

Biphasic Development of Focal Cerebral Hyperperfusion After Revascularization Surgery for Adult Moyamoya Disease Associated With Autosomal Dominant Polycystic Kidney Disease

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Background: Cerebral hyperperfusion (CHP) syndrome is a potential complication of superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis for moyamoya disease (MMD), but its biphasic and delayed development is extremely rare. **Case report:** A 47-year-old woman with autosomal dominant kidney disease (ADPKD) presented with transient ischemic attacks due to MMD, and underwent left STA-MCA anastomosis. N-isopropyl-p-[¹²³I] iodoamphetamine single-photon emission computed tomography (¹²³IMP-SPECT) 1 day after surgery revealed asymptomatic CHP at the site of anastomosis. Strict blood pressure control and minocycline hydrochloride relieved CHP at postoperative day 7. However, 2 days later, the patient complained of sensory aphasia, and ¹²³IMP-SPECT demonstrated significant focal CHP at the site of anastomosis accompanying high-intensity signal on magnetic resonance (MR) imaging of fluid attenuated inversion recovery (FLAIR) in her left temporal lobe near the site of anastomosis. We continued strict blood pressure control and additionally administered free radical scavenger (Edaravone) and anti-epileptic agents, which gradually improved sensory aphasia. MR imaging and ¹²³IMP-SPECT also confirmed the amelioration of the FLAIR-high lesion and focal CHP in her left temporal lobe. Two months later, the patient underwent right STA-MCA anastomosis without complications. **Conclusions:** Although the underlying mechanism is unknown, biphasic development of focal CHP after revascularization surgery in an MMD patient with ADPKD is unique. Due to the potential vulnerability of the systemic vessels in ADPKD, it is conceivable that intrinsic vascular wall fragility in MMD could be enhanced by ADPKD and have partly led to this rare complication.

Key Words: Moyamoya disease—cerebral hyperperfusion syndrome—autosomal dominant polycystic kidney disease—Revascularization surgery—surgical complication

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Introduction

Moyamoya disease (MMD) is a chronic and occlusive cerebrovascular disease characterized by bilateral stenotic changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain.¹ Superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis is widely performed for standard management of adult MMD.²⁻⁴ Cerebral hyperperfusion (CHP) syndrome is one of the potential complications of STA-MCA anastomosis for adult MMD,⁵⁻⁷ but it generally has a favorable prognosis under modern postoperative management protocols with strict blood pressure control and administration of

minocycline hydrochloride.^{8,9} However delayed and/or biphasic development of CHP is extremely rare. We herein report a patient with adult MMD who developed prolonged CHP with a biphasic pattern after revascularization surgery, despite intensive postoperative management, associated with autosomal dominant polycystic kidney disease (ADPKD).

Case Presentation

A 47-year-old woman with MMD developed transient paralysis of her extremities after laughing. Six years before the occurrence of the transient ischemic attacks (TIAs), she was found to have multiple cysts in the liver and kidney during a medical check-up, and was diagnosed with ADPKD. Initial magnetic resonance (MR) imaging for the screening of intracranial aneurysms did not reveal any saccular aneurysm formation, but stenosis of the terminal portion of her bilateral internal carotid arteries was noted. MMD was suspected and she began yearly follow-up by MR imaging/angiography. Her mother also had a history of ADPKD and MMD. After the development of transient ischemic attacks, the patient underwent catheter angiography, which demonstrated steno-occlusive changes at the terminal portion of the bilateral internal carotid arteries associated with abnormal vascular networks at the base of the brain (Fig 1A), leading to the definitive diagnosis of MMD. At this point, the patient was free from hypertension and renal dysfunction. On genetic analysis of RING-finger protein-213, a susceptibility gene for MMD, a heterozygous variant in c.14576 G>A of the RING-finger-213 gene was found. N-isopropyl-p-[¹²³I] iodoamphetamine single-photon emission computed tomography (¹²³I-IMP SPECT) revealed a significant decrease in cerebral blood flow (CBF) in the territory of left middle cerebral artery (Fig 1B). She then underwent left STA-MCA anastomosis with encephaloduro-myosynangiosis. The stump of the parietal branch of the STA was anastomosed to the M4 segment of the left MCA, which supplied the temporal lobe (Fig 2A). The diameter of the recipient artery was 1.0 mm, and the temporary occlusion time was 22 minutes. Intraoperative

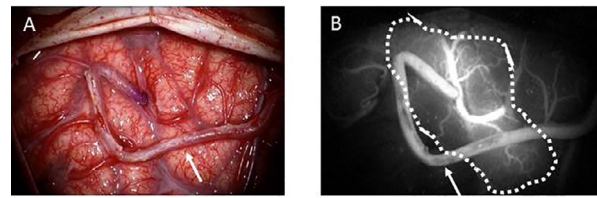


Figure 2. (A) Intraoperative microscopic view demonstrating the dilated cortical pial arteries near the site of anastomosis. The arrow indicates the superficial temporal artery (STA). (B) Intraoperative indocyanine green video angiography after the anastomosis showing focal early filling (dotted line) from the STA.

indocyanine green video angiography after the anastomosis demonstrated localized early filling through the STA with early venous filling of the cortical vein around the site of anastomosis (Fig 2B). No neurological deterioration was exhibited immediately after surgery, but a focal increase in CBF at the site of the STA-MCA anastomosis was observed on ¹²³I-IMP SPECT one day after surgery (arrowhead in Fig 3A) and fluid attenuated inversion recovery indicated increased ivy signs in her left temporal lobe (Fig 3B). The apparently patent left STA-MCA bypass with high signal intensity was observed on MR angiography (arrow in Fig 3C). Following our standard management of blood pressure lowering and minocycline hydrochloride administration,⁸ the patient did not develop neurological deterioration due to CHP for one week after surgery. ¹²³I-IMP SPECT on postoperative day 7 confirmed the amelioration of CHP (Fig 3D). Two days later, however, the patient complained of sensory aphasia, and MR imaging demonstrated high-intensity signal in the white matter of her left temporal lobe on fluid attenuated inversion recovery (Fig 3F), accompanying increased signal intensity on diffusion-weighted imaging in the surface of left temporal lobe (Fig 3G) with an increased apparent diffusion coefficient (Fig 3H). MR angiography revealed the increased intensity of left STA-MCA bypass (Fig 3I), which is in accordance with ¹²³I-IMP-SPECT finding.^{10,11} A focally intense increase in CBF at the site of anastomosis was noted on ¹²³I-IMP SPECT, indicating the biphasic occurrence of CHP (asterisk in Fig 3E), since the patient met the following diagnostic criteria for CHP; the

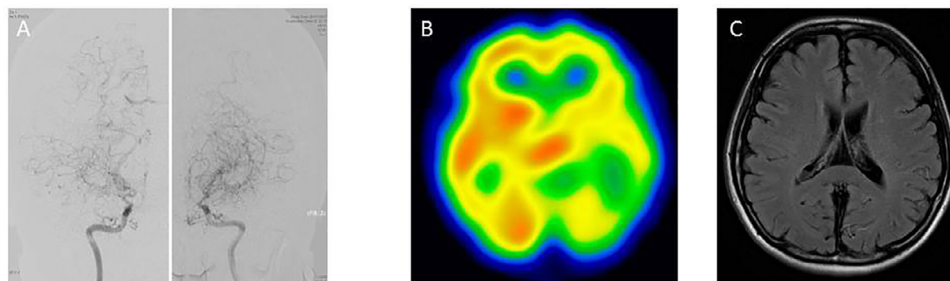


Figure 1. (A) Preoperative catheter angiography showing stenosis of the terminal portion of bilateral internal carotid arteries and abnormal vascular network at the base of the brain. (B) N-isopropyl-p-[¹²³I] iodoamphetamine single photon emission computed tomography (¹²³I-IMP SPECT) showing decreased cerebral blood flow in the territory of the left middle cerebral artery (MCA). (C) Fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) imaging showing ivy signs in the left hemisphere.

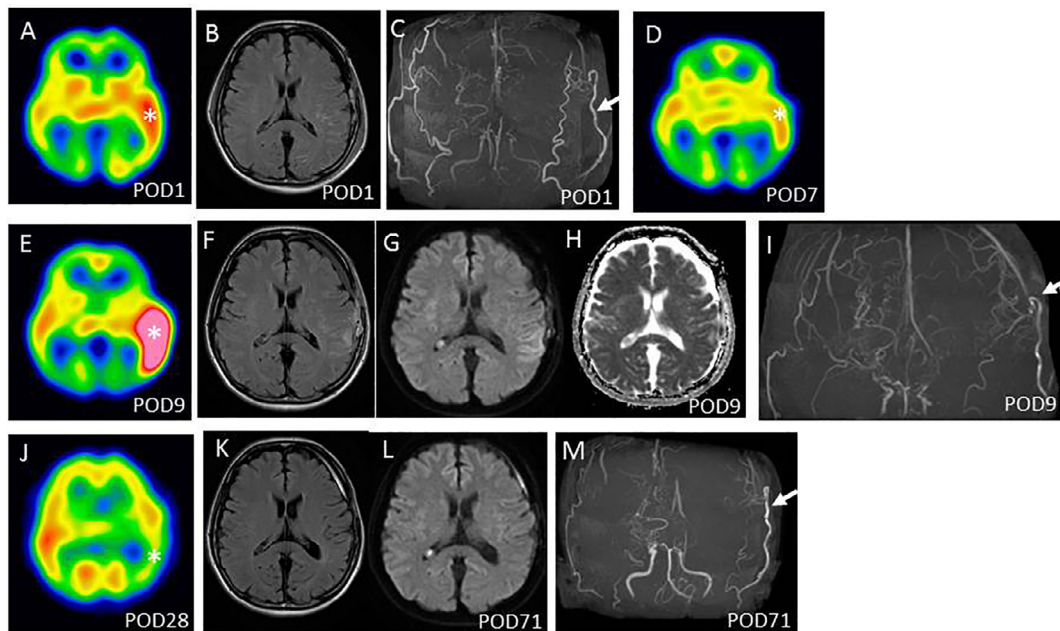


Figure 3. (A) ^{123}I -IMP SPECT on postoperative day 1 showing focal cerebral hyperperfusion (CHP) in the left temporal lobe (asterisk). (B) FLAIR MR imaging on postoperative day 1 showing increased IVS in her left temporal lobe. (C) MR angiography on postoperative day 1 showing the patency of left STA-MCA bypass (arrow). (D) ^{123}I -IMP SPECT on postoperative day 7 revealing amelioration of CHP in her left temporal lobe (asterisk). (E) ^{123}I -IMP SPECT on postoperative day 9 showing significant CHP at the site of anastomosis in her left temporal lobe (asterisk). F-H: MR imaging on postoperative day 9 showing a high-intensity signal on FLAIR (F) and diffusion-weighted imaging (DWI) (G), and increased apparent diffusion coefficient (H) in the left temporal lobe. (I) MR angiography on postoperative day 9 showing the increased intensity of left STA-MCA bypass (arrow). (J) ^{123}I -IMP SPECT on postoperative day 28 demonstrating complete disappearance of CHP (asterisk). K-L: FLAIR (K) and DWI (L) on postoperative day 71 showing complete disappearance of the high-intensity signal in the left temporal lobe. (M) MR angiography on postoperative day 71 showing the apparently patent left STA-MCA bypass (arrow). Abbreviations: FLAIR, fluid attenuated inversion recovery; IMP SPECT, iodoamphetamine single-photon emission computed tomography; MR, magnetic resonance; STA-MCA, superficial temporal artery-middle cerebral artery.

presence of a significant focal increase in CBF over 46.1 ml/100g/min at the site of the anastomosis and apparent visualization of STA-MCA bypass by MR angiography.^{6,12} In addition to reduction of blood pressure and minocycline chloride administration, we introduced the free radical scavenger (Edaravone) and antiepileptic agents, and her symptom was gradually relieved over the next 2 weeks. ^{123}I -IMP SPECT on postoperative day 28 (Fig 3J) and MR imaging on postoperative day 71 (Fig 3K-M) confirmed the complete disappearance of focal CHP and the high-intensity signal near the site of anastomosis. The patient underwent right STA-MCA anastomosis with encephalo-duro-myelo-synangiosis without complications by alleviation of blood pressure control more carefully and slowly in light of the biphasic development of CHP after the initial surgery on the left hemisphere.

Discussion

Biphasic development of CHP after revascularization surgery for adult MMD is extremely rare, as only 1 case has been reported previously. Among 288 patients with MMD who underwent STA-MCA anastomosis on 392 affected hemispheres by single surgeon (M.F.), 1 adult patient (.25%) manifested as biphasic development of

CHP after STA-MCA anastomosis (unpublished data). Both previously-reported case¹³ and our case showed biphasic development of CHP, but the onset of second phase of CHP is different. Namely, previously-reported case had intractable hypertension and authors speculated uncontrolled hypertension resulted in biphasic CHP at postoperative day 4. In contrast, our case demonstrated second phase of CHP after alleviation of blood pressure lowering 1 week after surgery based on the ^{123}I -IMP-SPECT finding.⁹ Thus, more deliberate blood pressure control in the intensive care unit could be warranted to prevent biphasic development of CHP, especially for the high-risk patient for CHP. In fact, our case did not show symptomatic CHP after revascularization surgery on the right hemisphere by deliberate blood pressure control in the intensive care unit for lengthy postoperative period. Alternatively, longitudinal pattern of postoperative hemodynamics should be clarified not only by serial ^{123}I -IMP SPECT, but also by additional methods such as transcranial Doppler sonography and arterial spin labeling of MR imaging in the future study.

Although the exact mechanisms underlying biphasic development of CHP remain uncertain, a lengthy period in a hemodynamically compromised state as well as characteristic pathophysiological conditions of ADPKD may

partly explain this rare complication. Mutations in either *polycystin-1* (*PKD1*) or *polycystin-2* (*PKD2*) account for most cases of ADPKD.¹⁴ Some experimental studies reported that *PKD1* and *PKD2* are expressed in vascular smooth muscle cells and endothelium, and regulate extracellular matrix formation and the structural integrity of blood vessels.^{14,15} These studies demonstrated gross edema and hemorrhage in *Pkd1* mutant mice that may be caused by vascular fragility.^{14,15} Therefore, intrinsic fragility of systemic vessel structures in ADPKD may be involved in not only intracranial aneurysm formation but also the biphasic development of CHP in the present patient. Moreover, previous reports demonstrated aberrant expression profiles of matrix metalloproteinases (MMP) in ADPKD, including MMP-9 in cell lines from the liver cysts of ADPKD patients¹⁶ and increased levels of MMP-1 in serum of ADPKD patients.¹⁷ Increased levels of vascular endothelial growth factor were also reported in patients with MMD¹⁸ or ADPKD.¹⁹ Excessive hemodynamic stress on the fragile vessel after STA-MCA anastomosis, in combination with elevated expression of MMPs and vascular endothelial growth factor, may promote increased vascular permeability in the pial artery in addition to intrinsic vascular fragility in patients with MMD.

ADPKD is the most common hereditary kidney disease, and is characterized by multiple cyst formation in the kidney and an increase in total renal volume.^{20,21} Renal dysfunction gradually progresses with age and becomes evident around the age of 40.^{20,22} Patients with ADPKD typically progress to end-stage renal failure by the age of 60.^{20,22} In addition, hypertension is often associated with ADPKD and multiple-organ damage caused by hypertension also progresses with age.²³ Another characteristic feature of ADPKD is the high frequency of vascular anomalies, including intracranial aneurysms, dissections of the thoracic aorta and coronary artery, aortic root dilation, and cerebral dolichoectasia.²⁴ Intracranial aneurysms causing subarachnoid hemorrhage are the most frequent and serious complications. However, ADPKD associated with MMD is extremely rare, and only 3 cases have been previously reported.²⁵⁻²⁷ In our patient, renal function and blood pressure were not affected by ADPKD, thus we were able to perform standard STA-MCA anastomosis and intensive perioperative management, including prophylactic blood pressure control, according to our protocol for MMD. Therefore, revascularization surgery in the early stage of disease, while renal function is preserved and multiple-organ damage due to hypertension is not evident, is especially important for MMD patients with ADPKD. This is also applicable to patients with ADPKD during follow-up for intracranial aneurysms. Close follow-up is critical in order to not miss an opportunity to perform procedures on ADPKD patients with intracerebral vasculopathy. In addition, we should perform more careful management for MMD cases

complicated with comorbidity that can cause vascular wall fragility since these patients may elicit severe CHP.

Conclusions

Although the underlying mechanism is undetermined, biphasic development of focal CHP after revascularization surgery in an MMD patient with ADPKD is unique. Due to the potential vulnerability of the systemic vessels in ADPKD, it is conceivable that intrinsic vascular wall fragility in MMD could be enhanced by ADPKD, leading to this rare complication.

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