Microvascular pathological features of immediate perinidal parenchyma in cerebral arteriovenous malformations: giant bed capillaries

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Object. The behavior of brain tissue in cases of arteriovenous malformations (AVMs) is a matter of debate. The authors believe that the local microvascular environment in the AVM bed shares the hemodynamic changes influencing that behavior in one way or another. The purpose of this study was to investigate the microvascular pathological features in the immediate perinidal brain tissue.

Methods. This retrospective study was conducted using excised AVM specimens obtained in 35 patients, from which the authors selected 20 specimens that fulfilled the criteria for sufficient brain tissue around the excised nidus. Specimens were stained with hematoxylin and eosin, and the immediate perinidal microvascular environment was examined using light microscopy.

Conclusions. Eighty-five percent of the AVMs studied showed the presence of huge, dilated capillaries, and 65% showed severe congestion of these capillaries. The authors have named these capillaries “giant bed capillaries.” In this study capillary bleeding was shown in AVMs, and a pericapillary space was seen around some vessels. The brain parenchyma containing AVMs with these findings proved to be significantly ischemic.

Keywords • arteriovenous malformation • perinidal brain tissue • histopathological study

Arteriovenous malformations are generally a collection of abnormal blood vessels interposed between feeding arteries and draining veins, and substitute for the normal capillaries. Structural imperfections and immaturity of the vascular walls may mean that AVMs result from histoembryonic maldevelopment, yet the presence of brain parenchyma between these vessels leads to the conclusion that it is a malformation rather than a vascular neoplasm. The accepted explanation of an AVM is that it is a focal, congenital absence of a capillary bed.

Published reports on AVMs are divided into two types, natural history and descriptive studies. The latter are more focused on operative methods than pathological findings. Most researchers in the field of pathology are interested mainly in the AVM itself. Our research focuses on the associated parenchymal pathological features.

Some embryological and histological investigations have proven that the capillary mesh precedes the more definable neurovascular system during embryological development, and the absence of direct connections between arteries and veins in the normal human brain has been reported. Other physiological and hemodynamic studies have proven that the nidus is the main determinant of physiological properties of AVMs, that the maximal effect of AVMs on local cerebral blood flow is at a 2- to 4-cm distance from its margin, and that the post–AVM resection blood redistribution effects are frequently observed intraoperatively. Spetzler’s normal perfusion pressure breakthrough theory and the overload phenomenon and its relation to the angiographic findings in “modja-modja” vessels have also been proven. These facts have attracted our attention to the possibility that there may be microenvironmental changes influencing the AVM behavior that go hand-in-hand with the hemodynamic ones. Spetzler pointed out that possibility in one of his comments accompanying a report by Young, et al. The aim of this study was to investigate the microvascular environment of the brain parenchyma immediately adjacent to the AVM nidus.

Clinical Material and Methods

In this retrospective study we randomly selected specimens obtained in 35 of our 250 patients with AVMs who underwent surgery between 1985 and 1998. Four patients underwent preoperative endovascular embolization therapy, and nine underwent multistage operations. No age, sex, or technical bias influenced our selection; demographic data are shown in Table 1.

Abbreviations used in this paper: AVM = arteriovenous malformation; RBC = red blood cell.
TABLE 1
Demographic data in patients with giant bed capillaries in cerebral AVMs*  

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Clinical Presentation</th>
<th>AVM Grade†</th>
<th>Nidus Location of Op</th>
<th>Stage (Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34.0, M</td>
<td>isch/hem</td>
<td>III</td>
<td>sup temporal</td>
<td>single</td>
</tr>
<tr>
<td>2</td>
<td>19.0, F</td>
<td>hem/isch</td>
<td>III</td>
<td>deep temporal</td>
<td>multiple</td>
</tr>
<tr>
<td>3</td>
<td>20.0, F</td>
<td>prog</td>
<td>III</td>
<td>deep splenial</td>
<td>single</td>
</tr>
<tr>
<td>4</td>
<td>1.6, F</td>
<td>hem/isch</td>
<td>III</td>
<td>deep occipital</td>
<td>multiple</td>
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<tr>
<td>5</td>
<td>18.0, M</td>
<td>hem/isch/prog</td>
<td>III</td>
<td>deep occipital</td>
<td>single</td>
</tr>
<tr>
<td>6</td>
<td>25.0, F</td>
<td>hem/isch</td>
<td>II</td>
<td>sup temporal</td>
<td>multiple</td>
</tr>
<tr>
<td>7</td>
<td>44.0, F</td>
<td>isch/hem</td>
<td>III</td>
<td>sup frontal</td>
<td>multiple</td>
</tr>
<tr>
<td>8</td>
<td>25.0, F</td>
<td>hem/isch</td>
<td>II</td>
<td>sup cerebellar</td>
<td>multiple</td>
</tr>
<tr>
<td>9</td>
<td>37.0, M</td>
<td>hem/isch</td>
<td>III</td>
<td>sup parietal</td>
<td>multiple</td>
</tr>
<tr>
<td>10</td>
<td>13.0, F</td>
<td>isch</td>
<td>I</td>
<td>sup frontal</td>
<td>multiple</td>
</tr>
<tr>
<td>11</td>
<td>37.0, M</td>
<td>hem</td>
<td>III</td>
<td>sup parietal</td>
<td>single</td>
</tr>
<tr>
<td>12</td>
<td>14.0, M</td>
<td>isch</td>
<td>I</td>
<td>sup temporal</td>
<td>single</td>
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<tr>
<td>13</td>
<td>4.0, M</td>
<td>isch</td>
<td>II</td>
<td>sup sylvian</td>
<td>single</td>
</tr>
<tr>
<td>14</td>
<td>16.0, F</td>
<td>hem/isch</td>
<td>II</td>
<td>sup parasilien</td>
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<td>15</td>
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<tr>
<td>16</td>
<td>41.0, M</td>
<td>isch</td>
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<tr>
<td>17‡</td>
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<td>II</td>
<td>sup frontoparietal</td>
<td>single</td>
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<tr>
<td>18‡</td>
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<td>prog/isch</td>
<td>IV</td>
<td>sup occipital</td>
<td>single</td>
</tr>
<tr>
<td>19‡</td>
<td>26.0, F</td>
<td>prog</td>
<td>II</td>
<td>sup temporal</td>
<td>single</td>
</tr>
<tr>
<td>20‡</td>
<td>22.0, M</td>
<td>isch</td>
<td>III</td>
<td>sup frontal</td>
<td>single</td>
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</tbody>
</table>

* Hem = hemorrhagic manifestations; isch = ischemic manifestations (epilepsy and/or headache); prog = progressive/fluctuating neurological manifestations; sup = superficial.
† Spetzler–Martin grade.
‡ Treated with preoperative embolization.

As a control we used three autopsy specimens; data for these are shown in Table 2.

Histological Preparation

Sections of 5-μm thickness were sliced from the paraffin blocks containing the 35 resected specimens and the control tissues, then stained in hematoxylin and eosin by using the ordinary staining method. Specimens with no perinidal tissue, those with destroyed, shredded brain parenchyma, and contaminated specimens were excluded. On that basis we selected 20 of the 35 specimens in which there was enough tissue, those with destroyed, shredded brain parenchyma, and other times it was disrupted and RBCs escaped to the surrounding brain tissue (Fig. 1d).

Other Parenchymatous Changes

Other pathological changes were detected in 90% of the perinidal parenchymas studied, including degenerating neurons (with pyknotic nuclei and dark cytoplasm [Fig. 2a]), gemistocytic astrocytes (Fig. 2b), increased number of astrocytes (Fig. 2c), and brain edema (Fig. 2a and c). These findings were absent in control specimens. They displayed the normal size for capillaries and their neurons were shaped normally (Fig. 2d).

Discussion

General Architecture of AVMs

There is no firm anatomical evidence of direct connections between arteries and veins in the normal human brain. Anatomically, the nidus is the point toward which feeding arteries converge and from which the enlarged veins drain. Functionally, it represents the low-impedance pathway (shunt) between arteries and veins.

Some researchers, such as Kaplan, et al., have emphasized that the underlying lesion of the AVM is a defect of a capillary network that preserves a primitive arteriovenous communication and replaces the normal intervening capillary network, and they considered the AVM to be composed of two parts: the shunt itself, and the feeding and draining vessels. Our study revealed an addition to this aspect of AVM pathology; we found that these perinidal capillaries are part of this entity’s pathological features, as evidenced by the abnormalities of these vessels in terms of size, engorgement with blood, and weakness. With the present

TABLE 2
Demographic data in control patients with AVMs

<table>
<thead>
<tr>
<th>Control No.</th>
<th>Age (yrs), Sex</th>
<th>Cause of Death</th>
<th>Interval Btwn Death &amp; Autopsy</th>
<th>Brain Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55, M</td>
<td>fulminating disseminating herpes infection</td>
<td>5 hrs postmortem</td>
<td>normal</td>
</tr>
<tr>
<td>2</td>
<td>43, M</td>
<td>familial amyloid polyneuropathy</td>
<td>15 hrs postmortem</td>
<td>normal</td>
</tr>
<tr>
<td>3</td>
<td>56, F</td>
<td>heart failure</td>
<td>8 hrs postmortem</td>
<td>normal</td>
</tr>
</tbody>
</table>
findings we add a third component to AVM pathology, which is these abnormal capillaries.

Dilated Capillaries

Woollam and Millen defined the normal range for diameter of the cerebral capillaries to be between 0.005 and 0.012 mm. Our findings show that the size of the capillaries in the specimen studied is larger than the known normal range and the control capillaries. If these capillaries were dilated secondary to acute congestion (operative effect) alone, they would have ruptured before reaching the giant size. Also, some of the capillaries studied had RBC diapedesis (not an acute event). Instead, there was a state of gradual compensatory dilation under the influence of a chronic pathological state (we believe it was chronic ischemia), which would have been associated in some cases with abnormalities in vessel permeability. Feindel and Perot and Nagasawa, et al. observed the effect of metabolic accumulation on opening of local vascular beds after acute ischemia, but did not specify capillaries in their studies. To the best of our knowledge, our report is the first to show the effect of chronic ischemia on local microvascular beds.

Capillary Congestion

The serious capillary congestion in our cases can be explained by the hyperemic phenomena of Young, et al., the overload phenomena of Takemae, et al., or the postulated flow reversal in AVM vessels in which the presence of blood distribution in many directions was assumed.

Capillary Bleeding

Our study gives the first proof of capillary bleeding in AVMs. The general idea is that the bleeding site in an AVM is always on the venous side, as stated by Miyasaka, et al., and Nores and Grip.

Hallervorden speculated about the concept of a blood–brain barrier defect (dysoria) in cerebral tissue by which RBCs may escape the capillary wall. This would occur through true hemorrhage, with disruption of the capillary wall continuity, or by RBC diapedesis, a passive act requiring two factors: increased permeability (endothelial damage) and a driving force (congestion).

The phenomenon of trapped RBCs presented in our study must be differentiated from the following four types of hemorrhage: ball hemorrhage, described by Haymaker and Johnston; miniature apoplectic hematomas, described by Anders and Eicke; contusion hemorrhage, described by Lindenberg and Freytag; and ring hemorrhage, described by Krogh. In all four types damaged parenchyma permeated with RBCs are seen. That is not the case in Fig. 1c, in which the RBCs are present in a clear pericapillary space devoid of brain tissue.

Pericapillary Space

Maynard, et al. stated that in the brain, 85% of the
capillary circumference is directly surrounded by the foot processes of glial cells with no intervening space. Thus, the presence of a space circumferentially surrounding the bed capillaries is a new finding. Duvernoy, et al.,8 classified the perivascular spaces in brain parenchyma into the Pfeifer space (the neural tissue perivascular zone devoid of capillaries) and the Virchow–Robin space (the subarachnoid sleeve surrounding the intracerebral vessels and ending at the level of the arterioles). Woollam and Millen31 spoke about the His perivascular space, which is perineural, surrounds the outer reticular layer of the Virchow–Robin space, and ends at the surface of the brain under the pia mater. This space develops due to brain shrinkage after fixation of the specimen (an artifact). The space we report is none of them; it is a complete space that separates the capillary wall from the surrounding brain parenchyma all around, and in our specimens it trapped escaping RBCs, which failed to disrupt it and which permeated the surrounding brain parenchyma. This observation would never be made if that were not a true space. The presence of that space clearly explains the RBC entrapment as differentiated in the foregoing discussion.

**Imprints of Chronic Ischemia**

The brain parenchyma containing these capillaries is seriously affected, as evidenced by the presence of damaged neurons and glial cells, together with brain edema. That holds true for most of the cases studied, whether they were treated with preoperative embolization. We consider these changes to be due to chronic ischemia, because no other chronic pathological processes were detected. This agrees with the findings of Okabe, et al.,23 Batjer, et al.,4 and Takeuchi, et al.29 Such effects are not caused by hemorrhage, because a large hemorrhage is needed to effect such changes, and because neurons are not affected by recent hemorrhages (they are damaged by iron leaching from RBCs in old hemorrhages). The bleeding demonstrated in the photomicrographs is small and recent (intact RBCs without iron pigments in the tissue), so these changes in parenchyma are not attributable to hemorrhage. The plasma escaping the capillary wall would create similar effects due to neuron suffocation. Plasma is basophilic in hematoxylin and eosin preparations, a finding that is absent in our photomicrographs. Thus, such parenchymal effects are not attributed to plasma escape. Brain edema may be better explained by the acute added to chronic hypoperfusion effect, as stated by Morgan and Sundt.19

We cannot deny the ischemic effect of preoperative embolization or staged surgery on the perinidal parenchyma, yet we believe that these procedures have an additive effect on that already imposed by the AVM. This agrees with the findings of Deruty, et al.7

We have named these vessels the giant bed capillaries, and define them as follows: cerebral parenchymal microvessels of capillary nature, lined by a single layer of flat endothelium, and arranged in a relatively peripheral position to the main pathological entity. Their size is larger
Pathology of the immediate perinidal parenchyma in AVMs

than the average for normal capillaries, and mostly congested.

Many points still exist as a matter of debate. Would these giant bed capillaries be a primary pathological feature of AVMs, or just a secondary neovascularization induced by the hypoperfusion state of the perinidal brain parenchyma? Would they be more dilated and congested in the living brain under the influence of blood pressure compared with the vessels observed in the fixed slides, or would they just return to their normal size after excision of the AVM? Would the permeability changes shown in this study be explained by different hemodynamic mechanisms as the transmission of undamped perfusion pressure to the capillary bed after AVM excision, as speculated by Wilson, et al.? Would the giant bed capillaries explain, on an anatomical basis, the “modjamosja” vessels as speculated by Takekamae, et al.? In a previous study conducted by our team, in which infrared thermography was used, a temporary local increase in temperature of the AVM bed immediately after AVM infrared thermography was used, a temporary local increase these points requires further research.

Would the permeability changes shown in this study be explained by different hemodynamic mechanisms as the transmission of undamped perfusion pressure to the capillary bed after AVM excision, as speculated by Wilson, et al. or by the theory of acute added to chronic hypoperfusion, as speculated by Morgan and Sundt? Would the giant bed capillaries explain, on an anatomical basis, the “modjamosja” vessels as speculated by Takekamae, et al.? Are these capillaries related in one way or another to spontaneous rupture of AVMs or to the normal perfusion pressure breakthrough phenomenon? The verification of all these points requires further research.

References


Manuscript received August 9, 2002. Accepted in final form November 26, 2002.
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