et al. and Yun et al.^{41,78} While such assessment is not standardized, these authors normalized perfusion to the cerebellum and defined vascular territories for assessment. Using a simple qualitative visual analysis, Lin et al. divided each cerebral hemisphere into 14 segments, normalized perfusion to the cerebellum, and assessed the TTP on each segment over time.⁴¹ The TTP delay improved on serial examinations over a 6-month time period, and the improvement correlated with the Matsushima grade.⁴¹ This or similar modifications can be applied to clinical practice. Although such an approach is straightforward, consideration of multiple perfusion parameters likely provides a more complete, albeit descriptive, picture of clinical status.

Others have incorporated perfusion/CVR with additional MR metrics. Ladner et al. proposed the PIRAMD (Prior Infarcts, Reactivity, and Angiography in Moyamoya Disease) scoring system, which incorporates assessment of infarcts, CVR, and angiographic findings on MRI into a scoring system of grades 1–3 for each hemisphere.³⁶ Higher grade correlated with symptoms, but this study is retrospective and further assessment is needed.

In the absence of recurrent ischemic or hemorrhagic symptoms or sequelae, clinical assessment of response to revascularization can be challenging. In addition to perfusion/CVR metrics, many of the cross-sectional imaging findings (ivy sign, brush sign, medullary streaks, parenchymal T2 FLAIR signal, DTI findings, and even cortical volume loss) may improve after revascularization. These imaging findings can help the clinician determine if there has been a positive treatment response and provide concrete findings to convey to the patient.

Until widely accepted standardized imaging protocols and methods of interpretation are established, application of a consistent imaging protocol that includes components from the key categories discussed herein is a reasonable approach. Consistent application of one of the few available scoring systems discussed or an adaptation of the scoring system to another related imaging technique seems reasonable. Ultimately, use of imaging findings to facilitate patient counseling and care will require some subjectivity, clinical judgement, and consideration of other patient factors.

Conclusions

Numerous recent technological advances offer potential to substantially enhance the multidimensional MRI evaluation of MMD. These include high-resolution volumetric imaging, high-resolution vessel wall characterization with suppression of signal from flowing blood, improved angiographic and perfusion techniques, high-field imaging, fast scanning methods, and potential applications of artificial intelligence. These imaging methods can aid clinical characterization, help direct treatment, assist in the evaluation of treatment response, and elucidate the pathophysiology of MMD.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Lehman, Cogswell, Rinaldo, Huston, Lanzino. Acquisition of data: Cogswell. Drafting the article: Lehman. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lehman.

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