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The Efficacy of Particulate Embolization Combined with Stereotactic Radiosurgery for Treatment of Large Arteriovenous Malformations of the Brain

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PURPOSE: To evaluate the efficacy of combined particulate embolization and single-stage stereotactic radiosurgery in the treatment of large arteriovenous malformations (AVMs) of the brain. **METHODS:** Twenty-four patients with large brain AVMs (diameter >3.0 cm; volume > 14 cm^3), who had previously undergone particulate embolization and stereotactic radiosurgery, were retrospectively evaluated 2 or more years after radiosurgery. **RESULTS:** In 12 (50%) of these patients there was complete AVM obliteration, comparing favorably with a 58% obliteration rate in a group of AVMs having a 4- to 10-cm^3 volume, treated by radiosurgery alone. Recanalization of embolized, but not radiated, AVM segments was identified in 3 (12%) patients. However, long-term occlusion was demonstrated in the embolized portions of most AVMs subsequently treated by radiosurgery. Complications included 1 (4%) patient with a mild upper extremity paresis after radiosurgery and 2 (8%) patients with transient neurologic deficits after embolization. **CONCLUSION:** Combined embolization and stereotactic radiosurgery was more efficacious than radiosurgery alone for large brain AVMs. Recanalization after embolization did occur but was a relatively minor cause of treatment failure.

Index terms: Surgery, stereotactic; Interventional neuroradiology; Arteriovenous malformations, embolization

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Stereotactic radiosurgery was pioneered in the early 1950s by Lars Leksell (1). The last 4 decades have seen a rapid proliferation of stereotactic radiosurgical technology. Currently used devices include the 201 source cobalt-60 gamma knife (2, 3), high-energy proton and heavy-ion charged–particle cyclotrons (4–8), and modified high-energy linear accelerators (9–11). The application of stereotactic radiosurgery to treat arteriovenous malformations (AVMs) of the brain began in the 1970s. Since that time, stereotactic radiosurgery has proved an effective alternative to microsurgery for selected brain AVMs (2–11).

Small AVMs (volume < 4 cm^3) treated with stereotactic radiosurgery have a total obliteration rate of 80% to 88% 2 years after radiosurgery (3). However, equipment geometry and dose limitations diminish the obliteration rate of single-stage radiosurgery to 58% for AVM volumes between 4 and 10 cm^3, with obliteration rates for AVMs greater than 10 cm^3 falling to 28% (12). Documenting the effect of reducing large AVMs to a manageable size and thereby increasing treatment efficacy, Dawson et al reported encouraging results in a small group undergoing initial staged embolization before stereotactic radiosurgery when the AVM nidus exceeded 10 cm^3 in volume (13).

From 1987 through 1992 at the University of Pittsburgh, 348 AVMs of the brain were treated with stereotactic radiosurgery. Fifty-six patients underwent preradiosurgical embolization; 24 of these met the criteria for inclusion in this study.

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These criteria include preembolization and postembolization studies and a follow-up study 2 or more years after radiosurgery. This report evaluates the combination of staged particulate embolization and stereotactic radiosurgery in the long-term follow-up group of 24 patients.

Materials and Methods

Each patient received a diagnostic angiogram to determine the vascular supply to the AVM. Magnification images were obtained in at least two projections using rapid-sequence imaging (four to six images per second). To allow accurate measurements corrected for magnification, radiopaque concentric sizing rings were affixed to the front, back, and sides of the head. Subsequent embolization was planned based on the diagnostic findings, with the goal of embolization being to reduce the size of the AVM to a 3.0-cm maximum diameter.

A Tracker-18 microcatheter (Target Therapeutics, Fremont, Calif) was introduced into the pedicle selected for embolization. Real-time digital fluoroscopic road-mapping was used for guidance. When positioned in a feeding pedicle, digital subtraction angiography was used to ensure that normal parenchyma was not also supplied. In addition, provocative testing was performed with a barbiturate (amobarbital or methohexital) administered through the microcatheter. The amount given was based on the type of barbiturate and the size of the pedicle being tested (14). A tailored neurologic examination immediately followed each barbiturate infusion.

Embolization was attempted only if the neurologic exam was unchanged from the baseline. The most common embolic agent was polyvinyl alcohol particles of various sizes ranging from 150 to 1000 μm. In early cases silk suture was occasionally used for closure of large shunts within the AVM nidus that proved problematic with polyvinyl alcohol alone. Platinum microcoils were later used for fistulas or for final occlusion of a pedicle after polyvinyl alcohol embolization. Polyvinyl alcohol particles were suspended in nonionic contrast material for continuous visibility during embolization. Embolization was terminated when the pedicle was occluded or the flow was so slow that additional particulate embolization was hazardous because of possible reflux.

Hemodynamic changes during embolization require constant assessment to avoid embolization of cortical branches not filled on initial angiograms. Significant changes in the hemodynamics of a pedicle require a repeat of provocative testing (15).

Most embolizations were staged. Staged procedures are usually better tolerated by the patients and may reduce the risk of normal perfusion pressure breakthrough (16–18).

Diagnostic angiography was performed at the end of the embolization. The patients continued to receive corticosteroids for 48 hours. All patients were monitored in a neurologic intensive care unit after embolization.

Stereotactic radiosurgery was performed 1 to 3 months after completion of staged embolization. A stereotactic headframe was affixed to the patient's head, and biplane angiography was performed, allowing coordinate calculation for subsequent stereotactic radiosurgery (19). Radiosurgery was performed as previously described (35).

After radiosurgery, interval follow-up was done with magnetic resonance imaging and angiography. Complete AVM resolution, suggested by magnetic resonance, was confirmed by angiography in all cases.

Results

Fifty-six patients with an initial AVM volume greater than 10 cm^3 were referred for angiographic evaluation and staged embolization before stereotactic radiosurgery. Thirty-two of the 56 patients were excluded from this study because follow-up time was less than 2 years or because there were insufficient data to assess AVM size accurately before and after embolization and 2 or more years after radiosurgery.

All patients in this series whose AVMs were classified as totally obliterated after combined embolization and stereotactic radiosurgery underwent only single-stage radiosurgery. Patients in whom AVM obliteration was achieved after a second-stage radiosurgery procedure are presented as having had residual AVMs 2 years after the initial radiosurgery (considered incomplete obliteration in this study).

Twenty-four patients met all criteria for inclusion in this study (Table 1). Twelve (50%) AVMs were totally obliterated 2 years after radiosurgery. Seven (30%) patients had residual but smaller AVMs at 2 years. The remaining 5 (20%) patients had residual AVMs that had variable degrees of recurrence after embolization. Two of these patients' procedures were considered technical failures because of unrecognized external carotid feeders; the other 3 patients had recurrent AVM in the area of prior embolization, considered definite evidence of postembolization recanalization.

Two (8%) transient neurologic complications resulted from embolization (Table 1). In addition, one asymptomatic complication occurred from a fragment of catheter that detached and remained intraarterially located. This catheter fragment was surgically removed with no neurologic sequelas. One patient (4%) experienced hemiparesis 6 months after radiosurgery. This deficit largely resolved but the patient was left with permanent, mild right-hand weakness. No patients in this series experienced hemorrhage

TABLE 1: Combined embolization and radiosurgery for brain AVMs

Case	AVM Location	Symptoms	Size before Embolization, cm (cm^3)	Size after Embolization, cm (cm^3)	Obliteration 2 yrs after Radiosurgery?	Complications
1	L parietal	Seizures	3.8 (29)	2.8 (11)	Yes	Hemiparesis after radiosurgery
2	L frontal	Seizures	3.2 (17)	2.4 (7.2)	Yes	None
3	R occipital	Seizure	5.1 (69)	3.2 (17)	Yes	None
4	R parietal	Seizure	3.5 (22)	3.0 (14)	Yes	None
5	L parietal	Hemorrhage	5.0 (65)	2.4 (7.2)	Yes	None
6	R parietal	Hemorrhage	3.0 (14)	1.7 (2.5)	Yes	None
7	L temporal	Headache	4.2 (39)	2.2 (5.5)	Yes	None
8	L parietal	Seizure	3.0 (14)	1.1 (.70)	Yes	None
9	R parietal	Hemorrhage	4.0 (34)	2.3 (6.4)	Yes	None
10	R basal ganglion	Hemorrhage	3.8 (29)	3.0 (14)	Yes	Catheter fragment after embolization
11	L occipital	Seizures	3.8 (29)	2.5 (8.2)	Yes	Transient visual field changes after embolization
12	R frontal	Headaches	3.5 (22)	2.4 (7.2)	Yes	None
13	L frontal	Seizures	4.8 (58)	3.6 (24)	No	None
14	R parietal	Hemorrhage	5.0 (65)	4.0 (34)	No	None
15	Cerebellar	Hemorrhage	5.5 (87)	4.4 (45)	No	None
16	R temporal	Seizure	6.0 (113)	4.5 (48)	No	None
17	R temporal	Headache	4.0 (34)	3.5 (22)	No	None
18	R frontal	Seizures	5.2 (74)	3.5 (22)	No	Transient R-hand paresthesia after embolization
19	R occipital	Seizure	3.9 (31)	2.3 (6.4)	No	None
20	Corpus callosum	Hemiparesis	3.0 (14)	1.8 (3.1)	No	None
21	L parietal	Seizures	4.3 (42)	2.4 (7.2)	No	None
22	L thalamic	Seizures	3.0 (14)	2.3 (6.4)	No	None
23	L parietal	Hemorrhage	5.0 (65)	3.3 (19)	No	None
24	L temporal	Hemorrhage	3.6 (24)	0.8 (.27)	No	None

after embolization or radiosurgery. There were no deaths (Table 2).

Discussion

Modern therapy for AVMs generally consists of (*a*) surgery alone, (*b*) surgery combined with preoperative embolization, or (*c*) stereotactic radiosurgery. Cases considered ideal for radiosurgery usually have maximum lesion diameters of less than 3.0 cm and have characteristics that would increase surgical risks (such as critical location, deep arterial supply, or central venous drainage). Primary radiosurgical treatment of AVMs larger than 3.0 cm in diameter requires reduction of the dose delivered to the AVM to maintain brain tolerance and minimize complications (20, 21). Dawson et al suggested that AVMs larger than 3.0 cm in diameter might be successfully treated with stereotactic radiosurgery if first reduced in size by embolization (13). The subsequent experience with combined embolization and stereotactic radiosurgery in the literature has been anecdotal, with no long-term follow-up available. Additionally, since the initial report by Dawson et al, there has been ongoing controversy regarding the best types of embolic material to use before radiosurgery, with the concern being that particulate embolization may be associated with an unacceptable risk of recanalization.

TABLE 2: Complications of embolization and radiosurgery for brain AVMs

Neurologic Deficit	Radiosurgery	Embolization
Permanent	1 (4%) Mild	0
Transient	0	2 (8%)
Technical	0	1 (4%) (Catheter fragment)
Hemorrhage	0	0
Death	0	0

This series demonstrates that a single stereotactic radiosurgery successfully produced total AVM obliteration in 50% of patients with an initial AVM diameter larger than 3.0 cm when preceded by particulate embolization (Fig 1). In this study, a maximum single dimension was measured for each AVM. In preparation for ra-

Fig 1. *A*, Lateral projection of a right internal carotid artery angiogram reveals a frontal AVM with rapid venous shunting.

B, Superselective digital angiogram confirms the presence of a high-flow fistula (*arrowheads*).

C, Residual AVM after microcoil (*arrow*) and polyvinyl alcohol embolization.

D, Lateral projection of a right internal carotid artery angiogram 2 years after stereotactic radiosurgery shows total AVM obliteration.

diosurgery, the nonuniform geometry of the malformation is used to calculate the targeted volume. (For comparison, the approximate AVM volume has been included in parentheses, where the volume was estimated using the maximum AVM dimension as the diameter of a sphere.) In the successful treatment group, the average AVM size before embolization was 3.8 cm (29 cm^3) and the average postembolization, preradiosurgical size was 2.4 cm (7.2 cm^3), resulting in an average postembolization diameter reduction of 37% (Table 3). Patients with residual AVM 2 years after radiosurgery had an average initial size of 4.4 cm (45 cm^3) and postembolization size of 3.0 cm (14 cm^3). These AVMs were typically larger and had a smaller effective diameter reduction associated with embolization (32%) (Fig 2). The statistical difference in the mean size of the total obliteration and residual AVM groups was found to be at the 0.5% and 0.1% levels for preembolization and postembolization diameters, respectively

TABLE 3: Results of combined embolization and radiosurgery

AVM Outcome	Patients	Average		Reduction in Diameter, %
		Preembolization Diameter (Volume)	Postembolization Diameter (Volume)	
Total obliteration	12 (50%)	3.8 cm (29 cm^3) (range, 3.0–5.1 cm)	2.4 cm (7.2 cm^3) (range, 1.2–3.2 cm)	37
Subtotal obliteration	12 (50%)	4.4 cm (45 cm^3) (range, 3.0–5.0 cm)	3.0 cm (14 cm^3) (range, 0.8–4.5 cm)	32
Embolization failures	5 (20%)			
Technical	2 (8%), unrecognized external feed			
Recanalization	3 (12%)			

Fig 2. Anteroposterior (*A*) and lateral (*B*) projections of a right vertebral angiogram show a vermian AVM before treatment.

Anteroposterior (*C*) and lateral (*D*) projections after particulate embolization reveal the residual AVM volume presented for stereotactic radiosurgery.

Anteroposterior (*E*) and lateral (*F*) images 2 years after radiosurgery demonstrates subtotal AVM obliteration.

(verified using Student's *t* test). These data show a total obliteration rate after combined embolization and radiosurgery of 50%, similar to the 58% total obliteration rate achieved in a group of initially smaller AVMs (2.0 to 2.7 cm diameter/4.2 to 10 cm^3 volume) treated by single-stage radiosurgery alone. At this institution, AVMs greater than 2.7 cm diameter and treated by single-stage radiosurgery alone have shown only a 28% total obliteration rate. In this group of patients, there was a beneficial impact of embolization and AVM size reduction with a subsequent improved efficacy of single-stage radiosurgery in initially large AVMs.

In five patients with residual AVM at 2 years, embolizations were considered failures. In two (8%) of these patients, follow-up studies revealed external carotid artery feeders to the AVM that either had been undetected at the time of embolization or were subsequently recruited. Three (12%) additional patients had obvious recanalization of portions of the AVM that had been previously embolized (Fig 3). Recanalization after embolization is a well-described phenomenon, with the rate of recanalization related to the type of embolic agent, method of embolization, and type of vascular lesion (22–27). Liquid acrylics (ie, *N*-butyl 2-cyanoacrylate) have been presented as permanent embolic agents; however, recanalization has been noted with liquid embolic agents as well (22–25). Although recanalization after particulate embolization was noted in this series, it was demonstrated conclusively in only three (12%) patients, with an additional two (8%) patients having initially unrecognized (and untreated) supply from external carotid artery branches. This recanalization rate compares favorably with revascularization with liquid adhesive embolization as reported by Fournier et al (23). In their report of 49 AVMs embolized with liquid adhesive, they subsequently found that in eight (16.3%) patients a newly formed dural supply developed and in six (12.2%) patients there was revascularization via intracranial collaterals.

In our series, one (4%) permanent neurologic deficit occurred after stereotactic radiosurgery, leaving the patient with a mild residual right-

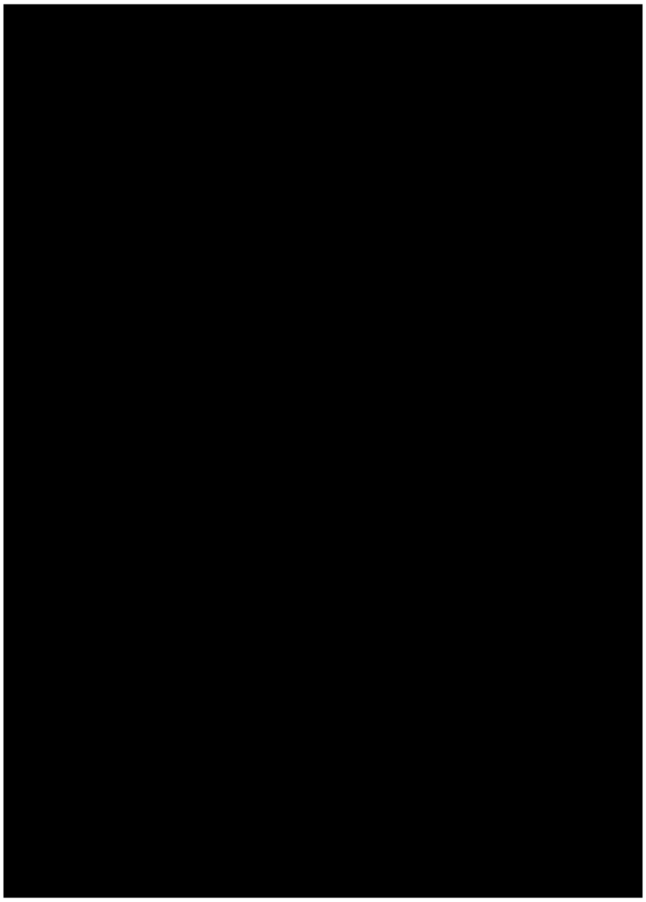

Fig 3. *A*, Anteroposterior angiogram shows the pretreatment AVM configuration.

B, The angiogram shows the residual AVM after embolization. The area designated *E* presents the embolized portion of the AVM.

C, Follow-up angiogram 2 years after stereotactic radiosurgery reveals recanalization of AVM in the previously embolized region. (The area designated *GK* represents the gamma knife volume.)

D, Three years after stereotactic radiosurgery the volume treated by radiosurgery remains obliterated.

hand weakness. This is consistent with the 4.4% complication rate in our overall experience with stereotactic radiosurgery for brain AVMs (3). It is also similar to the 3% complication risk predicted by the integrated logistic formula used to help select an allowable dose for a given AVM volume (21). Using helium-ion beam radiosurgery, Steinberg et al initially experienced a 50% complication rate in AVMs with diameters greater than 3 cm and doses greater than 18 Gy (8). Complications were subsequently decreased by a reduction in dose delivered (28). This result highlights the need to minimize the overall dose in large AVMs if a low complication rate is to be maintained.

There were no permanent neurologic complications associated with embolization in this series. However, 2 (8%) patients did have transient deficits that completely resolved. Also, a detached catheter fragment required vertebral arteriotomy and surgical removal; this event occurred without neurologic sequela. This rate of complication is consistent with that from other reports (24, 27, 29–31) (Table 4). The degree to which the AVM size is diminished may correlate with the incidence of complications just as does AVM location, number of feeders, and initial AVM size. Our goal was to achieve only an adequate size reduction (<3 cm in diameter) to allow acceptable radiosurgical coverage. When this target size was reached, we refrained from further attempts at embolization and therefore possibly avoided additional complications, even though additional AVM size reduction below the 3-cm target goal may ultimately prove desirable because of additional increased radiosurgical efficacy. Five of the 12 patients with AVMs not obliterated 2 years after radiosurgery had AVM diameters less than 2.5 cm after embolization (Table 1). This suggests that size is not the sole determinant of AVM response to stereotactic radiosurgery.

Postoperative complication rates after resection of large AVMs range from 14% to 24% in recently reported series (33, 34). Mortality rates range from 0% to 3.6%. In each of these surgical series, complications increase significantly as

TABLE 4: Complications associated with embolization

Series (Reference)	Patients	Embolic Agent	Transient	Permanent	Death	Technical
Present study	24	PVA	2 (8%)	0	0	1 (4%)
Purdy (27)	39	PVA	3 (8%)	2 (5%)	1 (3%)	2 (5%)
Pasqualin (29)	49	Silastic	5 (9.8%)	0	0	0
Viñuela (30)	101	IBCA/PVA	?	13 (12.9%)	1 (0.9%)	3 (2.9%)
Fournier (24)	49	IBCA	8 (16%)	4 (8%)	0	0
Nakstad (31)	20	PVA	1 (5%)	1 (5%)	0	0

Note.—PVA indicates polyvinyl alcohol; and IBCA, isobutyl cyanoacrylate.

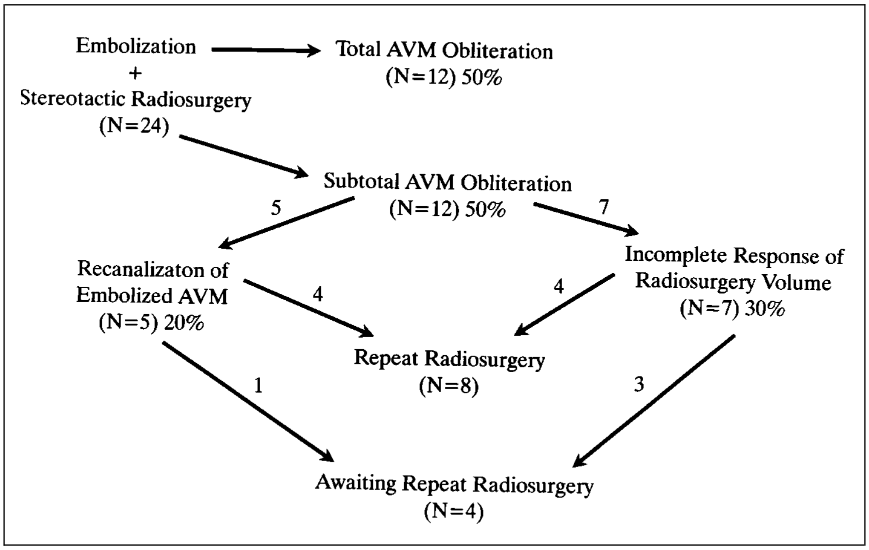

Fig 4. Flow chart shows the treatment plan of our 24 patients.

the size and Spetzler-Martin grade (32) of the AVM increases. Although there remains a latent period between radiosurgical treatment and AVM obliteration (with a portion of patients requiring a repeat treatment), the complication rate and lack of hemorrhage in this group of patients who underwent combined embolization and stereotactic radiosurgery is encouraging when compared with figures reported from surgical removal of large AVMs. Patients with AVMs that are not totally obliterated at 2 years after radiosurgery are considered candidates for repeat radiosurgery. One of our patients who underwent a second stereotactic radiosurgery has progressed to total AVM obliteration. Others in this group await repeat radiosurgery or have already been retreated (Fig 4).

Conclusions

In this evaluation, there was a benefit to embolization and AVM size reduction: they improved the efficacy of single-stage radiosurgery for the treatment of initially large AVMs. This improvement was achieved with a relatively low complication rate.

Embolization failures and recanalizations did occur after particulate embolization, but these results were similar to those reported with liquid adhesives. Additional evaluation, with direct comparison between long-term follow-up results of particulate and liquid embolic agents used in combination with stereotactic radiosurgery, is needed.

The combined therapeutic approach of embolization and stereotactic radiosurgery for large brain AVMs offers an additional treatment alternative when the risk of surgical resection is too high or surgery is unacceptable to the patient.

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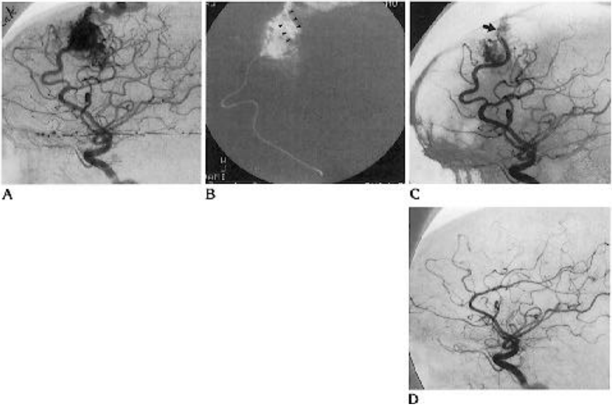
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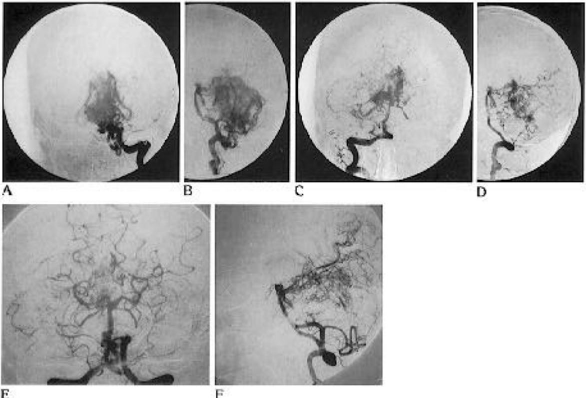
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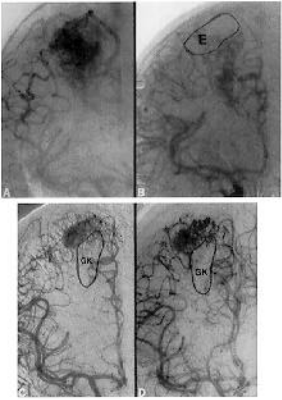
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