

Encephaloduroarteriosynangiosis for cerebral proliferative angiopathy with cerebral ischemia

Case report

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Cerebral proliferative angiopathy (CPA) is a rare clinical entity. This disorder is characterized by diffuse vascular abnormalities with intermingled normal brain parenchyma, and is differentiated from classic arteriovenous malformations. The management of CPA in patients presenting with nonhemorrhagic neurological deficits due to cerebral ischemia is challenging and controversial. The authors report a case of adult CPA with cerebral ischemia in which neurological deficits were improved after encephaloduroarteriosynangiosis (EDAS).

A 28-year-old man presented with epilepsy. Magnetic resonance imaging and angiography showed a diffuse vascular network (CPA) in the right hemisphere. Antiepileptic medications were administered. Four years after the initial onset of epilepsy, the patient's left-hand grip strength gradually decreased over the course of 1 year. The MRI studies showed no infarcts, but technetium-99m-labeled ethyl cysteinate dimer (^{99m}Tc-ECD) SPECT studies obtained with acetazolamide challenge demonstrated hypoperfusion and severely impaired cerebrovascular reactivity over the affected hemisphere. This suggested that the patient's neurological deficits were associated with cerebral ischemia. The authors performed EDAS for cerebral ischemia, and the patient's hand grip strength gradually improved after the operation. Follow-up angiography studies obtained 7 months after the operation showed profound neovascularization through the superficial temporal artery and the middle meningeal artery. A SPECT study showed slight improvement of hypoperfusion at the focal region around the right motor area, indicating clinical improvement from the operation. The authors conclude that EDAS may be a treatment option for CPA-related hypoperfusion.
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KEY WORDS • arteriovenous malformation • cerebral ischemia • cerebral proliferative angiopathy • encephaloduroarteriosynangiosis • epilepsy • vascular disorders

CEREBRAL proliferative angiopathy (CPA) is a rare clinical entity characterized by diffuse vascular abnormalities with intermingled normal brain parenchyma. This entity is distinguished from cerebral arteriovenous malformations (AVMs) by clinical, angiographic, and histopathological features.¹⁰ Patients with CPA commonly present with epileptic manifestations, headaches, and progressive neurological deficits due to ischemia with vascular steal. Treatments for CPA are challenging and controversial,¹⁰ and there are only a few detailed reports on the treatment of CPA with cerebral ischemia.^{4,12} We report the first case of adult CPA with cerebral ischemia successfully treated by encephaloduroarteriosynangiosis (EDAS).

Abbreviations used in this paper: AVM = arteriovenous malformation; CPA = cerebral proliferative angiopathy; ECA = external carotid artery; EDAS = encephaloduroarteriosynangiosis; ICA = internal cerebral artery; STA = superficial temporal artery; ^{99m}Tc-ECD = technetium-99m-labeled ethyl cysteinate dimer; VEGF = vascular endothelial growth factor.

Case Report

History, Examination, and Initial Treatment. A 28-year-old man presented with epilepsy in 2008. The patient suffered from simple partial seizures with jerking of the left upper and lower extremities for 1–10 minutes. An electroencephalogram obtained at nonepileptic status showed 9- to 10-Hz waves, no spikes, and no epileptic discharge. On MRI, contrast-enhanced CT, and conventional angiography studies, a diffuse vascular network was shown in the right frontal and parietal lobes (Figs. 1–3). There was no evident transdural supply from the right external carotid artery (ECA), whereas transdural supply through the anterior falx cerebri from the left ECA was observed. The margin of the nidus was not identifiable. Therefore, we diagnosed this vascular malformation as CPA. Epilepsy was controlled by antiepileptic medications.

Later Presentation. Four years after the initial onset of epilepsy, the patient's left-hand grip strength gradually decreased from 60 kg to 0 kg in the course of 1

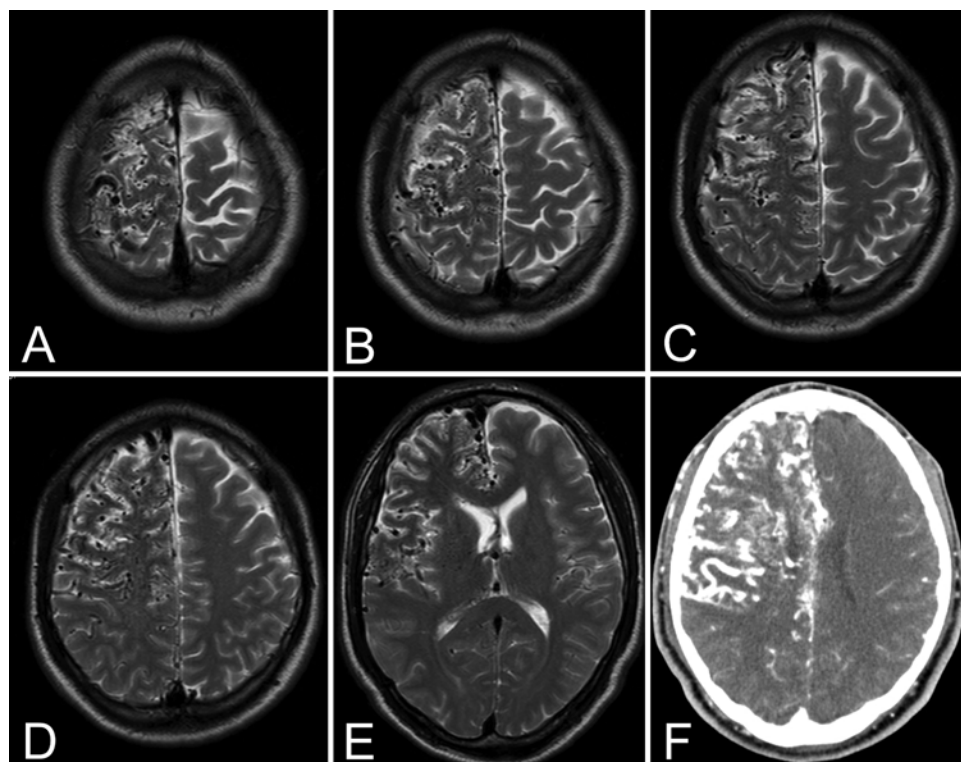


FIG. 1. A–E: Axial T2-weighted MRI studies show intraparenchymal flow voids in the right frontal and parietal lobes. F: Contrast-enhanced CT scan shows dilated vessels in the right frontal and parietal lobes.

year. In 2013, the patient could not move his left fingers to any degree. This neurological deficit was localized in his grip, and he had no arm weakness or sensory disturbance. The MRI sequences showed no infarcts (Fig. 4). Angiography studies obtained in 2013 demonstrated that

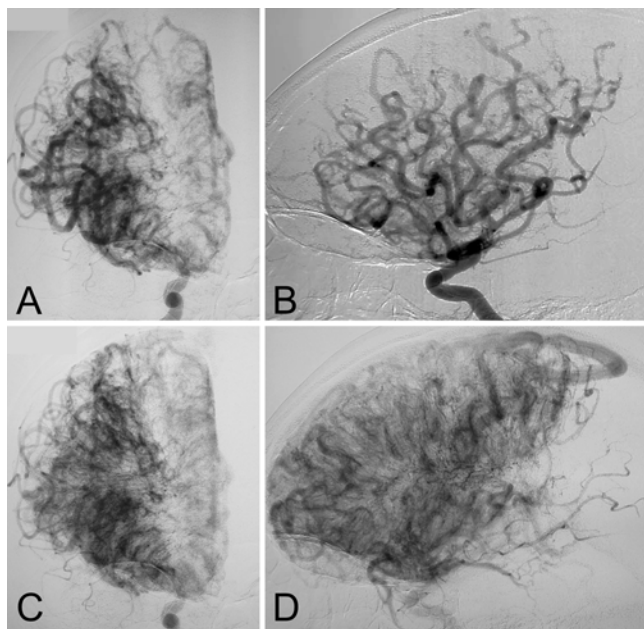


FIG. 2. Angiography studies of the right ICA obtained in 2008. The arterial phase (A and B) and capillary phase (C and D) are shown. Diffuse vascular malformation can be seen in the right frontal and parietal lobes.

a fuzzy nidus became denser around the precentral region (Fig. 5). A technetium-99m-labeled ethyl cysteinate dimer (^{99m}Tc -ECD) SPECT study demonstrated hypoperfusion and severely impaired cerebrovascular reactivity both without and with an acetazolamide challenge test over the affected hemisphere (Fig. 6 left). These imaging studies showed that cerebral ischemia caused the patient's neurological deficits. Although the patient kept working, the neurological deficits caused him inconvenience in his daily life.

Operation. We elected to perform EDAS because of the possibility of a progressive ischemic course in the future and because we anticipated recovery of the neurological deficits. The right parietal branch of the superficial temporal artery (STA) was dissected free from surrounding tissues. The skull was opened over the precentral region. The dura mater incision was as large as possible because there was no transdural supply on the right side. A surgical view of the brain surface of this patient with CPA is shown in Fig. 7. Dilated vessels passed through the brain surface and sulci. The dissected STA was placed on the pial surface of the brain and sutured with the dura. There were no complications.

Postoperative Course. The patient kept working and did not undergo any rehabilitation. The patient's hand grip strength improved to 5 kg 2 months after the operation. Follow-up angiography studies obtained 7 months after the operation showed profound neovascularization via the ECA (Fig. 8). A follow-up ^{99m}Tc -ECD SPECT study showed slight improvement of hypoperfusion at the fo-

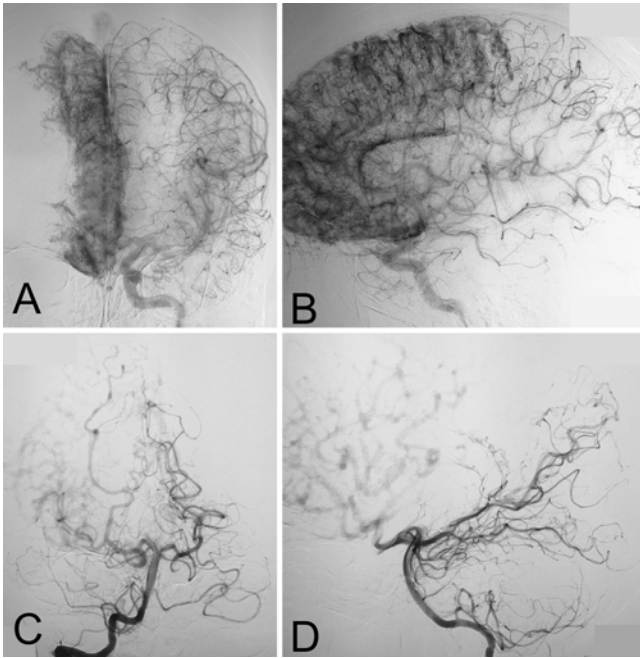


FIG. 3. **A and B:** Angiography studies of the left ICA obtained in 2008 show diffuse vascular malformation in the territory of the right anterior cerebral artery. **C and D:** Angiography studies of the left vertebral artery obtained in 2008 show vascular malformation through the right posterior communicating artery.

cal region around the right motor area (Fig. 6 right). The neurological deficits had not worsened, and the patient's grip strength was maintained at 5 kg during 9 months of the follow-up period. Inconvenience in his daily life was diminished.

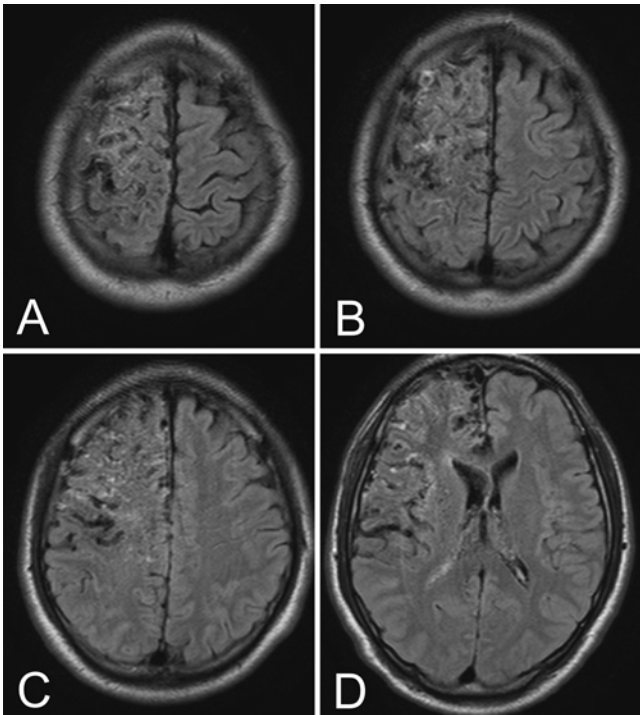


FIG. 4. Axial FLAIR MRI studies obtained in 2013 show no infarcts.

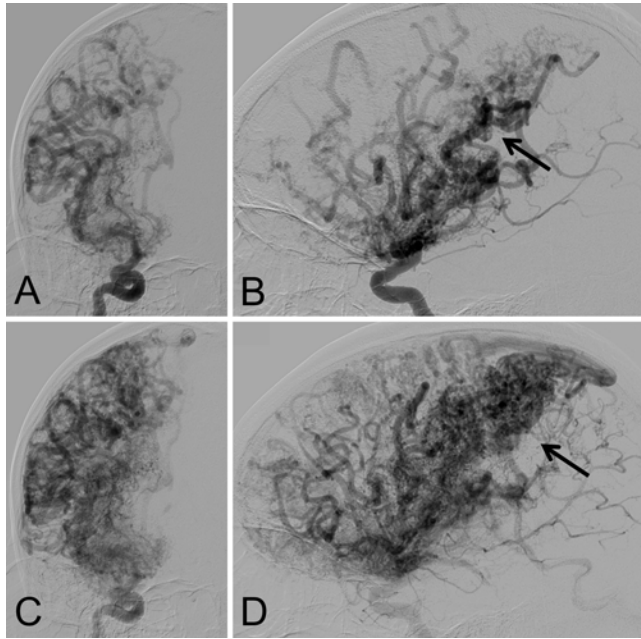


FIG. 5. Angiography studies of the right ICA obtained in 2013. The arterial phase (**A and B**) and capillary phase (**C and D**) are shown. In the course of 5 years, the precentral artery and shunts around the precentral region became prominent (arrows in **B** and **D**).

Discussion

Cerebral proliferative angiopathy is a different clinical entity from AVMs. There have been several case reports on patients with CPA,^{1-9,11,12,15} and one series of 49 patients with this disorder.¹⁰ In that study of 49 patients (mean age 22 years), 45% presented with seizures, 41% with severe and often disabling headaches, 12% with hemorrhage, and 16% with nonhemorrhagic neurological deficits. These cases were characterized angiographically by diffuse, often large vascular malformations with an absence of dominant arterial feeders, frequently of transdural supply. Patients with CPA usually do not present with acute neurological deficits or hemorrhage, but more commonly present with epileptic manifestations, headaches, and progressive neurological deficits. Our patient also presented with epilepsy and progressive neurologi-

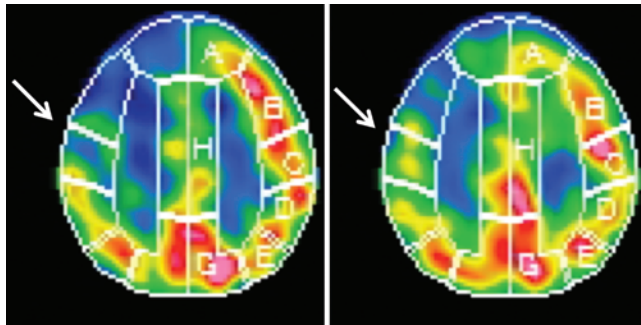


FIG. 6. **Left:** Axial ^{99m}Tc-ECD SPECT study obtained without acetazolamide challenge demonstrates hypoperfusion over the affected hemisphere (arrow) just before the surgical treatment in 2013. **Right:** Seven months after the surgery, an axial ^{99m}Tc-ECD SPECT study obtained without an acetazolamide challenge demonstrates slight improvement of hypoperfusion around the motor area (arrow).

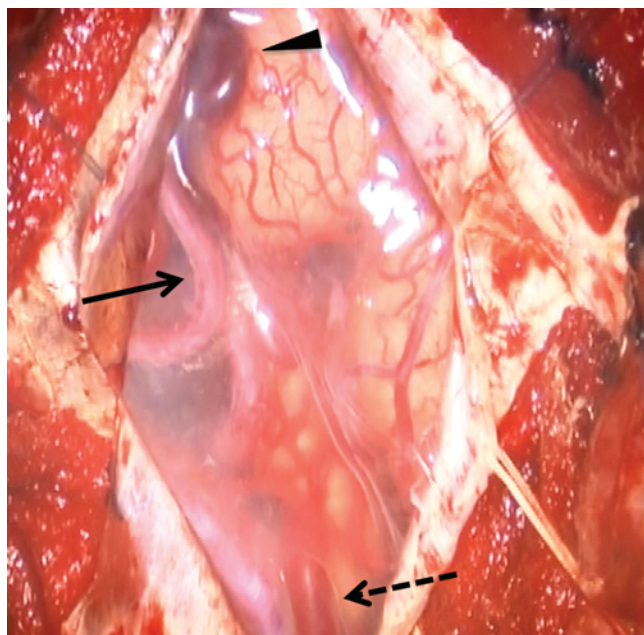


FIG. 7. Intraoperative view. The dura was opened, and brain parenchyma and vessels were observed. Abnormally large-diameter vessels are present on the surface of the brain and sulci. Dilated arteries (arrow), red draining veins (dashed arrow), and dilated non-draining veins (arrowhead) can be seen.

cal deficits. Although the risk of initial hemorrhage is low with CPA, the chance of rebleeding may be higher than in patients with normal brain AVMs.¹⁰ Although hemorrhage is usually not fatal, a single case report has described a patient with CPA who died as a result of the initial hemorrhage.¹¹

In the series of 49 patients with CPA,¹⁰ selected patients underwent perfusion-weighted MRI, which showed CPA-related cerebral hypoperfusion. Treatment indications were strictly specified, and were confined to hemorrhage, uncontrollable seizures, and disabling headaches. Partial targeted embolization using glue, preferably in noneloquent areas, was performed in 23 patients. In 2 (9%) of the treated patients new neurological deficits occurred, presumably due to the presence of normal neurological tissue interspersed with embolized vessels. Because of the ischemic nature of this disease, the investigators suggested that selected patients may benefit from treatments that enhance blood flow. Calvarial bur hole treatment was performed in 2 patients, and disabling headaches disappeared after treatment. However, there were no descriptions of treatments for CPA with neurological deficits due to cerebral ischemia.

Several studies in which perfusion-weighted MRI or SPECT was used have shown that cerebrovascular reserve is severely impaired in patients with CPA.^{5,9,10,15} In addition, angiographically and clinically progressive features have been reported, indicating the progressive nature of CPA.^{10,12} These features are similar to those of moyamoya disease, which is an idiopathic, noninflammatory vasculopathy characterized by progressive stenosis or occlusion of the supraclinoid internal cerebral arteries (ICAs).¹⁴ Patients with moyamoya disease who pre-

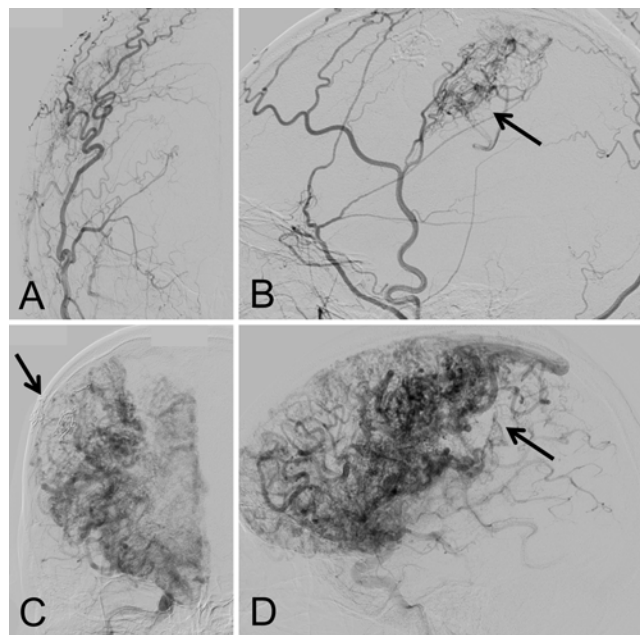


FIG. 8. Follow-up angiography studies obtained 7 months after the operation. **A and B:** Angiograms of the right ECA show profound revascularization through the STA and middle meningeal artery (arrow in B). **C and D:** Angiograms of the right ICA show the disappearance of vascular malformation around the region supplied from the ECA (arrows in C and D).

sent with recurrent ischemic events in the presence of impaired cerebrovascular reactivity are often considered for surgical treatment.¹³ Direct and indirect revascularization techniques are common treatments for enhancing blood flow to the hypoperfused brain. Whereas adults are often treated with a direct STA–middle cerebral artery bypass, indirect revascularization is often used in children. These similarities between CPA and moyamoya disease led to the idea that the same treatments might be applied to CPA with cerebral ischemia.

There are only two detailed case reports on CPA that was treated to improve hypoperfusion.^{4,12} In one case, a 2-year-old girl with CPA suffered from an acute infarct and was treated with pial synangiosis.⁴ Although no imaging studies for cerebral perfusion were performed, the authors considered that the patient had impaired cerebrovascular reserve. To prevent future ischemic events, the patient underwent pial synangiosis. An angiogram obtained 8 months after the operation showed robust revascularization supplied from the ECA. The patient had sustained no further transient neurological deficits. In our case, although the patient was an adult, direct revascularization was technically difficult because of diffuse and enlarged vessels running on the brain surface (Fig. 7). Furthermore, determining which superficial artery would be an appropriate recipient for direct revascularization was difficult. Therefore, we performed indirect revascularization (EDAS) for our adult patient. A SPECT study obtained after the operation showed slight improvement of hypoperfusion. This is consistent with clinical improvement of symptoms and angiographically confirmed neovascularization.

In the other case report on the treatment of CPA with cerebral ischemia, a patient in their early 30s was treated with partial embolization and bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor (VEGF).¹² The patient showed angiographic and clinical progression with cerebral ischemia. This patient was also found to have a markedly elevated level of VEGF in the CSF. The patient underwent partial embolization, but continued to decline neurologically. Treatment with bevacizumab was performed, but no improvement of neurological deficits was observed. In our case, we considered that partial embolization to reduce shunting and improve hypoperfusion would have a certain risk of ischemic complications because normal brain tissue might be embolized. The EDAS procedure probably has a lower risk of complications compared with targeted embolization. Although we did not measure VEGF levels in our patient, these might have been elevated, which might promote neovascularization, even in an adult patient.

Although long-term follow-up is necessary to evaluate the effects and durability of EDAS in our patient, the neurological deficits, notably, were improved after EDAS because of neovascularization. An EDAS procedure for CPA-related hypoperfusion may be a reasonable treatment option because there are currently no other appropriate treatments.

Disclosure

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Acquisition of data: Kono. Analysis and interpretation of data: Kono. Drafting the article: Kono. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Kono. Study supervision: Terada.

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