

# Cerebral Hyperperfusion and Concomitant Reversible Lesion at the Splenium after Direct Revascularization Surgery for Adult Moyamoya Disease: Possible Involvement of MERS and Watershed Shift Phenomenon

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## Abstract

Superficial temporal artery (STA)–middle cerebral artery (MCA) bypass is the standard surgical treatment for moyamoya disease (MMD). Local cerebral hyperperfusion (CHP) is one of the potential complications, which could enhance intrinsic inflammation and oxidative stress in MMD patients and accompany concomitant watershed shift (WS) phenomenon, defined as the paradoxical decrease in the cerebral blood flow (CBF) near the site of CHP. However, CHP and simultaneous remote reversible lesion at the splenium have never been reported. A 22-year-old man with ischemic-onset MMD underwent left STA–MCA bypass. Although asymptomatic, local CHP and a paradoxical CBF decrease at the splenium were evident on N-isopropyl-p-[<sup>123</sup>I] iodoamphetamine single-photon emission computed tomography 1 day after surgery. The patient was maintained under strict blood pressure control, but he subsequently developed transient delirium 4 days after surgery. MRI revealed a high-signal-intensity lesion with a low apparent diffusion coefficient at the splenium. After continued intensive management, the splenial lesion disappeared 14 days after surgery. The patient was discharged without neurological deficits. Catheter angiography 2 months later confirmed marked regression of posterior-to-anterior collaterals via the posterior pericallosal artery, suggesting dynamic watershed shift between blood flow supplies from the posterior and anterior circulation. Mild encephalitis/encephalopathy with a reversible splenial lesion could explain the pathophysiology of the postoperative splenial lesion in this case, which is associated with generation of oxidative stress, enhanced inflammation, and metabolic abnormalities. Rapid postoperative hemodynamic changes, including local CHP and concomitant WS phenomenon, might participate in the formation of the splenial lesion.

Keywords: moyamoya disease, direct revascularization surgery, cerebral hyperperfusion, MERS, watershed shift

## Introduction

Superficial temporal artery (STA)–middle cerebral artery (MCA) bypass is a standard surgical procedure

for patients with moyamoya disease (MMD).<sup>1,2)</sup> However, intensive perioperative management is required to avoid perioperative complications,<sup>3–15)</sup> such as cerebral hyperperfusion (CHP)<sup>3–9)</sup> and hemodynamic ischemia due to the “watershed shift (WS) phenomenon,”<sup>10–15)</sup> defined as the paradoxical decrease in the cerebral blood flow (CBF) value near the site of CHP, as reported previously. Previous reports showed that the WS phenomenon was evident in 10.9% of adult MMD patients after STA–MCA

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anastomosis.<sup>13)</sup> Although the outcome of the WS phenomenon is favorable,<sup>13)</sup> the WS phenomenon could result in cerebral infarction and permanent neurological deficits.<sup>13–15)</sup> In addition, STA–MCA bypass could enhance intrinsic inflammatory response and oxidative stress response in patients with MMD,<sup>16–20)</sup> which can contribute to the formation of vasogenic edema and intracerebral hemorrhage. Then, the detection of heterogeneous hemodynamic and inflammatory changes and intensive postoperative management is critical after STA–MCA anastomosis for MMD.<sup>10,13–15)</sup> To detect heterogeneous and dynamic hemodynamic changes and perform intensive management, such as prophylactic blood pressure lowering<sup>21)</sup> and administration of minocycline hydrochloride,<sup>22)</sup> we have introduced serial [<sup>123</sup>I] iodoamphetamine single-photon emission computed tomography (<sup>123</sup>I-IMP-SPECT)<sup>23,24)</sup> and MRI<sup>25)</sup> studies in the acute phase of revascularization surgery for MMD. Among 525 consecutive revascularization surgeries for MMD patients, we report a rare patient who developed local CHP and concomitant remote reversible lesion at the splenium after STA–MCA bypass, with marked regression of pericallosal artery.

### Case Report

A 22-year-old man with ischemic-onset MMD underwent left STA–MCA bypass. Intraoperatively, the stump of the left STA was anastomosed to the M4 segment of the left MCA (Fig. 1A and 1B). Postoperative magnetic resonance (MR) angiography confirmed patent STA–MCA bypass (Fig. 1C). Although asymptomatic, local CBF increased by over 150% from the preoperative CBF value, and a paradoxical decrease in the CBF value at the splenium was evident on N-isopropyl-p-<sup>123</sup>I-IMP-SPECT (Fig. 1D) on postoperative day (POD) 1, while no parenchymal lesions were found on MR imaging (Fig. 1E). Then we performed intensive management, such as strict blood pressure control (systolic blood pressure: 110–130 mmHg) and administration of minocycline hydrochloride, to avoid deleterious events due to CHP,<sup>1,24,25)</sup> but the patient developed delirium on POD 4. Diffusion-weighted MR imaging revealed a high-signal-intensity lesion with a low apparent diffusion coefficient at the splenium (Fig. 1F and 1G). Due to continued intensive management, he did not develop other symptoms later. We confirmed the amelioration of local CHP and the paradoxical decrease in the CBF at the splenium by <sup>123</sup>I-IMP-SPECT on POD 7 (Fig. 1D), and of the splenium lesion on POD 14 on MR imaging (Fig. 1H). Based

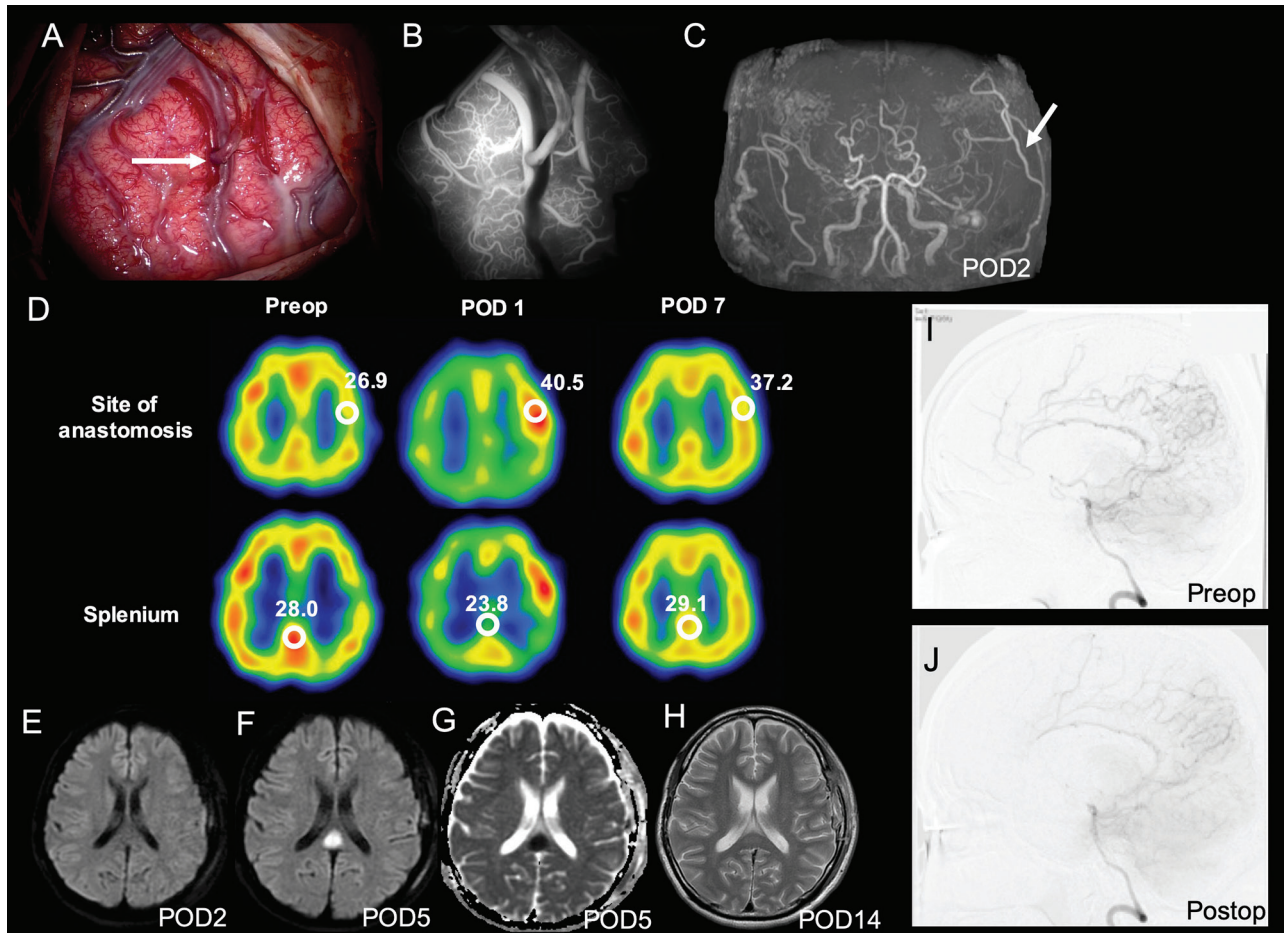
on the temporal profile of MR imaging, we diagnosed the splenium lesion as a reversible ischemic lesion. The patient was discharged without neurological deficits 18 days after surgery. Catheter angiography 2 months after revascularization surgery confirmed the marked regression of posterior-to-anterior collaterals via the posterior pericallosal artery, suggesting the dynamic watershed shift between blood flow supplies from the posterior and anterior circulation (Fig. 1I and 1J).

### Discussion

In this study, we report the extremely rare case of adult MMD patients who manifested local CHP and concomitant reversible lesions at the splenium after STA–MCA anastomosis. Although the etiology of remote reversible lesion at splenium remains uncertain, postoperative various factors, including generation of oxidative stress and inflammation, and hemodynamic changes could explain this extremely rare manifestation of this splenial lesion.

Postoperative generation of oxidative stress and enhanced intrinsic inflammation after STA–MCA anastomosis might participate in the formation of splenial reversible lesion in the present case. Splenial lesion in this case was limited in corpus callosum and showed high-intensity signal on diffusion-weighted imaging and decreased apparent diffusion coefficient (ADC) values (Fig. 1F and 1G). Similar findings are observed in patients with mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), which develop transient consciousness disturbance and seizure.<sup>26,27)</sup> However, the manifestation of MERS after bypass surgery has never been reported. Although major etiology of MERS is viral infection, previous study demonstrated increased interleukin-6, tau proteins, and 8-hydroxy-2'-deoxyguanosine in patients with MERS, suggesting the involvement of inflammation, axonal damage, and oxidative stress in the pathophysiology of MERS.<sup>28)</sup> After STA–MCA anastomosis for MMD, rapid hemodynamic changes can cause oxidative stress and enhance intrinsic inflammation in MMD, as increased production of matrix metalloproteinase-9, CD163, and CXCL5<sup>16–18)</sup> and the association between MMD and *human leukocyte antigen* allele<sup>19,20)</sup> have been reported. Then, we speculated that postoperative generation of oxidative stress and enhanced intrinsic inflammation, as well as hemodynamic changes could account for the reversible lesion at splenium in the present case.

Postoperative rapid hemodynamic changes could also participate in the formation of splenial lesion



**Fig. 1** Intraoperative view of left superficial temporal artery (STA)–middle cerebral artery (MCA) bypass (A). The frontal branch of the STA was anastomosed to the M4 segment of the left MCA. The arrow indicates the site of anastomosis. Indocyanine green video-angiography confirmed the patency of the bypass (B). Magnetic resonance (MR) angiography 1 day after the surgery, indicating left STA–MCA bypass as high-signal intensity (arrow) (C). [<sup>123</sup>I] iodoamphetamine single-photon emission computed tomography (<sup>123</sup>I-IMP-SPECT) before and 1 and 7 days after surgery, showing local cerebral hyperperfusion and concomitant decrease in the cerebral blood flow (CBF) at the splenium (D). The numbers represent the quantitative CBF values (ml/100 g/min) by the auto-radiographic method. Values in the parenthesis indicate the relative CBF ratio compared with the preoperative value. Temporal profile of MR images. Diffusion-weighted image (DWI) at 2 days after the surgery (E), DWI (F) and apparent diffusion coefficient (G) at 5 days after the surgery, and T2-weighted image (H) at 14 days after the surgery, together indicating the reversible ischemic lesion at the splenium. Catheter angiography before (I) and after (J) the surgery, showing regression of the posterior pericallosal artery after the surgery.

in the current case. Dynamic and heterogeneous hemodynamic changes are evident after STA–MCA anastomosis for MMD.<sup>3–15,29,30</sup> In the previous reports, the WS phenomenon was defined as paradoxical decrease of CBF adjacent to the site of local CHP.<sup>10–15</sup> On the contrary, the current case demonstrated CHP and concomitant reversible lesion at corpus callosum, which is atypical to WS phenomenon. Vascular supply to the splenium is provided by the anterior pericallosal artery, posterior pericallosal artery, and posterior accessory pericallosal artery.<sup>31,32</sup> Although prominent regression of posterior

pericallosal artery after STA–MCA anastomosis does not necessarily reflect the hemodynamic changes in the acute phase of STA–MCA anastomosis, this rapid and significant shift of watershed could partly participate in the formation of ischemia at corpus callosum. This kind of watershed shift is atypical to WS phenomenon, which is originally defined as paradoxical decrease of CBF adjacent to the site of local CHP.<sup>12–14</sup> Then, the precise understanding of perioperative hemodynamic changes in individual cases is extremely important in the perioperative management of revascularization surgery for MMD,

and serial quantitative evaluation of hemodynamic changes by  $^{123}\text{I}$ -IMP-SPECT is extremely useful.<sup>1,3,13,23,24)</sup> In addition, recent report demonstrated preoperative MR angiography has also diagnostic value of CHP by assessment of signal intensity of intracranial major arteries.<sup>25)</sup> Therefore, serial quantitative  $^{123}\text{I}$ -IMP-SPECT and MR imaging studies are useful to detect dynamic and heterogenous postoperative hemodynamic changes.

MR imaging, including ADC values, may be useful to predict whether splenic lesion is reversible or not. The ADC values significantly decrease spontaneously after the onset of focal brain ischemia. Complete or partial recovery of ADC reductions after blood flow restoration occurs in temporary focal ischemia, suggesting that early ADC reductions after focal ischemia can represent reversible ischemic brain injury. Some previous literatures suggested that ADC reductions do not accurately predict cerebral ischemia.<sup>33,34)</sup> Even significant reductions of ADC values can normalize in ischemic stroke, and ADC normalization depends on the duration and severity of ischemia rather than the absolute ADC values.<sup>35,36)</sup> In addition, splenic lesion in the present case may reflect generation of oxidative stress, inflammation, and intramyelin edema, as discussed previously.<sup>25,26)</sup> Then, ADC values could be useful to detect reversible ischemia, although not only oxidative stress and inflammatory changes but also postoperative hemodynamic changes could participate in the formation of the splenic lesion in the current case.<sup>26–28)</sup> Therefore, we strongly recommend serial quantitative  $^{123}\text{I}$ -IMP-SPECT and MR imaging studies to detect dynamic and heterogenous postoperative changes in patients with MMD after STA–MCA anastomosis.

## Conclusions

We report a markedly rare MMD case, manifesting as transient splenic lesion with postoperative marked remission of posterior-to-anterior collaterals. Although the etiology of reversible lesion at splenium remains unknown, generation of oxidative stress and inflammation, metabolic abnormalities, and postoperative hemodynamic changes, such as local CHP and concomitant WS phenomenon, might explain the transient ischemia at splenium. Then, serial and quantitative assessment of CBF using  $^{123}\text{I}$ -IMP-SPECT and MR imaging studies are useful to detect dynamic and heterogeneous postoperative changes.

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## Conflicts of Interest Disclosure

The authors have nothing to declare. The authors have registered online Self-Reported COI Disclosure Statement Forms through the website for Japan Neurosurgical Society (JNS) members.

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