Progressive Cerebral Ischemia and Intracerebral Hemorrhage after Indirect Revascularization for a Patient with Cerebral Proliferative Angiopathy

Tomomi Kimiwada, MD, PhD,* Toshiaki Hayashi, MD, PhD,† Misaki Takahashi, MD, PhD,* Reizo Shirane, MD, PhD,* and Teiji Tominaga, MD, PhD‡

We previously reported a patient with cerebral proliferative angiopathy (CPA) who showed cerebral ischemia in resting and acetazolamide-stressed *N*-isopropyl-*p*-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT). At onset, the patient was treated conservatively. However, during the 2 years following initial onset, his hemiparesis and aphasia had gradually aggravated and his IQ scores were markedly decreased. MRI revealed progressive vascular proliferation and brain atrophy. ^{123}I-IMP-SPECT showed more severely impaired cerebral blood flow (CBF) and cerebrovascular reactivity over the affected hemisphere. We performed an indirect revascularization to augment CBF; however, his neurological deficits were not improved and new arteriovenous shunts via extracranial-intracranial bypass were developed, followed by an asymptomatic small intracerebral hemorrhage.

There are no reports on CPA patients who have shown cerebral hemorrhage after indirect revascularization. Treatments for CPA are still challenging and controversial. Cases with severe stenosis of the proximal arteries may benefit from indirect revascularization. But indirect bypass should not be indicated for such patients without main arterial stenosis, even if they have persistent ischemia.

Key Words: Cerebral proliferative angiopathy—progressive cerebral ischemia—indirect revascularization—intracerebral hemorrhage

Introduction

We previously reported a case of cerebral proliferative angiopathy (CPA) that showed cerebral hypoperfusion in resting and acetazolamide-stressed *N*-isopropyl-*p*-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT).[1] CPA is a rare hypervascular lesion with intermingled normal brain parenchyma, and an effective treatment strategy has not yet been established. Because the main mechanism of this disease is ischemia, therapies that increase cortical blood supply, such as indirect revascularization procedures, can be indicated.[2-7]

Our previously reported patient was treated conservatively at the time of diagnosis,[1] but he showed progressive right hemiparesis and motor aphasia. Follow-up MRI revealed aggravation of the vascular malformation and brain atrophy, and resting and acetazolamide-stressed ^{123}I-IMP-SPECT demonstrated progressive cerebral hypoperfusion over the affected hemisphere. We performed indirect revascularization surgery to augment flow to the compromised hemisphere. However, neither his neurological deterioration nor cerebral hypoperfusion in ^{123}I-IMP-SPECT was improved. Furthermore, arteriovenous (A-V) shunts developed through the

From the *Department of Neurosurgery, Miyagi Children's Hospital, Sendai, Japan; †Department of Neurosurgery, Sendai City Hospital, Sendai, Japan; and ‡Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan.

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Address correspondence to Tomomi Kimiwada, MD, PhD, Department of Neurosurgery, Miyagi Children's Hospital, 4-3-17 Ochiai, Aoba-ku, Sendai 989-3126, Japan. E-mail: kimiwada@miyagi-children.or.jp.

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indirect extracranial-intracranial (EC-IC) bypass after surgery, followed by a small asymptomatic intracerebral hemorrhage.

It is indicated that, in the case of CPA, selected patients may benefit from a procedure to enhance blood supply to the hypoperfused cortex. However, the surgical indication for indirect revascularization still remains to be solved. There are no reports on CPA that show cerebral hemorrhage after indirect revascularization. Here, we review literature regarding indirect revascularization for patients with CPA, and discuss the surgical indication for this vascular malformation-related hypoperfusion.

Case Report

Initial History

A 13-year-old boy with disabling headaches and reversible focal neurological deficits (mild right extremity weakness, motor aphasia, finger agnosia, right-left disorientation, and acalculia) was referred to our department. Neuropsychological testing revealed an average IQ score and electroencephalography was normal. MRI confirmed the presence of a diffusely dilated extensive vascular lesion mainly located in the sulci of the left frontal and parietal lobes without a clearly identifiable margin (Fig 1, A). Evidence of acute ischemia and hemorrhages was not found. Cerebral angiography (in 2011) revealed a large hypervascular lesion with a diffuse arterial supply involving the left anterior cerebral artery, left middle cerebral artery, left posterior cerebral artery, and left middle meningeal artery. Early venous filling, flow-related aneurysms, and main arterial stenosis were not found (Fig 2, A-D); we diagnosed this vascular lesion as CPA. ^{123}I-IMP-SPECT at resting state showed preserved uptake within the vascular lesion, yet lower uptake in the area adjacent to the lesion. In addition, acetazolamide-stressed ^{123}I-IMP-SPECT exhibited severely impaired cerebrovascular reactivity (CVR) over the affected left hemisphere, suggesting that his focal neurological deficits were related to the cerebral ischemia (Fig 3, A). At that time, we decided to treat him conservatively with antiepileptic medication.

Later Presentation

Two years after initial onset, the patient's hemiplegia and motor aphasia had gradually aggravated, and neuropsychological testing revealed a marked decrease in IQ score from 102 to 76. MRI revealed progressive vascular proliferation and brain atrophy (Fig 1, B). Resting and acetazolamide-stressed ^{123}I-IMP-SPECT demonstrated more severely decreased cerebral blood flow (CBF) and impaired CVR over the affected hemisphere (Fig 3, B).

Operation

On the suspicion that the left cerebral hemisphere was hemodynamically compromised as a consequence of vascular steal from the large vascular lesion, we performed an indirect revascularization procedure including encephaloduroarteriosynangiosis (EDAS) and encephalomyosynangiosis (EMS) in an effort to augment flow to the compromised hemisphere. The left parietal branch of the superficial temporal artery (STA) was dissected from surrounding tissues, and the skull was opened over the precentral region. The dura matter incision was as large as possible because there was no transdural supply on the right convexity region. A surgical view is shown in

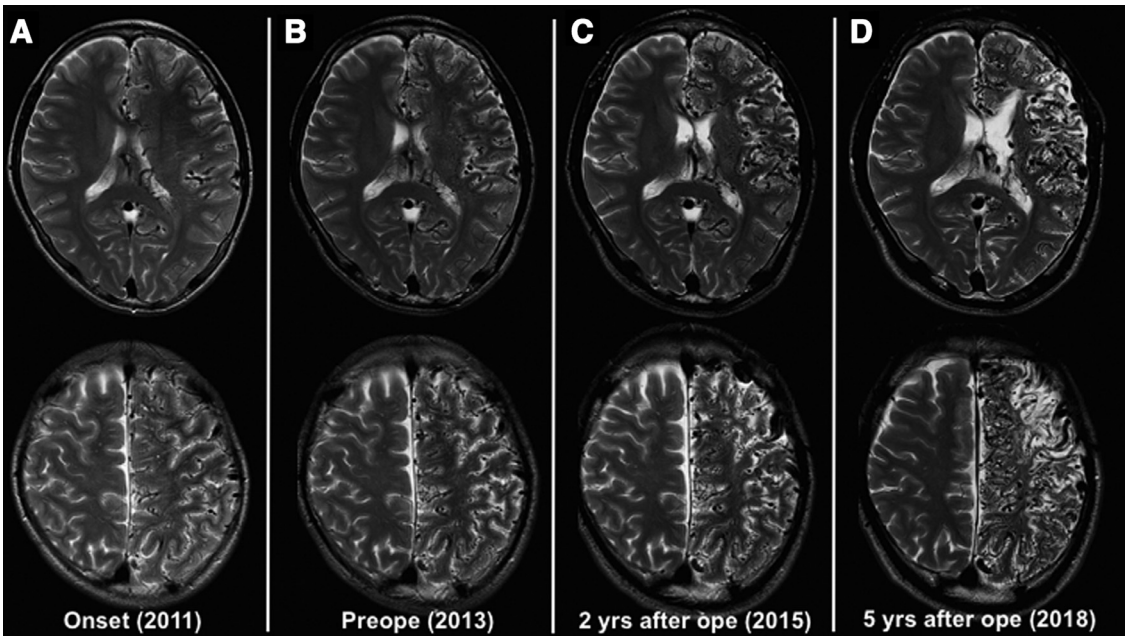

Figure 1. *Axial T2-weighted images at onset in 2011 (A); at preoperative state in 2013 (B); 2 years after indirect revascularization in 2015 (C); 5 years after indirect revascularization in 2018 (D). Progressive vascular proliferation and brain atrophy were found.*

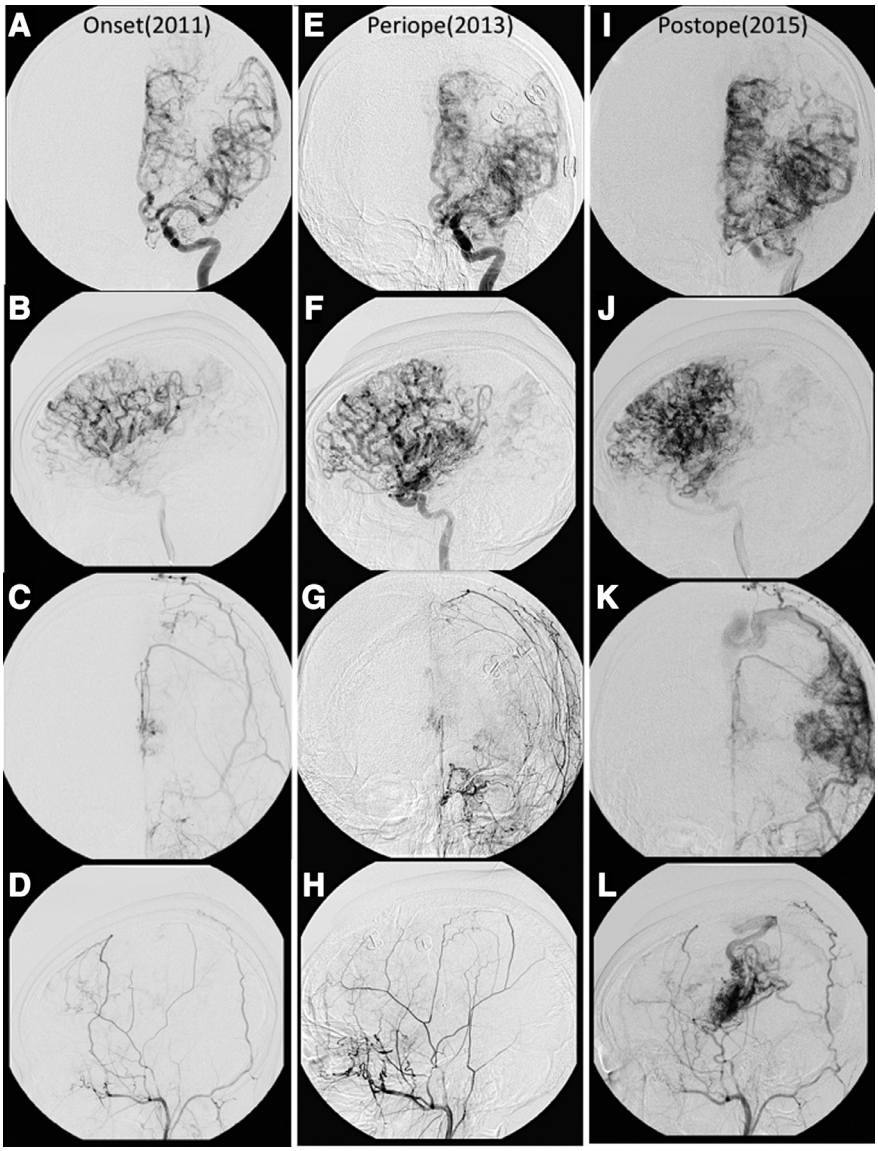

Figure 2. *Angiography studies of the left ICA (A, B) and left ECA (C, D) obtained at onset in 2011. Six-vessel catheter angiography revealed a large hypervascular lesion with diffuse arterial supplies. The early venous fillings, flow-related aneurysms, and main arterial stenosis were not identified.*

Angiography studies of the left ICA (E, F) and left ECA (G, H) obtained 7 days after indirect revascularization in 2013. Prominent vascular malformations were found via left ICA angiography, but early venous fillings, flow-related aneurysms, and main arterial stenosis were not identified.

Angiography studies of the left ICA (I, J) and left ECA (K, L) obtained 2 years after indirect revascularization in 2015. Vascular malformation became more prominent. A part of the vascular lesion in left parietal lobe followed by the early venous filling (arrow) were found via left ECA angiography. Abbreviations: ICA; ECA, external carotid artery.

Figure 4. The dissected STA was placed on the pial surface of the brain. The dura matter was closed with galea and temporal fascia. There were no complications.

Postoperative Course

Cerebral angiography, performed 7 days after indirect revascularization (in 2013), revealed more prominent vascular proliferation via left internal carotid artery (ICA) angiography. However, early venous filling, flow-related aneurysms, and main arterial stenosis were not found (Fig 2, E-H). The patient did not present any neurological aggravation during the first year of the follow-up period after the operation. However, 2 years after surgery, his right hemiparesis and motor aphasia had gradually aggravated, and neuropsychological testing revealed a further decrease in IQ score to 60. MRI showed more progressed proliferation of the vascular lesions and brain atrophy (Fig 1, C,D). In addition, a small asymptomatic intracerebral hemorrhage was observed in left frontal lobe (Fig 5, arrow). Cerebral angiography, performed 2 years after indirect revascularization (in 2015), revealed a more intense hypervascular malformation with diffuse arterial supplies. A part of the vascular lesion in left parietal lobe,

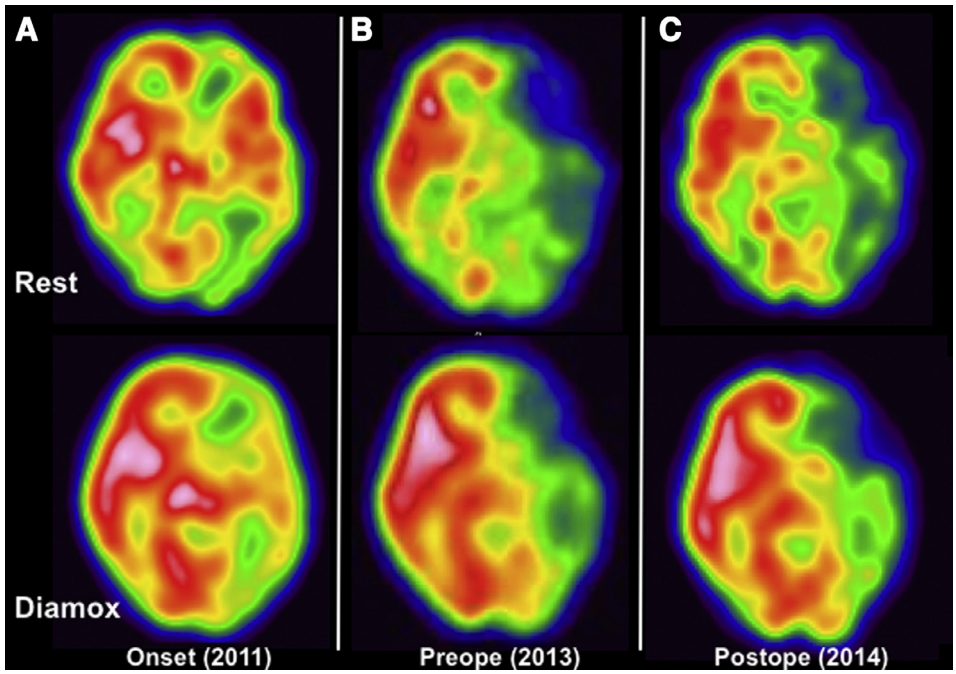

Figure 3. *^{123}I-IMP-SPECT studies at onset in 2011 (A); at preoperative state in 2013 (B); and 1 year after indirect revascularization in 2014 (C). Resting studies are shown in the upper row, and acetazolamide-stress studies are shown in the lower row. Progressive severely impaired CBF and CVR were found 2 years after onset, and were not improved after indirect revascularization. Abbreviations: ^{123}I-IMP-SPECT, [^{123}I] iodoamphetamine single-photon emission computed tomography; CBF, cerebral blood flow; CVR, cerebrovascular reactivity.*

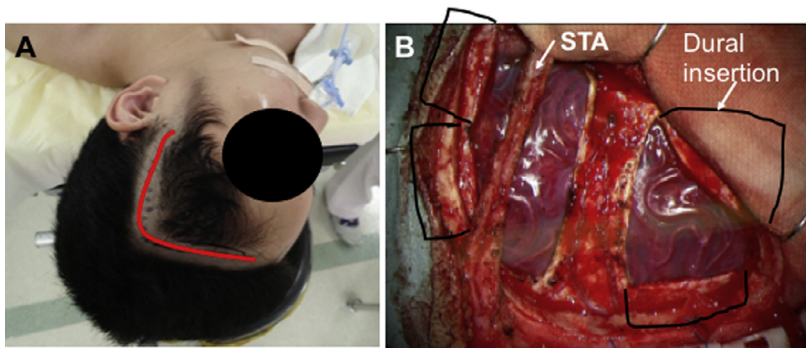

Figure 4. *A: A red line shows the skin incision. B: Intraoperative view. The dura was inserted in the brain surface (black lines). Abnormally dilated vessels were found on the brain surface. (Color version of figure is available online.)*

which had been supplied by left ICA in 2011 and 2013, was supplied by left STA via left external carotid artery angiography, which was the result of EDAS. In addition, early venous filling mainly supplied by left STA was newly observed, suggesting that indirect revascularization resulted in (A-V) shunts via EC-IC bypass (Fig 2, E-H). Flow-related aneurysms and main arterial stenosis were not found. Resting and acetazolamide-stressed ^{123}I-IMP-SPECT did not show improved CBF and CVR after surgery (Fig 3, C). We treat the patient conservatively after indirect revascularization.

Discussion

There are only a few reports that describe treatments for patients with CPA. Because hemorrhagic presentations are exceptional and a transient cerebral ischemia is a nature of this disease, we selected conservative therapy at onset. However, 2 years after onset, the patient's hand-grip strength and motor aphasia worsened, and neuropsychological testing revealed a marked decrease in IQ score from 102 to 76. In addition, resting and acetazolamide-stressed ^{123}I-IMP-SPECT demonstrated more severely decreased CBF and impaired CVR over the affected hemisphere. Thus, we decided to perform indirect revascularization to augment flow to the compromised hemisphere.

Lasjaunias et al described that one of the major pathomechanisms of CPA was ischemia (which in itself is probably multifactorial owing to incompetent angiogenesis, steal phenomena, arterial stenosis, and capillary wall involvement), and a therapy that enhanced cortical blood supply could be indicated.[4] To our knowledge, there are only 6 reports on

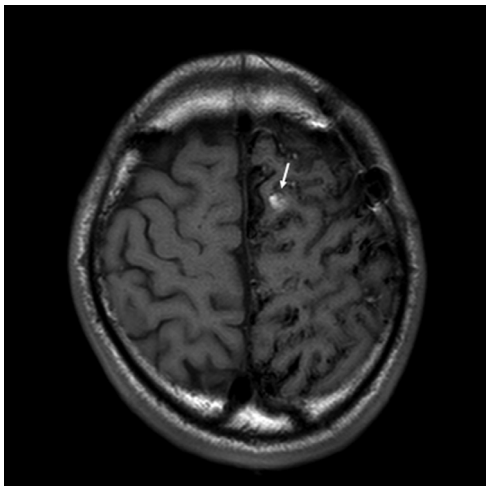

Figure 5. *Axial T1-weighted images at 2 years after indirect revascularization in 2015. A small intracerebral hemorrhage was found in left frontal lobe (arrow).*

CPA that was treated to improve cerebral hypoperfusion.[2-7] All 6 reports described indirect revascularization such as calvarial burr holes, pial synangiosis, EMS, dural inversion, and EDAS for hypoperfused cortex. Five reports among 6 demonstrated favorable outcome. One case, an 8-year-old boy with CPA, underwent pial synangiosis and EMS; nevertheless, he developed a permanent hemiparesis with progressive gait disturbance[6] as a natural course of CPA. These previous reports are summarized in Table 1. Our case also showed neurological aggravation after indirect revascularization with newly developed A-V shunts via EC-IC bypass and asymptomatic intracerebral hemorrhage. The patient's neurological aggravation is probably due to the progressive natural course of CPA, but there are no reports on CPA which showed cerebral hemorrhage after indirect revascularization. It is not clear why hemorrhagic presentation of this patient occurred. One speculation is due to a natural course of CPA, and the other is due to hemodynamic changes occurred in the affected hemisphere via newly developed EC-IC bypass, followed by intracerebral hemorrhage.

Several reports suggest that some selected patients may benefit from a procedure to enhance blood supply to the hypoperfused cortex and prevent further neurological aggravation. However, it is not clear which patients benefit from indirect revascularization. We have the following 2 speculations which affect the benefit to patients: 1 is the cause for cerebral ischemia. There are mainly 2 causes for the cerebral ischemia on CPA: stenosis of the proximal arteries and arterial steal. Our patient did not show any stenosis of the proximal arteries, suggesting the reason for cerebral ischemia was arterial steal due to the large vascular malformation. According to the previous reports shown in Table 1, cases without stenosis of the proximal arteries may not benefit from indirect revascularization. The other cause is relationship of the location of the vascular malformation and indirect revascularization. We performed indirect revascularization over the

Table 1. *Summary of literature cases of CPA with revascularization*

Authors (year)	No. of cases	Sex/age at surgery	Symptoms	Arterial stenosis	Progression of CPA	Surgery	Surgical benefit
Lasjaunias et al in 2008	2	NA	HA	NA	NA	Burr holes	+
Ellis et al in 2011	1	4/F	Hemiparesis	NA	+	EMS, pial synangiosis	+
Kono et al in 2014	1	33/M	Decreased hand-grip strength	–	+	EDAS	+
Sakata et al in 2016	1	8/M	TIA, IVH	+	+	Targeted embolization burr holes	+
Liu et al in 2016	1	36/M	TIA, HA	+	NA	EDAS	+
Puerta et al in 2017	1	8/M	TIA, HA papilledema	–	+	Pial synangiosis	–
Our case	1	15/M	Hemiparesis HA, decreased IQ	–	+	EMS, EDAS	–

Abbreviations: CPA, cerebral proliferative angiopathy; EDAS, encephaloduroarteriosynangiosis; EMS, encephalomyosynangiosis; HA, headache; IVH, intraventricular hemorrhage; NA, not available; TIA, transient ischemic attack.

vascular malformation because decreased CBF was prominent in this area. However, new A-V shunts via EC-IC bypass developed. In cases with vascular malformation on the brain surface, indirect revascularization for this hypervascularized brain surface may not be effective and can result in new A-V shunts via EC-IC bypass. Marks et al reported a markedly elevated level of vascular endothelial growth factor and basic fibroblast growth factor in the CSF with normal plasma levels.[8] These factors are thought to be implicated in the angiogenesis occurring in brain A-V malformations.[9-11] The authors tried bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor, in the hope that it would alter the vascular proliferation process, but without favorable outcome. Because the angiogenesis tends to occur in CPA as well, it is difficult to predict whether indirect revascularization can be effective. From the point of view of hemorrhage, Maekawa et al suggested that revascularization surgery for CPA may attenuate the vascular proliferation in the vicinity of the ventricle and prevent periventricular hemorrhage.[12] They discussed that vulnerable collateral vessels developed in response to cerebral ischemia were the supposed culprit of intraventricular bleeding like moyamoya disease, and might prevent bleeding. However, more cases are needed to establish management for CPA.

In conclusion, we have presented a patient with CPA who showed progressive cerebral ischemia over a 2-year period, with indirect revascularization followed by the development of EC-IC A-V shunts and intracerebral hemorrhage. It is questionable whether an indirect revascularization for CPA-related cerebral hypoperfusion is reasonable. But it seems to be possible that cases with severe stenosis of the proximal arteries may benefit from indirect revascularization. Further, restricted surgical indication should be confirmed and long-term follow-up is necessary to evaluate the effects of indirect revascularization for patients with CPA.

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