

Acquired cerebral arteriovenous malformation in a child with moyamoya disease

Case report

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✓ The authors report a unique case involving a 2-year-old child with idiopathic moyamoya disease who presented with cerebral infarctions and seizures. On initial evaluation, computerized tomography (CT) showed a left parietal infarct and angiograms demonstrated early moyamoya disease with no evidence of arteriovenous malformation (AVM). Approximately 9 years later, angiography and magnetic resonance (MR) imaging revealed an AVM centered on the same region of the left parietal lobe. Angiographic, CT, and MR images are presented that demonstrate the progression of moyamoya disease and *de novo* development of the AVM in the infarct site. The possible role of angiogenesis in the etiology of acquired AVMs and moyamoya disease is discussed.

KEY WORDS • moyamoya disease • cerebral arteriovenous malformation • stroke

MOYAMOYA disease is an uncommon cerebrovascular disease characterized by bilateral stenosis or occlusion involving the arteries of the circle of Willis with an abnormal network of fine collateral vessels at the base of the brain.¹⁵ The disease is idiopathic and has a characteristic pattern of progression.² Affected children typically present with seizures, transient ischemic attacks, and infarctions, whereas adults tend to present with cerebral hemorrhage.^{10,15,18,19} Intellectual and neurological deterioration increases with time. Unfortunately, no cure has yet been found; however, surgical therapies have been developed.^{10,15,17} The etiology and pathology of moyamoya disease remain unknown, although recent reports have shown increased angiogenic factors in the cerebrospinal fluid (CSF),²⁰ superficial temporal artery (STA), and dura of patients with moyamoya disease.⁶ Histological and pathological examination of the occlusive lesions have shown the dominant lesion to be fibrocellular intimal thickening with laminated and reduplicated elastic lamina.^{7,22} Lipid deposits and microthrombi are usually absent.¹¹ We report a child with moyamoya disease who presented with a cerebral infarction and later developed an arteriovenous malformation (AVM) in the infarct site. Our case raises interesting questions about the etiology of AVMs and moyamoya disease and the role of angiogenesis in these diseases.

Case Report

This 2-year and 9-month-old right-handed boy presented with right arm and leg weakness. The child was the

product of a normal pregnancy with caesarean section delivery at term because of failure of labor to progress. The parents have no known neurological disease.

Examination. On initial admission the patient was found by computerized tomography (CT) scanning to have a left frontal infarction; a left internal carotid angiogram showed stenosis of the left middle cerebral artery (MCA) with transthalamic and leptomeningeal collateral vessels. The child was started on a course of prednisone for a tentative diagnosis of vasculitis and was sent home with

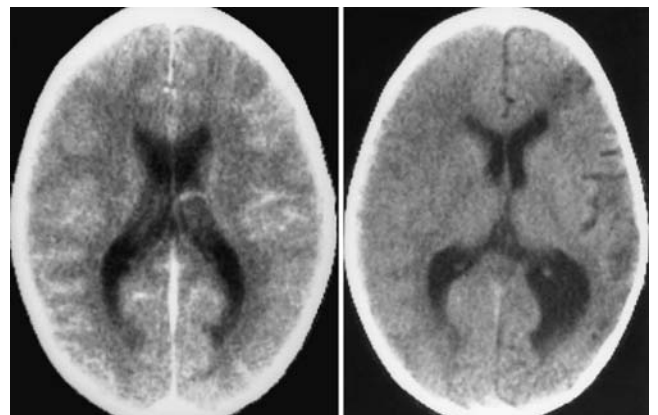


FIG. 1. Axial computerized tomography images with (left) and without (right) contrast enhancement obtained in a 3-year-old boy, 4 months after the initial presentation, showing left frontal and parietal infarcts.

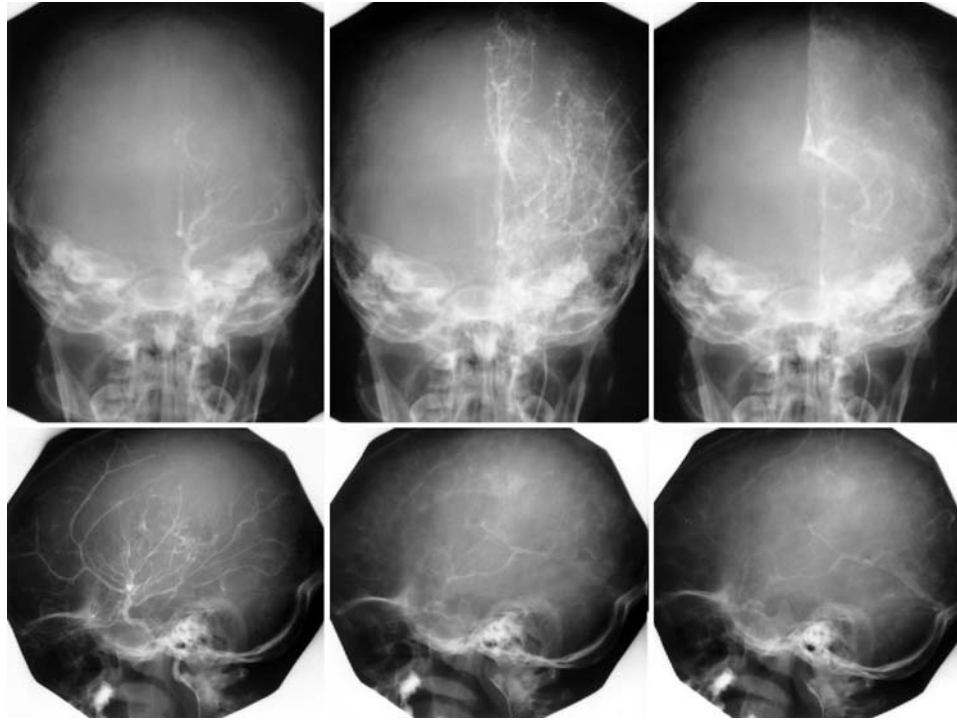


FIG. 2. Left internal carotid arteriograms obtained in a 3-year-old boy. *Upper Left:* Frontal projection, arterial phase demonstrating severe stenosis of the left middle cerebral artery and A_1 segment with transthalamic collateral vessels. *Upper Center:* Late-arterial phase demonstrating additional leptomeningeal collateral vessels but showing no early venous opacification. *Upper Right:* Venous phase demonstrating opacification of normal deep veins. *Lower Left:* Lateral projection, arterial phase showing arterial collateral vessels without arteriovenous shunting. *Lower Center and Right:* Early- and late-venous phase demonstrating no early venous filling.

improving symptoms. Routine analysis of CSF and blood was normal. Electrocardiogram and echocardiogram were also normal.

Second Admission. Four months later, the patient presented with seizures affecting the right side of his body,

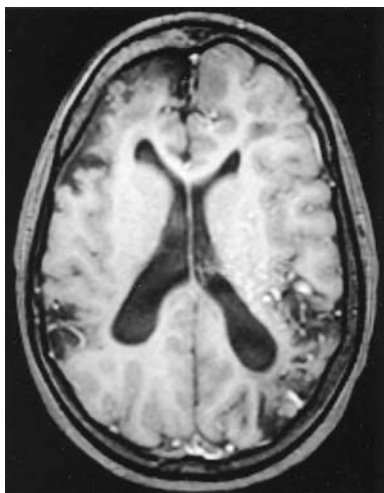


FIG. 3. Axial T_1 -weighted nonenhanced magnetic resonance image obtained in the same boy at age 11 years, suggesting an arteriovenous malformation in the same region as the infarct in Fig. 1.

and a repeat CT scan showed a new left parietal infarct adjacent to the occipital horn of the lateral ventricle (Fig. 1). He was started on a course of antiseizure medication (Tegretol and Dilantin). Bilateral internal carotid arteriograms (Fig. 2) performed at this time showed progression of the left MCA stenosis and stenosis of the A_1 segment of the left anterior cerebral artery (ACA), with increased prominence of the transthalamic and leptomeningeal collateral vessels. Severe stenosis of the right MCA and ACA with collateral vessels was also demonstrated and the diagnosis of moyamoya disease was made. No early-venous shunting was found. The patient returned 2 months later with left-sided weakness and seizures. Computerized tomography showed progressive bilateral cerebral atrophy, and the patient was started on a course of aspirin. Over the next 9 years, the seizures resolved with medical management and no further strokes occurred.

Subsequent Examination. At age 11, the patient was reevaluated for possible surgical intervention. Radionuclide brain scanning (technetium-99m hexamethylpropyleneamineoxime with single-photon emission CT) showed areas of markedly decreased or absent perfusion involving the left temporal, right frontal, and parietal lobes bilaterally. Magnetic resonance imaging showed multiple bilateral infarcts with transthalamic collateral vessels and unexpectedly prominent vascular channels in the left posterior parietal region suggesting an AVM at the level of the occipital horn (Fig. 3), in the same region in

Acquired AVM in moyamoya disease

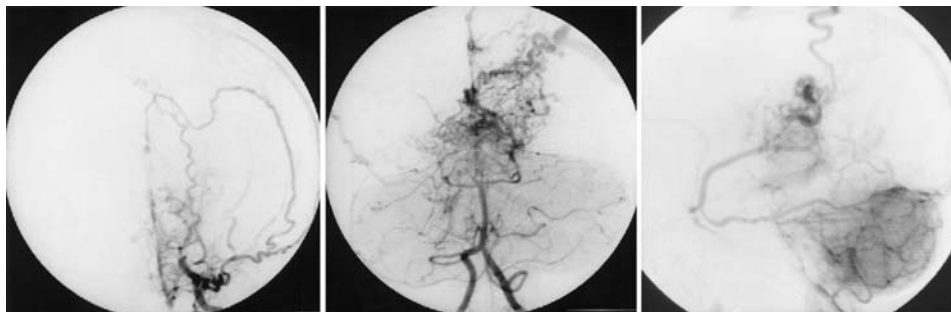


FIG. 4. Cerebral angiography performed in the patient at age 11 years. *Left:* Left internal carotid arteriogram, frontal projection, demonstrating occlusion of the left middle and anterior cerebral arteries with meningeal collateral vessels. *Center:* Left vertebral arteriogram, frontal projection, showing occlusion of both posterior cerebral arteries and transthalamic collateral vessels supplying an arteriovenous malformation in the left parietal lobe. *Right:* Left vertebral arteriogram, lateral projection, early-venous phase, demonstrating early opacification of the vein of Trolard, which was not visible on the angiograms obtained when the patient was 3 years old.

which the previous CT showed an infarct (see Fig. 1). Angiography revealed bilateral internal carotid artery (ICA) occlusion above the ophthalmic arteries with transdural collateral vessels from the middle meningeal artery (Fig. 4). The posterior cerebral arteries were also occluded with a dense network of collateral veins at the base of the brain. Extending from this collateral network, in the left parietal lobe adjacent to the occipital horn, was a wedge-shaped plexiform network of vessels shunting into the left vein of Trolard. This confirmed the diagnosis of cerebral AVM, which was not seen on the early angiograms or the early CT scans. Furthermore, the location of the AVM on both MR imaging and angiography correlated precisely with the location of the previous left parietal infarction seen on the early CT scan.

Discussion

This remarkable case documents the *de novo* development of a cerebral AVM in the exact location of a previous infarct in a child with moyamoya disease. No other published case of an acquired cerebral AVM is known to these authors. As cerebral infarction is common but subsequent AVM development is not, we speculate that the etiological process of vascular obstructions and collateral artery formation in moyamoya disease may have played a role in the formation of this patient's AVM.

Other authors have previously described an association of AVM and moyamoya disease.^{8,12,13} These reports describe patients in whom the AVM was present initially, indicating that the moyamoya phenomenon was a secondary process. Indeed, in those patients who had sequential angiographic examinations, ICA obstruction and collateral vessels were shown to develop after diagnosis of the AVM. Mawad, *et al.*,¹² hypothesized that the increased blood flow through the AVM causes turbulent flow at the carotid bifurcation leading to focal intimal hyperplasia with subsequent ICA stenosis and the development of "acquired" moyamoya phenomenon. In our case, the moyamoya disease and infarction both preceded the AVM development.

Angiogenesis is the process of new vessel formation that normally occurs during growth, healing, and fetal life,

but then remains quiescent.⁴ The process of angiogenesis was described by Ausprunk and Folkman¹ and involves the sprouting of capillaries, mainly from small venules. Local basement membrane degradation of the parent venule is followed by migration of endothelial cells toward the angiogenic stimulus. These endothelial cells form a solid sprout with subsequent luminization that occurs through the curving of each individual cell. Two hollow sprouts form a loop by joining at the tip and circulation can then begin. Basic fibroblast growth factor (bFGF) is a known angiogenic factor found in many cell lines, including brain and macrophages⁴ as well as endothelium and smooth-muscle cells.^{5,6,16,21} Basic fibroblast growth factor is a powerful mitogen for fibroblasts, vascular endothelium, and smooth-muscle cells.^{3,4,9}

The exuberant collateral formation and the intimal hyperplasia found in patients with moyamoya disease suggest enhanced angiogenesis. Takahashi, *et al.*,²⁰ reported significantly increased levels of bFGF in the CSF of patients with moyamoya disease, compared with patients with atherosclerotic occlusive disease. Hoshimaru, *et al.*,⁶ used immunohistochemical techniques to assay for bFGF in the STA and dura of four patients with moyamoya disease. They found intense staining in the intima and media of the STA. There was also intense staining in the meningeal and vascular cells of the dura.

The elevated levels of bFGF in these arterial tissues should be accompanied by cellular evidence of angiogenesis. Histologically, there should be migrating and proliferating target cells such as smooth-muscle cells. Masuda, *et al.*,¹¹ used immunohistochemical techniques to demonstrate that the intimal hyperplasia found in intracranial lesions of six moyamoya patients was predominantly composed of smooth-muscle cells with scattered macrophages and T cells. Furthermore, the nuclear and cytoplasmic markers indicated these smooth-muscle cells were actively proliferating.

Angiogenesis is known to be stimulated by brain injury, tumor, or inflammation.⁴ In a rat model of surgically induced cerebral infarction,² bFGF expression was increased after 1 day in the periinfarct neurons. This was followed by capillary proliferation that peaked 3 to 6 days after the infarct. Increased bFGF production was also seen

in macrophages recruited to the infarct area and in the surrounding endothelial cells and reactive glial cells. Chen, *et al.*,² suggested that angiogenesis in the infarct may be initiated by neuronal derived bFGF and sustained by bFGF production from endothelial cells, macrophages, and glial cells.

Recent angiogenic studies in rat models have shown that intraventricular injection of bFGF resulted in periventricular capillary proliferation.¹⁴ This angiogenic effect was increased when mild cerebral ischemia was induced via bilateral carotid ligation.⁹ Cuevas, *et al.*,³ directly applied bFGF to the cerebral cortex of rats and demonstrated large-caliber vessels forming a tortuous network at the site of bFGF application. Some of these vessels extended long distances into the cerebral cortex and had disorganized, bizarre vessel architecture. New vessel sproutings included dilation, extensive capillary networking, and neovascular sprouts. Cuevas and colleagues recognized the therapeutic potential for pharmacologically induced angiogenesis to protect critically ischemic brain by inducing collateral formation. Likewise, ischemic cerebral tissue could be sustained in its recovery by such collateral vessels.

The hyperangiogenic environment of moyamoya disease in combination with the local angiogenic stimulation of cerebral infarction were unique factors in the development of this patient's AVM. We speculate that some cerebral vascular malformations can result from hyperstimulated angiogenesis. However, it remains unclear how overstimulated angiogenesis may relate to the development of typical congenital AVMs.

Conclusions

We present the first published case demonstrating an acquired AVM forming in the site of previous infarction. Little is known regarding the mechanism or process of cerebral AVM formation. We believe hyperactive angiogenesis can lead to AVM formation and may prove to be a complication in future attempts at cerebral angiogenic therapy. We hope this unique case will encourage further clinical investigation and will draw attention to a possible sequela of cerebral infarction.

References

1. Ausprunk DH, Folkman J: Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. **Microvas Res** 14:53–65, 1977
2. Chen HH, Chien CH, Liu HM: Correlation between angiogenesis and basic fibroblast growth factor expression in experimental brain infarct. **Stroke** 25:1651–1657, 1994
3. Cuevas P, Giménez-Gallego G, Carceller F, *et al*: Single topical application of human recombinant basic fibroblast growth factor (rbFGF) promotes neovascularization in rat cerebral cortex. **Surg Neurol** 39:380–384, 1993
4. Folkman J, Klagsbrun M: Angiogenic factors. **Science** 235:442–447, 1987
5. Gospodarowicz D, Ferrara N, Haaparanta T, *et al*: Basic fibroblast growth factor: expression in cultured bovine vascular smooth muscle cells. **Eur J Cell Biol** 46:144–151, 1988
6. Hoshimaru M, Takahashi JA, Kikuchi H, *et al*: Possible roles of basic fibroblast growth factor in the pathogenesis of moyamoya disease: an immunohistochemical study. **J Neurosurg** 75:267–270, 1991
7. Hosoda Y: Pathology of so-called “Spontaneous occlusion of the circle of Willis.” **Pathol Annu** 19:221–241, 1984
8. Kayama T, Suzuki S, Sakurai Y, *et al*: A case of moyamoya disease accompanied by an arteriovenous malformation. **Neurosurgery** 18:465–468, 1986
9. Lyons MK, Anderson RE, Meyer FB: Basic fibroblast growth factor promotes *in vivo* cerebral angiogenesis in chronic forebrain ischemia. **Brain Res** 558:315–320, 1991
10. Maki Y, Enomoto T: Moyamoya disease. **Childs Nerv Syst** 4:204–212, 1988
11. Masuda J, Ogata J, Yutani C: Smooth muscle cell proliferation and localization of macrophages and T cells in the occlusive intracranial major arteries in moyamoya disease. **Stroke** 24:1960–1967, 1993
12. Mawad ME, Hilal SK, Michelsen WJ, *et al*: Occlusive vascular disease associated with cerebral arteriovenous malformations. **Radiology** 153:401–408, 1984
13. Montanera W, Marotta TR, ter Brugge KG, *et al*: Cerebral arteriovenous malformations associated with moyamoya phenomenon. **AJNR** 11:1153–1156, 1990
14. Puumala M, Anderson RE, Meyer FB: Intraventricular infusion of HBGF-2 promotes cerebral angiogenesis in Wistar rat. **Brain Res** 534:283–286, 1990
15. Sato K, Shimoji T: Moyamoya disease, in Raimondi AJ, Choux M, DiRocco C (eds): **Cerebrovascular Diseases in Children**. New York: Springer-Verlag, 1992, pp 227–243
16. Schweigert L, Neufeld G, Friedman J, *et al*: Capillary endothelial cells express basic fibroblast growth factor, a mitogen that promotes their own growth. **Nature** 325:257–259, 1987
17. Scott RM: Surgical treatment of moyamoya syndrome in children. **Concepts Pediatr Neurosurg** 6:198–212, 1985
18. Suzuki J, Kodama N: Moyamoya disease—a review. **Stroke** 14:104–109, 1983
19. Suzuki J, Takaku A: Cerebrovascular “moyamoya” disease. Disease showing abnormal net-like vessels in base of brain. **Arch Neurol** 20:288–299, 1969
20. Takahashi A, Sawamura Y, Houkin K, *et al*: The cerebrospinal fluid in patients with moyamoya disease (spontaneous occlusion of the circle of Willis) contains high level of basic fibroblast growth factor. **Neurosci Lett** 160:214–216, 1993
21. Tsuboi R, Sato Y, Rifkin DB: Correlation of cell migration, cell invasion, receptor number, proteinase production, and basic fibroblast growth factor levels in endothelial cells. **J Cell Biol** 110:511–517, 1990
22. Yamashita M, Oka K, Tanaka K: Histopathology of the brain vascular network in moyamoya disease. **Stroke** 14:50–58, 1983

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