Recurrent cerebral arteriovenous malformations after negative postoperative angiograms

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Angiography has been considered to be the gold standard to judge the success of treatment for cerebral arteriovenous malformations (AVMs). Patients without residual nidus or early draining veins on postoperative angiograms are considered cured, with the risk of hemorrhage eliminated. A series of five patients with recurrent AVMs after negative postoperative angiography is described. All patients had hemispheric AVMs, presented initially with hemorrhage, and were between 5 and 13 years of age. Recurrence was noted 1 to 9 years later (at 12–16 years of age); after a hemorrhage in three patients, seizures in one, and on follow-up magnetic resonance imaging in one. Four patients underwent angiography that showed recurrence of the AVM at or adjacent to the original site. Three years postsurgery, the fifth patient died from a large intracerebral and intraventricular hemorrhage originating in the previous location of the AVM; however, the patient did not undergo angiography at the time of recurrence. The initial negative angiograms obtained postoperatively in these patients may be explained by postoperative spasm or thrombosis of a small residual malformation. However, in the authors’ cumulative experience with 808 patients who have undergone complete surgical removal of AVMs (of whom 667 were older than 18 years of age), no case of recurrent AVM has been observed in an adult. Therefore, actual regrowth of an AVM may occur in children and could be a consequence of their relatively immature cerebral vasculature and may involve active angiogenesis mediated by humoral factors. The present findings argue against the assumption that AVMs are strictly congenital lesions resulting from failure of capillary formation during early embryogenesis. It is concluded that delayed imaging studies should be considered in children at least 1 year after their initial negative postoperative arteriogram to exclude a recurrent AVM.

KEY WORDS • arteriovenous malformation • cerebral angiography • embryogenesis • congenital angiogenesis

Clinical Material and Methods

The five patients in the present study were taken from a cumulative group of 808 patients who underwent surgical removal of their cerebral AVMs. Of the larger group, 141 were 18 years of age or younger. All five patients presented with hemorrhage and were between 5 and 13 years of age. Recurrence was noted 1 to 9 years later (at 12–16 years of age); after a hemorrhage in three, seizures in one, and follow-up magnetic resonance imaging in another. There were four girls and one boy. Angiograms were obtained 7 days postsurgery in three patients, immediately after the operation in one and intraoperatively in one. All five patients had an official report stating that there was no residual AVM (no residual nidus or abnormal shunting) after the first surgery. We were able to study four of these postoperative angiograms in detail retrospectively and again found no residual malformation.

All AVMs were hemispheric. Three were located at least partially within the Sylvian fissure, one was in the medial parietal lobe, and another was in the occipital lobe. One patient had two distinct AVMs growing from separate
areas of the original site. The recurrent lesions in two patients were larger than the original. Four patients underwent angiography that showed recurrence of the AVM at or adjacent to the original site. Three of these had recruited deep arterial feeding vessels (choroidal or lenticulostriate) that were not present originally. The recurrent AVM in another patient (Case 5) was discovered just 1 year after surgery (by means of a follow-up MR image) and had not recruited deep arterial blood supply.

One patient (Case 3) died 3 years after surgery from a massive intracerebral and intraventricular hemorrhage originating from the previous location of the AVM. However, angiograms were not obtained at the time and an autopsy was not performed. Therefore we can only presume that the AVM recurred because the hemorrhage occurred in the previous location of the lesion. This child had a negative postoperative angiogram 1 week after his original surgery and therefore was considered cured at the time.

**Illustrative Cases**

**Case 1**

This 8-year-old girl presented in 1980 with a left hemiparesis as a result of a hemorrhage in the right frontal lobe and sylvian fissure. The angiogram showed a 4 × 3-cm nidus with diffuse borders in the orbitofrontal and anterior sylvian areas (Fig. 1 left). It was fed by several branches from the internal carotid artery, proximal middle cerebral artery (MCA), and the anterior cerebral artery (ACA) and drained into the superior sagittal sinus. After resolution of the patient’s symptoms, a gross-total removal of her malformation was obtained via a frontotemporal craniotomy. While still anesthetized, she was taken to radiology where an angiogram showed complete removal of her malformation (Fig. 1 right). She was neurologically stable after surgery and was discharged on Day 5 postoperatively. Six years later, she presented with meningismus, decreased level of consciousness, and left hemiparesis. The hematoma was found to be located in the area of the previous AVM but this time it also extended into the ventricle. The angiogram showed two separate areas of AVM, one measuring 1.5 × 2 cm just above the orbital roof and the other in the anterior sylvian region measuring 3 × 2 cm. The anterior nidus was partially fed by anterior ethmoidal branches through the cribriform plate. The sylvian nidus was partially fed by choroidal branches that were not feeding the AVM when it was first treated. The recurrent malformations were resected and a postoperative arteriogram confirmed complete removal. However, her left hemiparesis from the second hemorrhage did not resolve.

**Case 2**

This 6-year-old girl presented in June 1984 with sudden onset of severe headache and hemiplegia. After 3 months, she recovered significantly and was left with only a mild hemiparesis. An angiogram showed a very small (< 1 cm) right Sylvian AVM (Fig. 2 left) that drained into a superficial sylvian vein. At surgery, the AVM was removed uneventfully. Six days postsurgery, an angiogram showed no residual AVM. The patient was discharged with an unchanged mild left hemiparesis. Nine years later, she had a large hemorrhage that resulted in acute hemiplegia. The angiogram showed a much larger AVM located just posterior to the original one (Fig. 2 center and right). The AVM was now fed by a lateral lenticulostriate artery that was not present in the original AVM, in addition to other MCA branches, and drained into the superior sagittal sinus via a large cortical vein. She has recovered significantly and has undergone embolization in preparation for surgery.
Case 3
This 11-year-old boy had an intraventricular hemorrhage in February 1991 from which he fully recovered. An angiogram showed a 2.5-cm left medioparietal AVM fed by branches from the right and left ACA and the posteromedial choroidal and splenial branches of the left posterior cerebral artery (PCA) (Fig. 3A). The AVM drained into the ventricle, in which there was a venous dilation, as well as into superficial cortical veins. One month later, a gross-total resection of the AVM was achieved at surgery. An angiogram obtained on Day 7 postoperatively showed no residual AVM (Fig. 3B). Three years later, the patient died from a hemorrhage located at the site of the previous AVM, and extending into the ventricle. Angiography was not performed. C and D: Noncontrast computerized tomography scans obtained on admission.

Case 4
This 5-year-old girl presented with lethargy, aphasia, and right hemiparesis from a left parietal hemorrhage in November 1987. An angiogram revealed abnormal arteriovenous shunting without a discrete nidus in the area of the posterior sylvian fissure with drainage into the superior sagittal and transverse sinus via a superficial cortical vein (Fig. 4 left). After 5 weeks, her deficits had resolved for the most part and she underwent surgery. Intraoperative angiography was used to identify the area of abnormal shunting, which was located in the cortical area under the arterialized superficial vein. This area had a collection of small abnormal blood vessels that were cauterized and the draining vein was interrupted with aneurysm clips. The blood in the draining veins turned blue and a repeat intraoperative arteriogram revealed no abnormal vascularity or arteriovenous shunting. The patient did well postoperatively but was lost to follow-up review until 7 years later when she presented with a seizure. A CT scan showed no evidence of hemorrhage. An MR image and an angiogram revealed a 3-cm AVM more medial than the original and reaching into the ventricle. This time, it was fed by the anterior choroidal artery in addition to branches from the MCA. It drained mainly into superficial cortical veins (Fig. 4 right). The AVM was surgically removed and the patient remained neurologically intact. Both postoperative and 6-month follow-up angiography revealed no recurrent malformation.

Case 5
This 13-year-old girl presented in 1993 with a hemorrhage from a left parietooccipital AVM. The small irregular nidus was fed by branches of the PCA and drained into the galenic system (Fig. 5A). She underwent surgery, and an angiogram obtained 7 days later showed no residual AVM or abnormal shunting (Fig. 5B). Fifteen months later, follow-up MR imaging that was consistent with AVM recurrence was obtained by the referring physician. An angiogram demonstrated a smaller, more diffuse nidus in the same location, fed by the PCA and again draining into the vein of Galen (Fig. 5C). The family refused surgery and the patient underwent radiosurgery of the recurrent lesion in November 1994. Angiographic follow-up results are not presently available.

Discussion
Angiography has been considered to be the gold stan-
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Fig. 5. Case 5. Left vertebral angiogram, anteroposterior view (A), demonstrating a small occipital arteriovenous malformation in a 13-year-old girl. Complete resection was followed by an angiogram 7 days later demonstrating no residual malformation or early draining veins; the anteroposterior view of the vertebral injection is shown (B), but the internal carotid angiogram was also negative. Fifteen months later a follow-up magnetic resonance image appeared suspicious for recurrence. Therefore angiograms were obtained (C and D) that revealed a small recurrent diffuse nidus at the site of the original lesion (arrows). The anteroposterior view of the vertebral injection (C) and the lateral view of the internal carotid artery injections are shown (D).

It has been assumed that AVMs are congenital nonneoplastic lesions.11 They are generally believed to arise when capillaries fail to develop in an area of the brain during early embryogenesis, resulting in abnormal communications between arteries and veins.2,18 Yasargil,22 however, hypothesized that AVMs occur due to abnormal proliferation of capillaries that eventually develop into “metamorphic, dysplastic vessels” and coined the term “proliferative capillaropathy.” He argued that because capillaries are the driving force for the formation of arteries and veins, failure of capillary formation would lead to a completely avascular territory rather than a vascular malformation, unless there is secondary destruction of capillaries.

The phenomenon of AVM recurrence may have several explanations. It could be argued that the initial postoperative angiograms in these children did not show residual AVM because of local spasm, thrombosis, or mass effect, which may occur during the first days after surgery. Later on, resolution of spasm and mass effect and recanalization of thrombus would reactivate a small residual arteriovenous shunt. The AVMs would then have to enlarge by any of the mechanisms described above. However, recurrence has not been described in adults, who, in our series, comprised approximately 85% of patients undergoing opera-

dard to judge the success of treatment for cerebral AVMs. Patients without residual nidus or early draining veins on postoperative angiograms are considered cured, and the risk of hemorrhage eliminated. The present study indicates that a negative postoperative angiogram within the 1st week after surgery in children does not necessarily indicate a cure and that the risk of future hemorrhage may not be eliminated without follow-up studies.

The incidence of recurrent cerebral AVMs after negative angiograms cannot be determined from this study. The cases described here are part of a large population of patients who underwent complete surgical removal of cerebral AVMs by the authors. Postoperative angiograms were obtained in most of these patients within the first 10 days postsurgery, and only a very few patients had repeat studies several months later. It is therefore possible that there are more patients in this population who may harbor recurrent AVMs that are presently asymptomatic.

Other authors have mentioned possible recurrence of AVMs in children posttreatment. Kondziolka, et al.,7 reviewed their 40-year experience with 132 cerebral AVMs seen at Children’s Hospital in Toronto. Of the 70 patients who had complete removal of their lesions, there were two with recurrent AVMs after negative postoperative angiograms. Both patients presented 3 years later with recurrent hemorrhage and both had a small recurrent AVM. Sano, et al.,15 reported the case of a 14-year-old boy who underwent removal of a right cingulate gyrus AVM and presented 9 years later with a hemorrhage from an AVM in the right lateral ventricle with choroidal blood supply. It is unclear whether an angiogram was obtained in this patient after the initial surgery. Yaşargil13 reported five cases from a series of 414 surgically treated patients who may have had AVM recurrence after what was considered a complete resection. Of these patients, a negative postoperative angiogram was obtained in only one, whereas the others underwent postoperative contrast-enhanced CT scanning suggestive of complete resection. Interestingly, all of his patients with possible recurrence were younger than 18 years of age. To our knowledge, there are no reports of adults in whom this phenomenon may have been seen.

Increase in the size of AVMs with time has been documented in the literature8,11,17,21 but the mechanism of growth has been a matter of controversy. Enlargement may occur purely as a hemodynamic consequence of increased flow into the poorly differentiated vessels of the nidus and draining veins and/or recruitment of collateral arterial feeding vessels into the low-pressure shunt.4,5,17,21 Another theory argues that growth may result from small hemorrhages that can progressively destroy surrounding neural tissue, allowing vascular dilation and tortuosity to continue.3,14 Finally, Krayenbühl,4 who noted the phenomenon of AVM growth in seven cases (most of them children) suggested that the shunt itself may stimulate proliferation of new abnormal blood vessels.
tion for AVMs. This suggests that the relative immaturity of children’s cerebrovasculature is an important factor in the etiology of this phenomenon.

Simple hemodynamic enlargement of preexisting vessels in a residual nidus is unlikely in at least two of our patients (Cases 2 and 4), who had a recurrent AVM with several new abnormal blood vessels in adjacent locations and even established new choroidal and/or perforating vessel supply. It is evident from these angiograms that enlargement of preexisting vessels cannot solely account for AVM recurrence and that new abnormal vessels formed in the interim. Recent experiments have revealed marked immunoreactivity to vascular endothelial growth factor (VEGF) in cells surrounding the AVMs resected during the original surgery in these children. Because VEGF is associated with angiogenesis in neoplasia and development, our findings indicate that VEGF may also be related to the formation of abnormal vascularity seen in these AVMs.

These observations indicate, as Yaşargil suggested, that AVM formation may not be a passive process resulting from absence of capillary formation during embryogenesis. It may instead be an active phenomenon in which synthesis of abnormal vascularity is induced by humoral factors such as VEGF. Although this process may begin in utero, we have shown that it can certainly continue into childhood, which argues against the assumption that AVMs are strictly congenital lesions. We hypothesize that this active angiogenic process eventually subsides and the AVM reaches “maturity.” If the malformation is resected during the active growth stage and the cells responsible for the synthesis of angiogenic growth factors remain in the brain, the patient may be at risk for AVM recurrence.

We believe that the risk of recurrence after a negative postoperative angiogram is low, even in children. Still, the morbidity and mortality from hemorrhage are high. Therefore, follow-up imaging studies should be obtained 6 months to 1 year after surgery in children to rule out AVM recurrence. Because the risk of hemorrhage is high in the early postoperative course from retained AVM nidus, early postoperative or intraoperative angiography should still be performed.

References

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