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CASE REPORT

Uneven cerebral hemodynamic change as a cause of neurological deterioration in the acute stage after direct revascularization for moyamoya disease: cerebral hyperperfusion and remote ischemia caused by the 'watershed shift'

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Abstract Superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis is the standard surgical treatment for moyamoya disease (MMD). The main potential complications of this treatment are cerebral hyperperfusion (CHP) syndrome and ischemia, and their managements are contradictory to each other. We retrospectively investigated the incidence of the simultaneous manifestation of CHP and infarction after surgery for MMD. Of the 162 consecutive direct revascularization surgeries performed for MMD, we encountered two adult cases (1.2%) manifesting the simultaneous occurrence of symptomatic CHP and remote infarction in the acute stage. A 47-year-old man initially presenting with infarction developed CHP syndrome (aphasia) 2 days after left STA-MCA anastomosis, as assessed by quantitative single-photon emission computed tomography (SPECT). Although lowering blood pressure ameliorated his symptoms, he developed cerebral infarction at a remote area in the acute stage. Another 63-year-old man, who initially had progressing stroke, presented with aphasia due to focal CHP in the left temporal lobe associated with acute infarction at the tip of the left frontal lobe 1 day after left STA-MCA anastomosis, when SPECT showed a paradoxical decrease in cerebral blood flow (CBF) in the left frontal lobe despite a marked increase in CBF at the site of anastomosis. Symptoms were ameliorated in both patients with the normalization of CBF, and there were no further cerebrovascular events during the follow-up period. CHP and cerebral infarction may occur simultaneously not only due to blood pressure lowering against CHP, but also to the 'watershed shift' phenomenon, which needs to be elucidated in future studies.

Keywords Moyamoya disease · Surgical complication · Cerebral hyperperfusion · Cerebral infarction

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Introduction

Moyamoya disease (MMD) is a chronic, occlusive cerebrovascular disease of unknown etiology characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain [1]. Superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis is the standard surgical treatment for MMD [2]. Although the long-term outcome of surgical revascularization is favorable, the early postoperative period is regarded as a vulnerable time during which complications frequently occur. Cerebral hyperperfusion (CHP) and cerebral ischemia are the most prominent of these complications, and their managements are contradictory to each other [3]. Throughout the years, we have implicated strict strategies to reduce the manifestation of CHP following combined surgery; these strategies include strict blood pressure control and the administration of minocycline. These strategies have significantly reduced the incidence of symptomatic CHP without increasing the risk of ischemic complications [4, 5]. Theoretically, the patency of the bypass pedicle may induce CHP without ischemia or infarction. However, Hayashi et al. reported the "watershed shift" phenomenon after STA-MCA anastomosis in pediatric MMD [6], which may induce new cerebral infarction remote from the site of anastomosis. Alternatively, further blood pressure lowering against severe CHP may cause cerebral infarction at a remote area in rare occasions [5].

Of the 162 consecutive surgeries performed for MMD under a standardized protocol {postoperative prophylactic intensive blood pressure control (systolic blood pressure <130 mmHg)} [5], we herein present two cases of adult-onset MMD, which manifested the simultaneous occurrence of HPS and cerebral infarction after STA-MCA anastomosis. This rare association may indicate a limitation in the current perioperative management protocol, suggesting the necessity for further evaluations of the underlying pathology during the early perioperative period of revascularization surgery for MMD.

Case reports

Of the 162 consecutive direct/indirect combined revascularization surgeries performed for MMD by the same surgeon (M.F.) under a standardized protocol {postoperative prophylactic intensive blood pressure control (systolic blood pressure <130 mmHg)} from 2010 [5], we encountered two adult cases (1.2%) manifesting the simultaneous occurrence of symptomatic CHP and remote infarction in the acute stage. The *N*-isopropyl [123I]-p-iodoamphetamine (^{123}I-IMP-SPECT) was performed at 1 day and 7 days after surgery in all 162 revascularization surgeries as routine perioperative care.

Case 1

History and examination

A 47-year-old man with a previous history of hypertension initially presented with cerebral infarction on the left hemisphere (Fig. 1a, b). Cerebral angiography revealed occlusive changes at the terminal portion of the bilateral ICAs associated with abundant moyamoya vessels on both sides, leading to a diagnosis of MMD (Fig. 1c–f).

Operation

STA-MCA anastomosis with encephalo-duro-myo-synangiosis (EDMS) in the left hemisphere was performed 3 months after the onset of stroke. The stump of the frontal branch of STA was anastomosed to MCA (M4 segment), which supplied the frontal lobe (arrow in Fig. 2b). The temporary occlusion time was 27 min (Fig. 2a). The patency of the bypass was promptly confirmed by indocyanine green video-angiography (arrow in Fig. 2c).

Postoperative course

Accompanied by the administration of minocycline hydrochloride (200 mg/day) [5], systolic blood pressure was strictly maintained at <130 mmHg starting immediately after surgery [4]. The patient did not display any additional neurological sign immediately after surgery. Postoperative magnetic resonance angiography (MRA) showed an apparently patent left STA-MCA bypass (asterisk in Fig. 2e), and there was no evidence of a newly developed parenchymal lesion on T2-weighted images (Fig. 2d). Quantitative ^{123}I-IMP-SPECT by auto-radiographic (ARG) method 1 day after surgery (Fig. 3b) showed a more focally intense increase in cerebral blood flow (CBF) at the site of anastomosis (CBF value of 41.7 ml/min/100 g) than at the pre-operative status (CBF value of 23.6 ml/min/100 g) (Fig. 3a). The patient developed transient aphasia 2 days after surgery, and we continued strict blood pressure control between 100 and 130 mmHg based on the diagnosis of focal CHP by ^{123}I-IMP-SPECT.[1] This symptom was ameliorated within a few days and ^{123}I-IMP-SPECT 7 days after surgery showed improved focal CHP with a CBF value of 28.1 ml/min/100 g (Fig. 3c); however, magnetic resonance imaging (MRI) revealed acute cerebral infarction at a remote area, such as the right frontal lobe and the left temporal lobe (dotted circles in Fig. 3d). The patient had mild mono-paresis on his left foot due to acute cerebral infarction on the right hemisphere. This symptom was relieved by rehabilitation within 1 month of surgery, and there were no further cerebrovascular events during the follow-up period of 4 months.

Case 2

Clinical manifestation and examinations

A 63-year-old man with a previous history of hypertension presented with mild right upper limb motor weakness for 2 months. MRI showed minor cerebral infarctions in the left periventricular area that were progressively increasing during the pre-operative period (Fig. 4a). MRA indicated steno-occlusive changes at the terminal portion of bilateral ICAs, while superior and inferior divisions of the MCA were visualized clearly (Fig. 4b). Cerebral angiography revealed severe bilateral stenosis of ICAs at the terminal portion and complete bilateral occlusion of the anterior cerebral arteries (Fig. 4c–e). Due to the development of abnormal vascular networks at the base of the right brain (Fig. 4c) associated with evidence of transdural anastomosis (Fig. 4c, e), we diagnosed this patient with MMD.

Surgery

The patient underwent STA-MCA anastomosis with EDMS on the left hemisphere. Anastomosis was performed between the frontal branch of the STA and the M4 segment supplying the

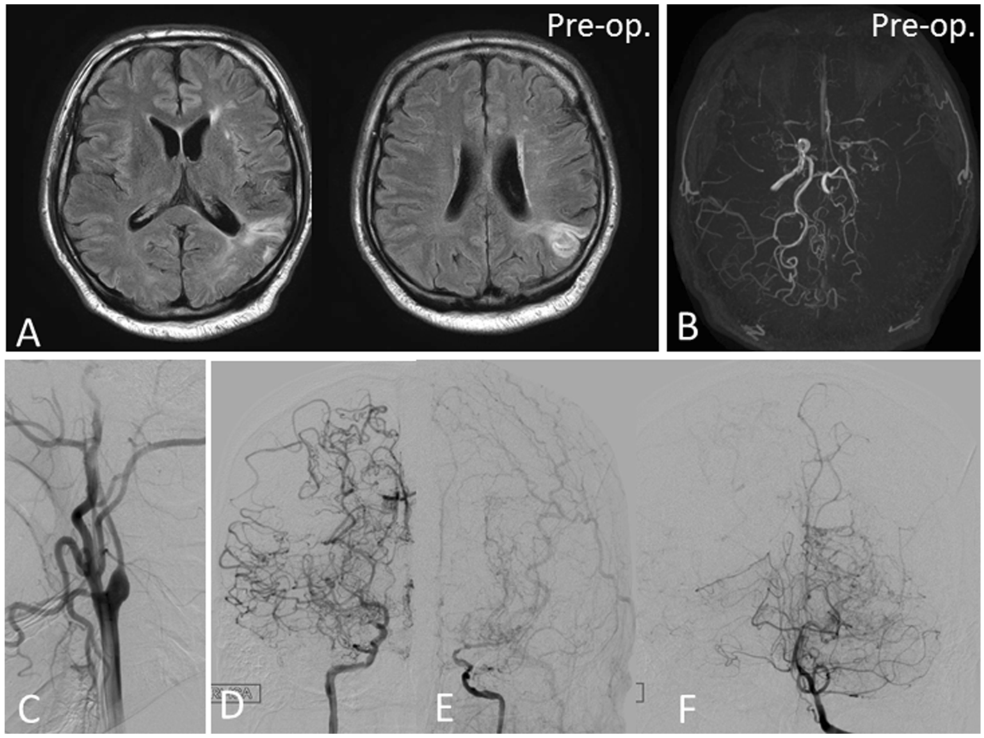

Fig. 1 **a** Initial FLAIR MRI. **b** Pre-operative MR angiography showing steno-occlusive changes at the terminal portions of the bilateral ICAs. **c–f** Pre-operative catheter angiography showing stenosis of the terminal portions of ICA and the occurrence of abundant moyamoya vessels in the brain base bilaterally (**c**, **d**, **e**), which were more evident on the left side, and peripheral PCA stenosis on the left side (**f**)

parieto-occipital lobe (arrows in Fig. 5b). The temporary occlusion time of M4 was 21 min during the anastomosis phase. The patency of the bypass was promptly confirmed using indocyanine green video-angiography (arrow in Fig. 5c).

Postoperative management and evolved course

Accompanied by the administration of minocycline hydrochloride (200 mg/day) [5], systolic blood pressure was strictly maintained at <130 mmHg starting immediately after surgery [4]. Immediately after surgery (postoperative day 0), the patient developed aphasia, and motor weakness in the right upper limb and lower limb deteriorated. Postoperative CT revealed mild subarachnoid hemorrhage over the cortex supplied by the bypass (data not shown), and, thus, we adjusted the therapeutic window of his blood pressure between 100 and 120 mmHg. One day after surgery, aphasia improved slightly while motor weakness continued to deteriorate. The quantitative ^{123}I-IMP-SPECT by ARG method 1 day after surgery demonstrated a more focally intense increase in CBF at the left temporal lobe (CBF value of 48.0 ml/min/100 g) (red circle in Fig. 6b) than the pre-operative status (CBF value of

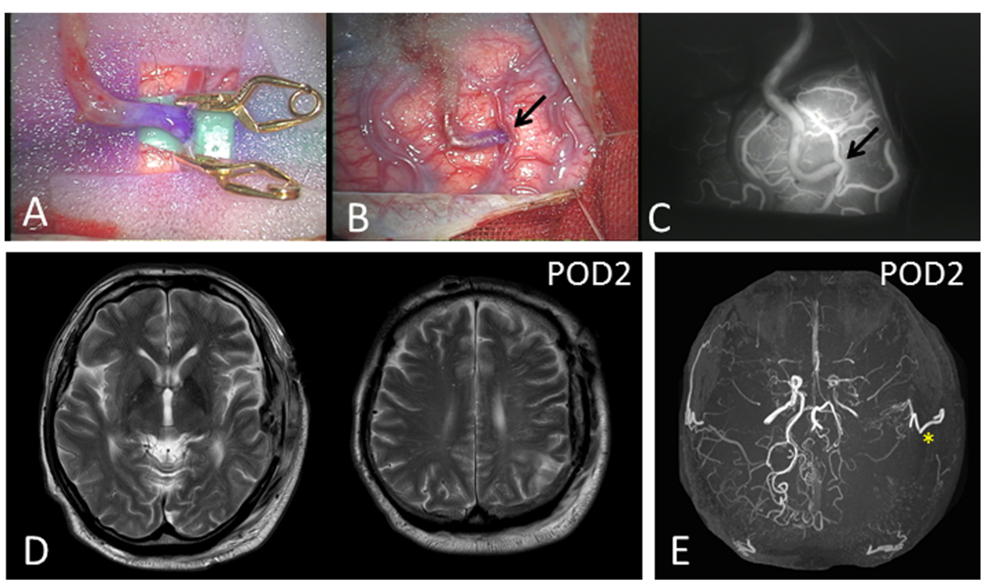

Fig. 2 **a–b** Surgical view of left STA-MCA anastomosis. The MCA (M4 segment) was temporarily occluded (**a**) to perform left STA-MCA anastomosis (*arrow* in **b**). **c** Indocyanine green video-angiography demonstrated apparent patent bypass with the favorable distribution of bypass flow. **d** Postoperative T2-weighted MRI showing no evidence of a newly developed parenchymal lesion 2 days after surgery. **e** Postoperative MR angiography showing an apparently patent left STA-MCA bypass (*asterisk*) 2 days after surgery. *POD2* postoperative day 2

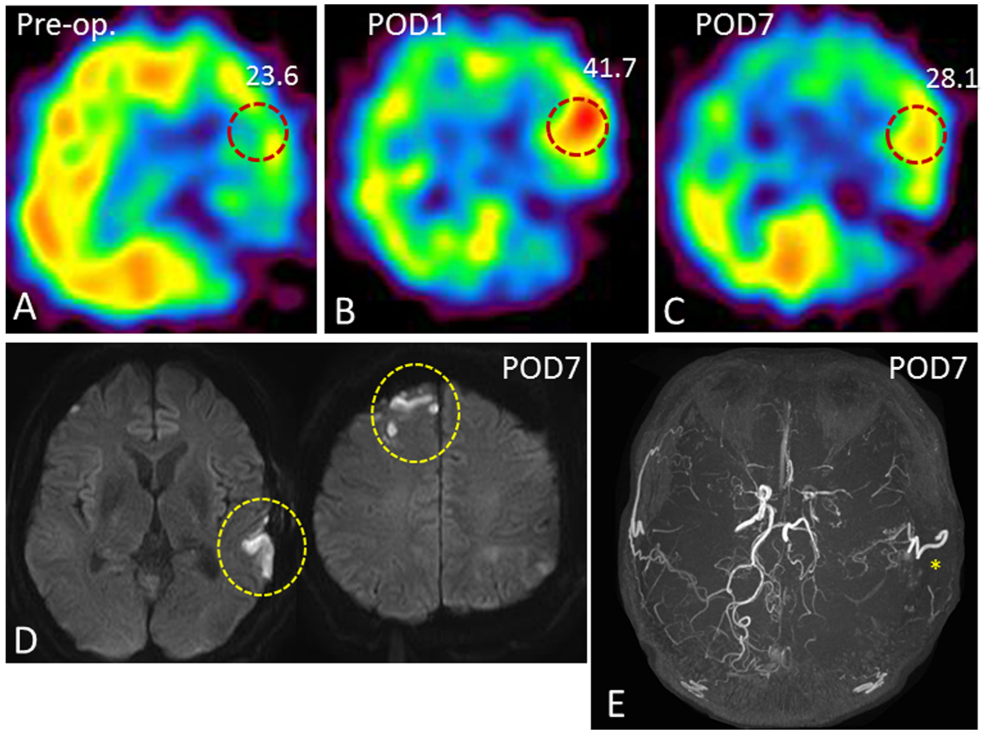

Fig. 3 **a–c** Temporal profile of ^{123}I-IMP-SPECT images **a** before surgery, **b** 1 day after surgery, and **c** 7 days after surgery. Quantitative local CBF values are shown in **a–c** (*dotted circles*). Pre-operative SPECT showing decreased CBF in the left frontotemporal lobe; direct bypass surgery resulted in prominent hyperperfusion at the site of anastomosis 1 day after surgery, which improved 7 days after surgery. **d** Postoperative diffusion-weighted MRI demonstrating acute cerebral infarction at the right frontal lobe and left temporal lobe (*yellow dotted circles*) 7 days after surgery. **e** Postoperative MRA showing the patent left STA-MCA bypass (*asterisk* in **e**) 7 days after surgery. *Pre-op* means pre-operative; *POD* means postoperative day

21.0 ml/min/100 g) (Fig. 6a), when MRI revealed acute infarction at the tip of the left frontal lobe, the most remote area from the site of anastomosis (Fig. 5d). Paradoxically, ^{123}I-IMP-SPECT performed on the same day revealed that CBF in the ipsilateral frontal lobe was lower, with a CBF value of 15.1 ml/min/100 g (Fig. 6b), than that of the preoperative status, with a CBF value of 20.8 ml/min/100 g (Fig. 6a). Postoperative MR angiography showed that signal intensity was weaker in the MCA bifurcation (dotted circle in Fig. 5f) than that pre-operatively (dotted circle in Fig. 4b). These results led to the diagnosis of the simultaneous occurrence of CHP and cerebral infarction on the same hemisphere that was operated on. Over the next few days, the right hemiparesis improved, and there were no further cerebrovascular events during the follow-up period of 4 months. MR angiography 43 days after surgery showed an apparently patent STA-MCA bypass (asterisk in Fig. 6d).

Discussion

In the present retrospective analysis of 162 consecutive surgical cases undergoing STA-MCA anastomosis for MMD, we presented two adult cases (1.2%) that manifested as the simultaneous occurrence of HPS and remote infarction in the acute stage after STA-MCA anastomosis. In case 2, we demonstrated, for

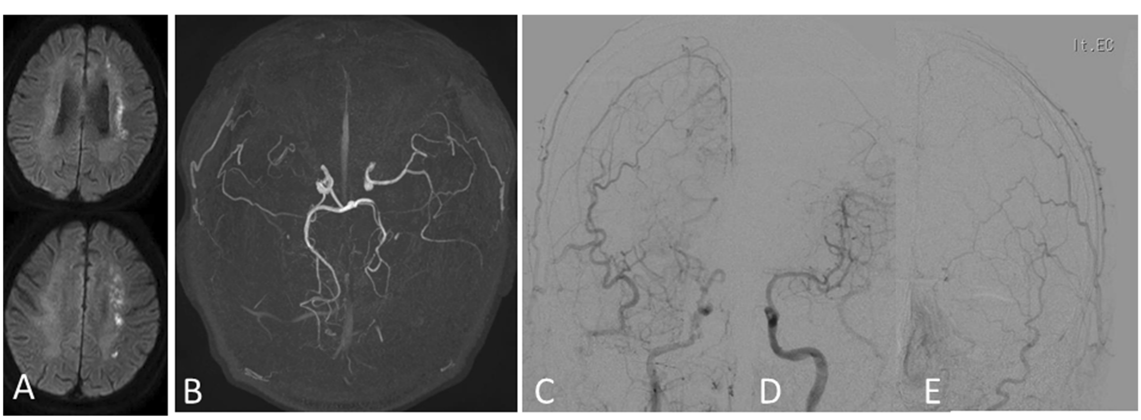

Fig. 4 Initial diffusion-weighted MRI demonstrating scattered infarctions around the periventricular region of the left hemisphere. **b** Pre-operative MRA showing steno-occlusive changes at the terminal portions of the bilateral ICAs. **c–e** Pre-operative catheter angiography showing the stenosis of bilateral terminal portions of ICA and moyamoya vessels in the brain base (**c**, **d**), which were more obvious on the right side, with the development of transdural anastomosis shown by the left external carotid angiography (**e**)

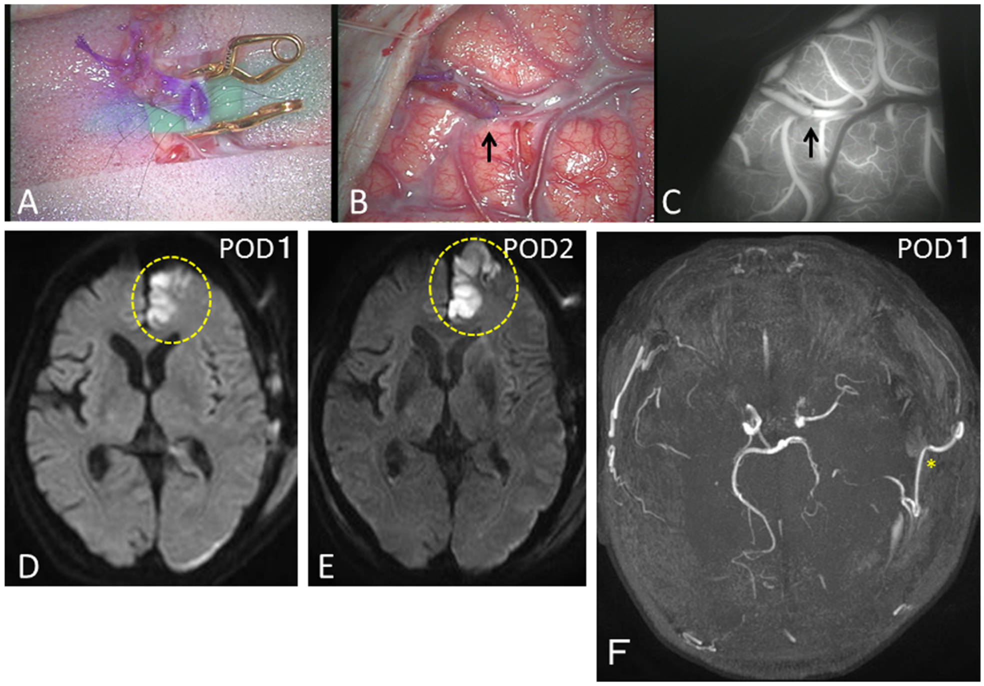

Fig. 5 **a–b** Surgical view of left STA-MCA anastomosis. The MCA (M4 segment) was temporarily occluded (**a**) to perform left STA-MCA anastomosis (*arrow* in **b**). **c** Indocyanine green video-angiography demonstrating the apparently patent bypass with the favorable distribution of bypass flow. **d–e** Postoperative diffusion-weighted MRI showing acute cerebral infarction (*yellow dotted circles*) 1 day after surgery, which became more evident 2 days after surgery. **e** Postoperative MR angiography demonstrating patent STA-MCA bypass as a thick high signal (*asterisk* in **e**) 1 day after surgery. *POD* post-operative day

the first time, that direct revascularization surgery for adult MMD caused focal CHP and simultaneous remote cerebral infarction, and this was explained by the watershed shift phenomenon [6]. Our result was confirmed by the temporal profile of the quantitative CBF value in each territory in Fig. 6. Since the watershed shift phenomenon after direct revascularization surgery for MMD is regarded as a rare complication of pediatric MMD [6], which has yet to be reported in adult cases, the simultaneous development of symptomatic CHP and infarction in adult MMD appears to be unique.

CHP is one of the severe complications associated with direct revascularization surgery for MMD and may cause focal neurological deterioration and/or delayed intracerebral hemorrhage [2, 6–10]. Since adult cases are at a higher risk of symptomatic CHP than pediatric cases [8, 11, 12], we mainly focused on the prevention of postoperative hemorrhagic conversion due to CHP in the present cases because both exhibited intense focal increases in CBF that caused focal neurological symptoms. Based on our previous finding that prophylactic blood pressure control (systolic blood pressure of 110–130 mmHg) after STA-MCA anastomosis significantly decreased the incidence of symptomatic CHP without increasing that of perioperative cerebral infarction [4], we consider mild but strict blood pressure lowering to be beneficial for MMD patients undergoing direct revascularization, particularly adult cases. Furthermore, we combined this strategy with the

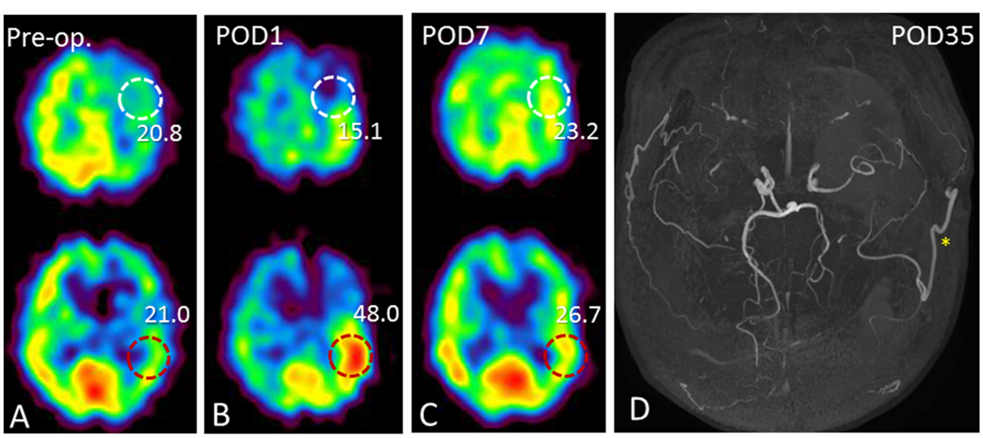

Fig. 6 **a–c** Temporal profile of ^{123}I-IMP-SPECT images **a** before surgery, **b** 1 day after surgery, and **c** 7 days after surgery. Quantitative local CBF values are shown in **a**–**c** (*dotted circles*). Pre-operative SPECT images showing decreased CBF in the left frontotemporal lobe; STA-MCA bypass caused prominent hyperperfusion at the temporal lobe 1 day after surgery, which improved 7 days after surgery. In contrast, CBF in the left frontal lobe was transiently lower 1 day after surgery than the pre-operative value. **d** Postoperative MRA showing the apparently patent left STA-MCA bypass (*asterisk* in **d**) 35 days after surgery. *Pre-op* pre-operative; *POD* post-operative day

administration of minocycline hydrochloride, a neuroprotective antibiotic agent [5]. Case 1 in the present series had symptomatic CHP even with a systolic blood pressure of 125 mmHg. We attempted to achieve further reductions in blood pressure in order to improve CHP; however, he ultimately developed infarction at a remote area several days later, which revealed a major difficulty and limitation associated with the current perioperative management protocol to prevent both CHP and ischemia in the same period. On the other hand, case 2 developed remote cerebral infarction in the ipsilateral hemisphere immediately after STA-MCA anastomosis, which may be explained by the watershed shift phenomenon [6]. Since the manifestation of severe CHP and remote ischemia occurred within 1 day in this case, surgical complications appeared to be inevitable under the current management strategy. It is conceivable that double-barrel STA-MCA anastomosis is favorable from the viewpoint of reducing the risk of acute ischemia at a remote area caused by the watershed shift phenomenon.

The exact mechanism why our two cases manifested as the simultaneous occurrence of CHP and remote ischemia is undetermined. Since both cases had a previous history of hypertension and their angiographic findings involved the atherosclerotic changes in addition to definitive characteristics of MMD (Figs. 1e and 4c), it is conceivable that coexistence of the atherosclerosis with MMD could contribute in part to this complex pathology. In fact, we have reported a 64-year-old woman with hypertension, suffering ipsilateral occipital lobe infarction during intensive blood pressure lowering against CHP in our initial series [5]. Furthermore, elderly patients with MMD, who could have more prominent atherosclerotic changes, were reported to be more vulnerable to symptomatic CHP associated with hemorrhage compared to younger patients [7]. Further evaluation of a larger number of patients with this rare complication is warranted to answer this important question. Since we employed single STA-MCA anastomosis with EDMS in our present series, alternative surgical strategy such as double-barrel STA-MCA anastomosis should be considered for the high-risk patients of simultaneous CHP and remote ischemia due to watershed shift phenomenon.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals The ^{123}I-IMP-SPECT, MRI and MRA are routine postoperative examinations, which are covered by medical insurance in the Japanese healthcare system. All procedures are performed in accordance with the Declaration of Helsinki.

Informed consent Informed consent to publish their clinical courses and radiological data was obtained from two individual patients included in the study.

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