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Impact of intraoperative cortical indocyanine green extravasation on local vasogenic edema immediately after direct revascularization in an adult with moyamoya disease: illustrative case

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BACKGROUND Local vasogenic edema induced after direct revascularization in moyamoya disease (MMD) is associated with blood–brain barrier dysfunction, potentially leading to postoperative cerebral hyperperfusion (CHP) or delayed intracerebral hemorrhage. This phenomenon allows the leakage of fluids, proteins, and other substances from the blood vessels into the extracellular compartment. Typically, such edema is observed postoperatively rather than intraoperatively.

OBSERVATIONS A 48-year-old female with ischemic-onset MMD underwent revascularization on her left hemisphere with Suzuki's angiographic stage III. Direct bypass was successfully performed, as confirmed by intravenous indocyanine green (ICG) video angiography. Subsequently, ICG extravasation was observed near the anastomosis site, despite the absence of cortical injury or bleeding under white light microscopy. Postoperative radiological imaging showed reversible pure vasogenic edema in the corresponding area, with no evidence of CHP. The patient did not exhibit neurological deterioration and was discharged home on postoperative day 16.

LESSONS ICG, characterized by low molecular weight, water solubility, and high affinity with plasma proteins, can extravasate, serving as a direct indication of local vasogenic edema induced by direct revascularization in MMD. To enhance comprehension of the vulnerability of the blood–brain barrier in MMD, it is advisable to gather cases with prolonged observations of ICG video angiography after direct revascularization.

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KEYWORDS blood-brain barrier; case report; indocyanine green video angiography; moyamoya disease; vasogenic edema; vascular disorder

Moyamoya disease (MMD) is an idiopathic cerebrovascular disorder characterized by steno-occlusive lesions at the arteries centered on the terminal portion of the intracranial internal carotid artery and abnormal vascular networks, known as "moyamoya vessels," in the vicinity of the steno-occlusive vascular lesions.[1,2] Extracranial-intracranial bypass procedures, such as superficial temporal artery (STA) to middle cerebral artery (MCA) anastomosis, represent the standard surgical procedures aimed at improving compromised cerebral hemodynamics.[3–5] These procedures play a crucial role in preventing future cerebral ischemic attacks and reducing the risk of rebleeding. The long-term outcome of STA-MCA anastomosis is generally favorable, contingent on successful complication avoidance in the early postoperative period.[3,5]

Local vasogenic edema, induced after direct STA-MCA anastomosis, serves as one of the postoperative indicators of underlying conditions, including focal cerebral hyperperfusion (CHP), ischemia, and epilepsy.[6–8] This vasogenic edema is closely associated with blood–brain barrier dysfunction, allowing the leakage of fluid, proteins, and other substances from the blood vessels into the extracellular compartment.[9] When vasogenic edema occurs in conjunction with CHP, it can lead to transient neurological deficits and, more critically, delayed intracerebral hemorrhage.[6–8] Therefore, routine postoperative radiological assessments, including cerebral blood flow measurements, are recommended.[8] It is worth noting that in the existing context, the observation of local vasogenic edema is typically postoperative and not intraoperative. In this report, we present an exceptionally rare and

ABBREVIATIONS CHP = cerebral hyperperfusion; ICG = indocyanine green; ^{123}I-IMP SPECT = *N*-isopropyl(^{123}I)-p-iodoamphetamine; MCA = middle cerebral artery; MMD = moyamoya disease; MMP-9 = matrix metalloproteinase 9; MR = magnetic resonance; MRI = magnetic resonance imaging; NaFL = sodium fluorescein; POD = postoperative day; STA = superficial temporal artery; VAG = video angiography.

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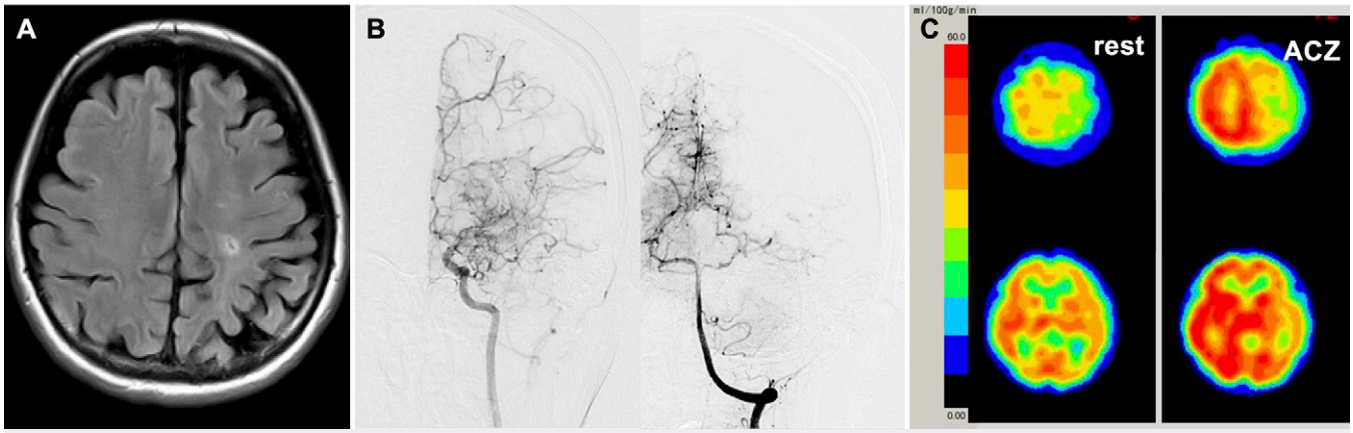

FIG. 1. A: Preoperative fluid-attenuated inversion recovery imaging depicted a subcortical infarct in the left frontal lobe. **B:** Cerebral angiography showed severe stenosis in the terminal portion of the left internal carotid artery, MCA (*left*), and posterior cerebral artery (PCA; *right*) accompanied by abnormal vascular networks in the vicinity of stenotic lesions in the arterial phase, suggesting Suzuki angiographic stage III with PCA involvement. **C:** ^{123}I-IMP SPECT without (*left*) and with acetazolamide (ACZ) challenge (*right*) revealed decreased cerebral blood flow and cerebrovascular reserve in the left frontal lobe.

illustrative case involving intraoperative indocyanine green (ICG) extravasation after direct revascularization for ischemic-onset MMD in an adult. This unique observation provides direct visualization of local vasogenic edema during the surgical procedure, offering valuable insights into the dynamics of blood–brain barrier dysfunction in MMD.

Illustrative Case

A 48-year-old female presented with dysarthria–clumsy hand syndrome in her right hand due to a left frontal subcortical infarct (Fig. 1A). Cerebral angiography revealed severe stenosis at the terminal portion of the left internal carotid artery and the proximal portion of the MCA with an abnormal vascular network in the vicinity of these stenotic lesions (Fig. 1B), leading to a diagnosis of MMD. Single-photon emission computed tomography with *N*-isopropyl (^{123}I)-p-iodoamphetamine (^{123}I-IMP SPECT) revealed decreased cerebral blood flow and impaired cerebrovascular reactivity to acetazolamide in the left hemisphere (Fig. 1C). Therefore, we performed a direct STA-MCA anastomosis combined with encephaloduromyosynangiosis on her left symptomatic hemisphere with Suzuki angiographic

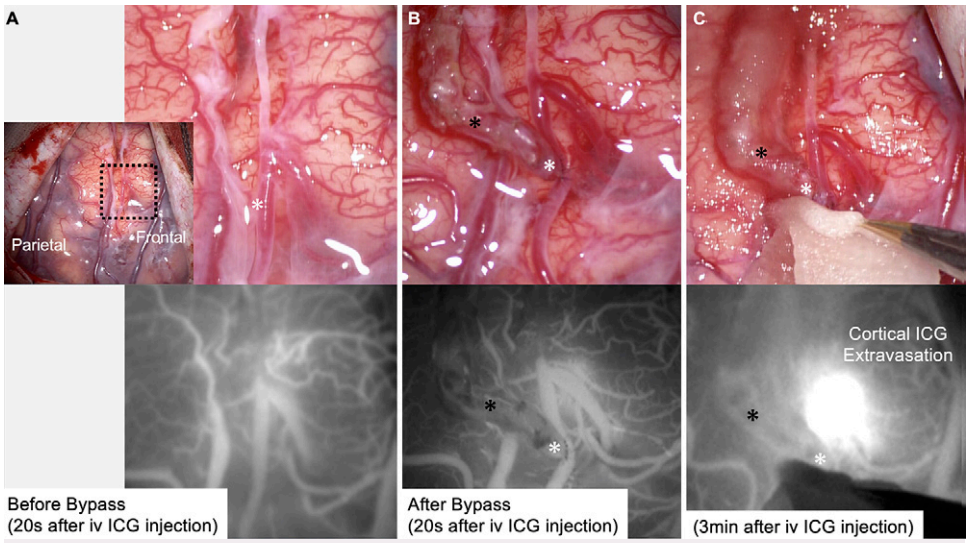

FIG. 2. A: Intraoperative photograph and ICG fluorescence VAG before the STA-MCA anastomosis showing a nonaberrant cortical surface under the white light microscope (*upper*) and no extravasation of ICG dye under the fluorescence microscope (*lower*). The *dotted rectangle* denotes the field of view for these intraoperative and ICG-VAG images. **B:** After completion of the STA-MCA anastomosis, there was no bleeding or extravasation of the ICG dye at the site of anastomosis observed 20 seconds after a single intravenous (IV) ICG injection (*lower*). Notably, after revascularization, suboptimal hemodynamic distribution was observed. *Black asterisks* indicate the STA (donor artery), and *white asterisks* indicate the anastomosis site. **C:** Subsequently (approximately 3 minutes after IV ICG injection), extravasation of the ICG dye was observed along with the cortical MCA branch near the anastomosis site (*lower*), although no cortical surface bleeding or injury was evident (*upper*).

stage III (Fig. 2A). The STA stump was successfully anastomosed to the cortical branch of the MCA in 20 minutes (Fig. 2B), confirmed by intravenous ICG video angiography (VAG). Significantly, after revascularization, suboptimal hemodynamic distribution was observed, likely attributable to inadequate network formation among the pial arteries. Thereafter (approximately 3 minutes after the intravenous ICG injection), extravasation of the ICG dye was observed along with the recipient MCA branch near the anastomosis site, although no cortical surface bleeding or surgical injury was evident under white light microscopy (Fig. 2C).

The patient recovered from general anesthesia immediately after surgery without neurological deterioration. On postoperative day (POD) 1, a non–contrast-enhanced computed tomography scan revealed a low-density parenchymal change in the frontal subcortical white matter at the site of the STA-MCA anastomosis, and ^{123}I-IMP SPECT showed relatively decreased cerebral blood flow in the area corresponding to the low-density lesion (Fig. 3A). Postoperative brain magnetic resonance imaging (MRI) performed on POD 2 showed increased intensity on apparent diffusion coefficient, T2-weighted, fluid-attenuated inversion recovery, and T2*-weighted images at the site of the STA-MCA anastomosis, although no apparent signal intensity changes were observed on diffusion-weighted and time-of-flight magnetic resonance (MR) angiography source image (Fig. 3B). These postoperative radiological changes where intraoperative ICG extravasation had been observed indicated pure vasogenic edema without cerebral hyperperfusion after STA-MCA anastomosis. On the basis of these observations, including a patent STA-MCA anastomosis, intraoperative ICG extravasation, and the above-mentioned postoperative radiological findings, we applied meticulous postoperative management of the patient, such as intensive blood pressure control with the use of a neuroprotective antibiotic agent (i.e., minocycline), blocking matrix metalloproteinase 9 (MMP-9),[10] and a free radical scavenger (i.e., edaravone). Although the patient did not show any postoperative neurological deterioration (i.e., postoperative seizure, stroke, or CHP syndrome) or nonneurological complication, including wound trouble, we recommended that she stay in the hospital for about 2 weeks after the surgery. Subsequently, she was discharged home on POD 16. Postoperative MRI and MR angiography were repeated until 4 months after surgery, showing the local vasogenic edema had resolved on PODs 48 and 126 (Fig. 4). She has not had a repeat cerebral stroke for more than 1 year after surgery.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

The main observation of our illustrative case is the intraoperative cortical ICG extravasation, providing in vivo direct visualization of

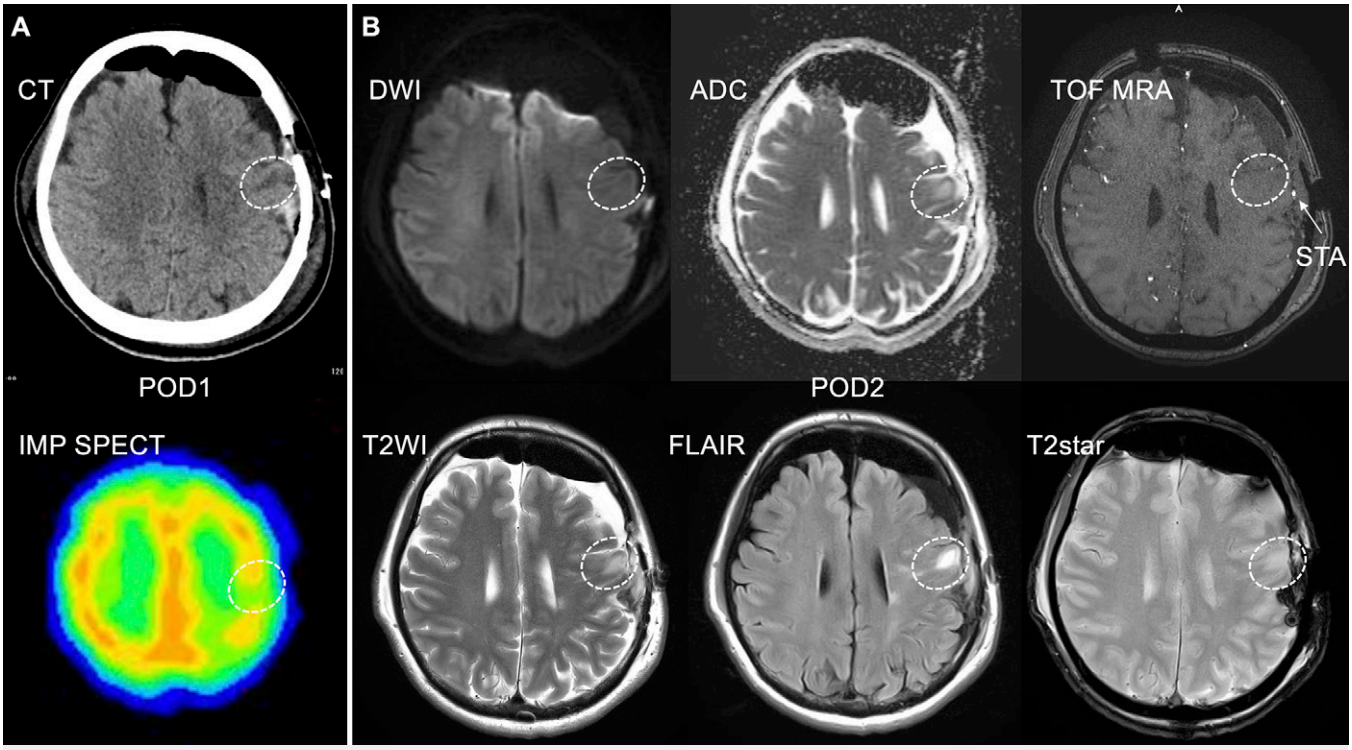

FIG. 3. A: Non–contrast-enhanced computed tomography (CT) (*upper*) obtained on POD 1, showing a low-density parenchymal change in the frontal subcortical white matter at the site of the STA-MCA anastomosis. ^{123}I-IMP SPECT (*lower*) showed relatively decreased cerebral blood flow at the site of the low-density lesion (*dashed circle*). **B:** POD 2 MR images of the corresponding slice of the CT and ^{123}I-IMP SPECT revealed increased intensity on apparent diffusion coefficient (ADC), T2-weighted (T2WI), fluid-attenuated inversion recovery (FLAIR), and T2*-weighted (T2star) images at the site of the STA-MCA anastomosis, although no apparent changes were observed on the diffusion-weighted image (DWI) or time-of-flight MR angiography source image (TOF MRA). These postoperative radiological findings where intraoperative extravasation of the ICG dye had been observed suggested local vasogenic edema without cerebral hyperperfusion after STA-MCA anastomosis.

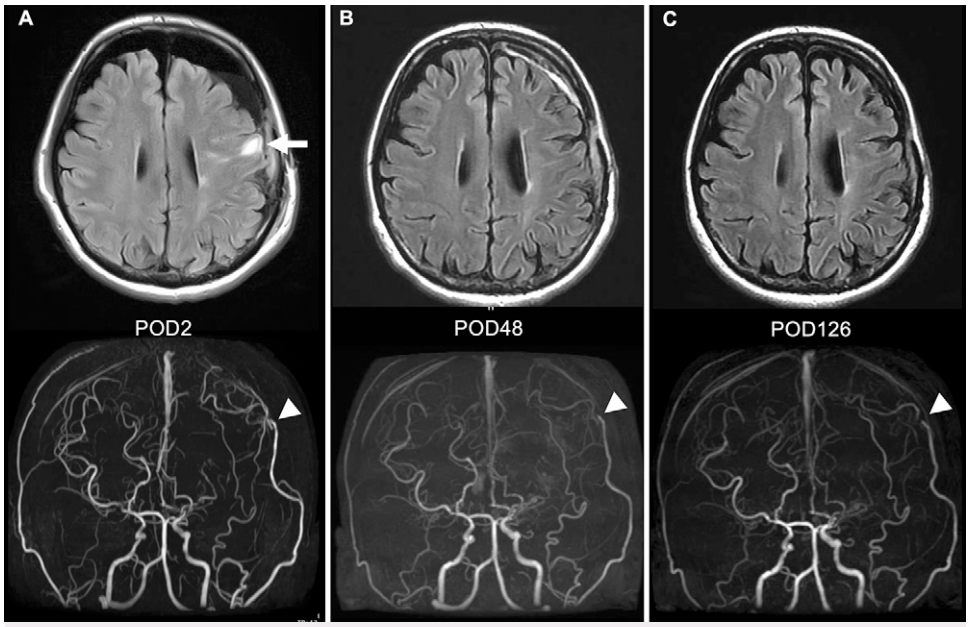

FIG. 4. Chronological changes of local vasogenic edema after STA-MCA anastomosis. Temporal profile of fluid-attenuated inversion recovery images (*upper*) showing a high-signal-intensity lesion in the left frontal subcortical white matter (*white arrow*) at the site of the successful STA-MCA anastomosis (*arrowheads*), visible on MR angiography (*lower*), 2 days after surgery (**A**). The lesion was resolved 48 days (**B**) and 126 days (**C**) after surgery.

local vasogenic edema after direct revascularization in MMD. Following intravenous ICG video angiography to confirm the patency of STA-MCA anastomosis, ICG extravasation was noted near the anastomosis site, devoid of cortical surface bleeding or surgical injury. Subsequent postoperative radiological examinations revealed local vasogenic edema at the corresponding site in this adult MMD case. Remarkably, there were no neurological deterioration and postoperative seizures as a result of strict postoperative management (i.e., prophylactic blood pressure lowering, prophylactic blockade of MMP-9, and postoperative use of free radical scavengers).[6–8,10,11]

Delayed intracerebral hemorrhage after STA-MCA anastomosis in patients with MMD is a rare but severe complication associated with significant morbidity and mortality.[4,12] As initially reported by Fujimura et al. in 2009,[7] CHP is linked to increased vascular permeability, which can lead to vasogenic edema and subsequent delayed intracerebral hemorrhage at the site of the anastomosis without discernible ischemic changes on postoperative MRI. Thus, in other words, the local vasogenic edema can be regarded as a warning sign of delayed intracranial hemorrhage due to CHP in MMD.[7] In addition, increasing evidence has revealed that local vasogenic edema formation can occur in many postoperative conditions, including global hypoperfusion and/or normalization of the cerebral hemodynamics,[13–16] and presumably in association with *RNF213* gene polymorphism.[17] The precise mechanisms underlying this rare complication remain unclear, with potential contributors including (1) excessive hemodynamic stress induced by direct revascularization; (2) chronic ischemic stress; (3) inadequate network formation among the pial arteries, resulting in suboptimal hemodynamic distribution after revascularization; and (4) the inherent fragility of vessels, along with the increased vascular permeability associated with MMD.[6–8,10–17] In our analysis, we propose that early detection of vasogenic edema induced after direct STA-MCA anastomosis may serve as an ideal predictor of delayed intracerebral hemorrhage, although the intraoperative cortical extravasation of ICG does not necessarily link to the post–direct bypass intracerebral hemorrhage. Although unique cases of local vasogenic edema unaccompanied by CHP after STA-MCA anastomosis for MMD have been reported,[13–16] our observation of intraoperative ICG extravasation, representing the first instance of in vivo direct visualization of local vasogenic edema, adds valuable clinical insight. On the basis of our case, we emphasize the importance of prolonging ICG video angiography to at least 3 minutes after intravenous ICG injection, exceeding the duration typically used to confirm patency of the direct bypass. However, we are still unsure of how long we should monitor the fluorescence video angiography. A previous study by Vajkoczy et al.[18] recorded a sodium fluorescein (NaFL) video angiography for a minimum of 2 minutes as part of their clinical intraoperative video angiography protocol. As a first attempt in this case, we conducted longer monitoring of ICG video angiography for 3 minutes. In a future study, the clinically relevant length of monitoring should be determined.

A previous study demonstrated NaFL extravasation in most patients with MMD who had undergone direct revascularization compared with those with atherosclerotic cerebrovascular disease.[18] Despite a high incidence of intraoperative NaFL extravasation in patients with MMD, none exhibited postoperative radiologically confirmed vasogenic edema. In contrast, our observation of intraoperative ICG extravasation resulted in postoperative local vasogenic edema, as confirmed by postoperative MRI. The distinctive binding properties of ICG, characterized by the molecular weight of 775 Da, water solubility,

and high affinity with plasma proteins (e.g., lipoproteins and albumin), set it apart from NaFL (360 Da).[18,19] NaFL's lower molecular weight and lack of affinity to circulating macromolecules allow freedom from extravasation,[18] which did not directly lead to postoperative radiologically proven local vasogenic edema. Consequently, we contend that intraoperative ICG extravasation holds greater clinical relevance for perioperative management in direct revascularization for MMD.

Lessons

ICG, characterized by its low molecular weight (775 Da), water solubility, and high affinity with plasma proteins such as lipoproteins and albumin, can exhibit extravasation as an intraoperative manifestation of local vasogenic edema induced by direct revascularization in MMD. To enhance our comprehension of the vulnerability of the blood–brain barrier in MMD, it is advisable to gather cases with prolonged observations of ICG video angiography after direct revascularization. Such data collection can contribute to an improved understanding of postoperative local vasogenic edema, providing valuable insights into the intricacies of the disease and aiding in refining perioperative management strategies.

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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: Ito, Yamasaki, Fujimura. Acquisition of data: Uchino. Analysis and interpretation of data: Uchino, Sugiyama, Fujimura. Drafting the article: Ito, Yamasaki. Critically revising the article: Fujimura. Reviewed submitted version of manuscript: Ito, Yamasaki, Sugiyama. Approved the final version of the manuscript on behalf of all authors: Ito. Administrative/technical/material support: Sugiyama. Study supervision: Sugiyama, Fujimura.

Supplemental Information

Previous Presentations

This case was presented at the semiannual conference of the Japan Neurological Society Hokkaido branch on March 25, 2023, in Sapporo, Japan.

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