Endothelial proliferation, neoangiogenesis, and potential de novo generation of cerebrovascular malformations

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Object. To date, both arteriovenous malformations (AVMs) and cavernomas have been considered to be congenital malformations. A recent survey of the literature has shown the potential for de novo generation of both familial and sporadic cavernomas as well as AVMs. Therefore, it was of interest to determine the biological behavior of these lesions in detail.

Methods. The proliferative and angiogenic capacities of the endothelium of 13 cavernomas and 25 AVMs obtained in patients recently treated (1997–1998) at one institution were studied. Immunohistochemical staining for proliferating cell nuclear antigen (PCNA), MIB-1, and vascular endothelial growth factor (VEGF) and its receptor Flk-1 was performed using standard staining procedures. Positive immunostaining of the nuclei of endothelial cells was observed in specimens of both AVMs and cavernomas for PCNA (80% of AVMs and 85% of cavernomas), and Flk-1 (80% of AVMs and 31% of cavernomas). Endothelial expression of VEGF in the 18 incompletely embolized AVMs was found in 72% of cases but only in 28% of the seven cases in which patients did not undergo endovascular treatment; it was found in 38% of cavernomas. Endothelial expression of MIB-1 was found in 12% of AVMs but in no cavernomas.

Conclusions. These results indicate that there is endothelial proliferation as well as neoangiogenesis in cerebral cavernomas and AVMs. The increased level of angiogenesis in only partially obliterated AVMs underscores the need for radical and complete occlusion of cerebral AVMs to avoid recurrences and further risks of morbidity.

KEY WORDS • endothelium • cavernoma • arteriovenous malformation • immunohistochemistry

The growth and de novo appearance of cerebrovascular malformations have been documented in a number of clinical studies. The underlying developmental and pathogenetic mechanisms of cavernomas and AVMs are not completely understood, although many authors have addressed these issues for both cavernomas and AVMs.

Recent immunohistochemical studies have focused on the proliferation of cavernomas and the expression of angiogenic growth factors in cerebral AVMs. Expression of PCNA has been detected in the endothelium of cavernomas, indicating a growth potential in these lesions. Furthermore, expression of VEGF in AVMs has been shown to be correlated with the recurrence of cerebrovascular malformations. The receptor for VEGF has been identified and is called Flk-1. Recently, Flk-1 was detected in the endothelium of a patient in whom spontaneous obliteration of an AVM occurred.

In the present study, we used immunohistochemical analysis to investigate the endothelium of cerebrovascular malformations (AVMs and cavernomas) to determine more fully the biological activity of these lesions. We investigated the following parameters: 1) endothelial proliferation in both cavernomas and AVMs; 2) expression of VEGF and Flk-1 in the endothelium of cavernomas and AVMs; and 3) the impact of preoperative embolization on the endothelial expression of the aforementioned proteins in AVMs.

Materials and Methods

Specimen Selection and Clinical Characteristics

We investigated 38 consecutive cases of symptomatic cavernomas (13 patients) and AVMs (25 patients) treated at our institution between June 1997 and July 1998. Endovascular treatment was performed in all cases of elective AVM surgery as a first treatment option of choice. Feeding arteries were identified using superselective angiography and were embolized with polyacryl. In the majority of patients, the malformation could not be completely occluded using endovascular therapy. These patients either underwent excision of the lesion or were excluded from our study and underwent stereotactic radiation treatment. All patients who underwent elective surgery for their AVMs were treated by the senior author (H.B.). The specimens obtained by resection were fixed in 4% buffered paraformaldehyde and embedded in paraffin. Following this procedure, 5-μm thick sections were cut and stained with hematoxylin and eosin and with elastica von Gieson for routine diagnosis. All speci-
Endothelial proliferation

mens were also stained immunohistochemically with antibodies for PCNA, MIB-1, VEGF, and Flk-1.

Control Specimens

In addition to the specimens obtained from patients with known cavernomas or AVMs, we investigated 14 cerebral specimens obtained during autopsy. Seven samples were removed from patients who had died of ICH. A review of the autopsy charts of our institution revealed only one case of an incidentally found AVM and no case of incidentally found cavernoma. In 12 of the specimens obtained at autopsy we studied both leptomeningeal and intracerebrovascular immunoreaction to the aforementioned antibodies.

Immunostaining Procedures

The specimens were cut at 5-μm intervals and mounted on 3-aminopropyltriethoxysilane-treated slides. After standard deparaffinization and rehydration, in which the specimens were exposed to xylene for 10 minutes, 100% alcohol for 5 minutes, 96% alcohol for 5 minutes, and 70% alcohol for 5 minutes, endogenous peroxidase activity was quenched by exposure to 1% hydrogen peroxide for 20 minutes. The citrate-buffered (pH 6) slides were then placed in a microwave set at 800 W for 20 minutes. A solution containing 20% bovine serum was used to suppress nonspecific reactions to the antibodies. After adding the specific antibody, the slides were incubated at room temperature for 45 minutes. Both positive and negative control specimens were also stained during the immunohistochemical protocol. Incubation with a streptavidin–biotin complex kit (Duett-Kit [model K0492]) and trypsin were obtained from Dako (Glostrup, Denmark). The MIB-1 antibody (DIA 505) was obtained from Dianova (Hamburg, Germany) and the anti–human vascular growth factor was detected in 60% of patients (Tables 1 and 2).

Clinical Aspects

Twenty-five patients (13 male and 12 female patients) underwent surgery. The mean age at surgery was 40.4 years (range 8–78 years). Of these 25 patients, 14 (56%) had suffered a previous ICH. The time interval between the ICH and surgery was less than 6 months in seven patients (28%). Eighteen supratentorial and seven infratentorial AVMs with a median Spetzler–Martin grade of 2.96 were treated by microsurgical procedures (Table 1). Eighteen patients (72%) underwent preoperative embolization therapy. The other seven did not undergo this treatment because their AVMs manifested with an ICH that required immediate evacuation of the hematoma and removal of the malformation or because endovascular treatment was not possible.

Immunohistochemical Findings. In general the control specimens obtained at autopsy did not exhibit a positive immunoreaction to the antibodies studied in either the intracerebral or leptomeningeal endothelium. One exception did exist in the case of the AVM that was incidentally found at autopsy. In that case the endothelial immunoreaction was positive for PCNA and Flk-1, but it was negative for the MIB-1 and VEGF. Examples of immunohistochemically stained AVM specimens obtained during surgery are shown in Fig. 1. The endothelium displayed positive immunostaining for PCNA in 80% of patients and a positive reaction for the MIB-1 antibody in 12% of patients (Tables 1 and 2). Regardless of whether prior embolization therapy had been performed, the Flk-1 antibody could be detected in 80% of the malformations studied (Tables 1 and 2, and Fig. 1). Vascular endothelial growth factor was detected in 60% of patients (Tables 1 and 2). Correlations between clinical and immunohistochemical data are listed in Table 2. In AVMs that had been embolized before surgery, VEGF was expressed in 72% of cases. In contrast, in those cases in which prior embolization had not been performed, there was a positive immunoreaction in only 28% of cases. Endothelial cells from female patients exhibited immunoreaction more frequently than those from male patients for all proteins stained. There was no correlation between immunohistochemical findings and AVM location, prior hemorrhage, or patient age (Tables 1 and 2).

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TABLE 1
Clinical and immunohistochemical data in 25 patients with AVMs*

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<th>Lesion Location</th>
<th>S–M Grade</th>
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* Emb = embolization; emerg = emergency; parocc = parietooccipital; S–M = Spetzler–Martin; surg = surgical; tempocc = temporoparietal; temp = temporal; – = negative; + = positive.
Cavernoma Specimens

Clinical Aspects. Thirteen patients (six men and seven women) harboring cavernomas at various locations were surgically treated. The mean age of these patients at surgery was 39 years (range 19–67 years; Table 3). All cavernomas manifested with hemorrhages. In 12 patients, surgery was performed at least 6 months (range 6 months–10 years) after the last hemorrhage. One patient underwent surgery after experiencing acute neurological deterioration following a hemorrhage. Preoperative magnetic resonance imaging was routinely performed to exclude the presence of multiple lesions. Cases in which multiple cavernomas or known familial syndromes occurred were not available for review. In three cases in which an associated developmental venous anomaly was suspected on the basis of the magnetic resonance image, additional cerebral angiography was performed to rule out the presence of an AVM.

Immunohistochemical Findings. A positive immunoreaction for PCNA was observed in 11 specimens (85%), whereas no positive immunoreaction was observed for the MIB-1 antibody (Table 3). A specimen was judged to be positive for PCNA when cells exhibiting a positive reaction were clearly of endothelial origin. A positive reaction for VEGF was found in five cases, whereas the Flk-1 antibody stained positively in only four cases (Table 3 and Fig. 1F and 1G).

Discussion

Vascular Proliferation, Angiogenesis, and Growth of Cavernomas, and De Novo Cavernomas

The biological behavior of cavernous angiomas is not yet completely understood. So far, cavernomas are thought to arise during the early stages of embryogenesis and to grow according to malformatve mechanisms and blood-flow changes, leading to the formation of dilated blood vessels. Many reports have been published about the progression of cavernoma growth and changes in size. Furthermore, de novo formation of cavernomas with and without radiotherapeutic induction has been reported in cases of both familial and sporadic cavernomas. Consequently, questions have arisen concerning whether these lesions have a developmental or acquired nature and whether they bear a proliferating and/or neoangiogenic capacity. Notelet, et al., reported posi-
Endothelial proliferation

TABLE 2
Correlation between clinical and immunohistochemical data in 25 patients with AVMs

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<th>Factor</th>
<th>Case</th>
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TABLE 3
Clinical and immunohistochemical data in 13 patients with cavernomas

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Familial and Multiple Cavernomas

The cavernomas treated in this series were more likely of sporadic origin because there was no family history of neurological disorders in any of our cases. Because de novo genesis and growth of cavernomas have been reported in cases of multiple and familial cavernomas, it would be interesting to investigate the endothelial expressions of PCNA, MIB-1, VEGF, and Flk-1 in specimens resected from such patients, because the biological behavior of inherited lesions seems to be more aggressive than that of sporadic cavernomas. Such a study might provide a deeper insight into the mechanisms responsible for the de novo generation of cavernomas.

Angiogenesis of AVMs, Vascular Proliferation, Recurrent AVMs, and the Cause of AVMs

Clinical reports on the presence of enlarged AVMs and the recurrence of cerebral AVMs after normal findings have been revealed on postoperative angiograms have fostered arguments against the assumption that AVMs are strictly congenital lesions. Mullan and colleagues have pointed out that the current methods of intrauterine and neonatal ultrasonography have been used to identify aneurysms of the vein of Galen at a very early stage but so far have not aided in the discovery of an equivalent number of cerebral AVMs, even though these anomalies are far more frequently seen in neurosurgical practice. These clinical data lead to the hypothesis that cerebral AVMs may not be congenital lesions. The expression of VEGF in recurrent pediatric and adult AVMs has indicated a humoral mechanism mediated by VEGF that might play a role in AVM recurrence. Abdulrauf, et al., detected Flk-1 and VEGF in the endothelium of one patient who experienced a spontaneous obliteration of a cerebral AVM, documented by angiography. These authors have postulated an active angiogenic process in that case, with possible neovascularization occurring in that lesion in association with thrombosis. Therefore, it was of further interest to investigate whether VEGF and Flk-1 are expressed in the endothelium of a larger series of cerebral AVMs. Data obtained during the present study have confirmed the assumption that, regardless of a prior hemorrhage, both the ligand VEGF and its receptor Flk-1 were expressed in the endothelium of a consecutive series of 25 AVMs. The positive immunostainings for PCNA and Flk-1 in the one AVM specimen that was obtained at autopsy also indicate the potential for proliferation and neoangiogenesis in the endothelium of untreated AVMs. Sonstein, et al., described a predominant expression of VEGF in AVMs in children. This finding could not be confirmed by data from the present study because only one patient was a child. According to our data, however, the assumption of predominant expression of VEGF in pediatric patients may be questionable because VEGF expression was detected in the endothelium of specimens from 15 of our 24 adults. This contrasts with the findings of the series of Sonstein, et al., a fact that may be explained by their small group of eight adult patients in whom there were two cases of VEGF expression. Our clinical and immunohistochemical data on the endothelial proliferation and neoangiogenesis of AVMs showed that these lesions can grow
without induction by prior hemorrhage (Tables 1 and 2). In contrast with patients with cavernomas, in whom no positive reaction for MIB-1 was detected, we found posi-
tive immunostaining for this antibody in three of 25 AVM specimens. These results may be explained by the small number of cavernomas studied in the present series, but they may also provide a first hint that the endothelium of AVMs proliferates more aggressively than that of caver-
nomas.22

Recently, the theory that AVMs are not purely develop-
mental lesions was supported by a case report on an AVM that recurred at a different location after the patient had undergone radiosurgery.30 To elucidate the possible mech-

aism operative during the development of AVMs, it would be of particular interest to study surgical specimens of recurrent,20 de novo, and growing37,39,48 lesions.

Impact of Incomplete Obliteration on Angiogenesis of AVMs

The natural history of AVMs includes a high risk of morbidity and mortality2,10,14,23,31,48 and calls for a tailored treatment regimen for each patient. In cases deemed elec-
tive, three treatment options can be offered, including en-
donovascular occlusion, stereotactic radiation treatment, and microsurgical treatment. At our institution, the patients for whom treatment is elective first undergo endovascular

obliteration. The residual nidus is later treated either radiosurgically or by microsurgical resection. In cases in which an ICH has caused a space-occupying mass, how-

ever, emergency evacuation of the AVM is performed. It was of interest to compare immunohistochemical data ob-
tained in emergency cases with data obtained in elective
cases to elucidate the effect of preoperative embolization

therapy on the residual AVM nidus. In the present study, we found the Flk-1 epitope to be expressed in the endo-
thelium of the AVM nidus in both emergency and elective
cases. The embryological character of the AVM nidus ves-
sels is shown by this immunohistochemical staining, be-
cause Flk-1 immunoreactivity can also be detected in ves-
sels of the developing human fetal brain but not in vessels of the adult brain.15,28,38 The fact, however, that VEGF is expressed in a much higher percentage of cases deemed elec-
tive (embolized), compared with emergency cases of

AVMs, is of interest. It is known that hypoxia leads to the

secretion of VEGF.24 The VEGF binds to Flk-1 and medi-

ates angiogenesis and, thus, regrowth and vascular prolif-
eration.26 The partial embolization of cerebral AVMs (or

the partial occlusion resulting from radiotherapy and/or surgery) most probably leads to a local endothelial hypox-

ia within the obliterated portion of the AVM nidus, which,
in fact, mediates the neovascularization and growth of the

malformation. So far, we have not surgically treated pa-
tients with completely embolized AVMs. Nevertheless, it

cannot be excluded that these patients, as well as patients

with radiosurgically obliterated AVMs, also experience re-
currences in response to the mechanism described earlier.

The clinical significance of these data is evident because recurrent AVMs obviously may cause significant morbidity or even mortality. For this reason, complete obliteration of the nidus should be the goal in any AVM treatment. A larger and prospective study should be conducted to determine which of the possible treatment regimens has more prognostic value for the prediction of regrowth by using both the aforementioned immunohistochemical pro-
cedures and long-term follow-up data.

Conclusions

Vascular proliferation and angiogenesis of cavernomas and AVMs were documented using immunohistochemical studies. The increased level of angiogenesis in partially

obliterated AVMs clearly points out the need for a radical and complete occlusion of cerebral AVMs, because recur-
rences may lead to significant risks of morbidity.

Future studies on the molecular mechanisms operating during the development of cavernomas and AVMs may help elucidate the pathomechanism of the growth and/or de novo appearance of these lesions.

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