Platelet aggregation within cerebral arteriovenous malformations

GARNETT R. SUTHERLAND, M.D., F.R.C.S.(C), MARTIN E. KING, PH.D.,
CHARLES G. DRAKE, M.D., F.R.C.S.(C), SIDNEY J. PEERLESS, M.D., F.R.C.S.(C), AND
WILLIAM C. VEZINA, M.D., F.R.C.P.(C)

Departments of Clinical Neurological Sciences (Division of Neurosurgery) and Nuclear Medicine, University of Western Ontario, London, Ontario, Canada

Turbulence within cerebral arteriovenous malformations (AVM's) may lead to endothelial disruption, platelet aggregation, and thrombus formation. This hypothesis would account for many of the pathological features in AVM's, including intimal hyperplasia and arterial thrombosis with or without organization. In this study, a dual-isotope method employing indium-111-labeled platelets and technetium-99m-labeled red blood cells was used to evaluate in vivo platelet aggregation in 20 patients with AVM's. The use of two isotopes allows subtraction of the blood-pool platelets and calculation of the ratio of the indium deposited: the indium in the blood pool (In(D)/In(BP)).

After a 24-hour incubation period, eight of the 20 patients demonstrated platelet aggregation in their AVM's with a mean In(D)/In(BP) ratio of 0.71 ± 0.36 (± standard deviation). Seven of these AVM's were available for pathological study and all of them demonstrated evidence of arterial thrombosis of variable age. In the remaining 12 patients, the In(D)/In(BP) ratio was not significantly elevated (mean 0.02 ± 0.13), indicating the absence of active platelet aggregation during this short interval of study. Five of these AVM's were pathologically examined, four of which showed evidence of arterial occlusion. It is concluded that platelet aggregation is a common occurrence in cerebral AVM's and may account for the dynamic histopathology often seen in these lesions.

KEY WORDS • platelet aggregation • isotope-labeled platelets • arteriovenous malformation

Cerebral arteriovenous malformations (AVM's) are lesions characterized by numerous large abnormal vascular channels with poorly developed media and elastica layers. Kaplan, et al., divided the AVM complex into two parts: 1) the shunt, consisting of poorly developed vessels at the precapillary and capillary level; and 2) the arteries and veins involved in the conduction of high flow through the low-resistance shunt. The vessels are further characterized by a low intraluminal pressure and a high flow velocity, resulting in irregular flow patterns and turbulence. The turbulent flow may result in endothelial injury followed by platelet adhesion to the exposed subendothelial collagen matrix with subsequent thromboxane and prostaglandin synthesis and platelet degranulation. This would lead to further platelet aggregation and, together with fibrin derived from the activated clotting cascade, the building of a stable platelet plug or thrombus. Repeated endothelial injury may account for the pathological findings of vascular thrombosis and focal endothelial thickening seen almost universally in these lesions. It would also explain the pathophysiology reported in cases of spontaneous thrombosis.

Recently, we have used indium-111 (111In)-labeled platelet scintigraphy to evaluate in vivo platelet aggregation within giant intracranial aneurysms, correcting the blood-pool volume with technetium-99m (99mTc)-labeled red blood cells. As the pathophysiology of AVM's suggests ongoing endothelial injury, we have applied the same technique in a series of patients with AVM's.

Clinical Material and Methods

Patient Population

This report is based on 20 consecutive patients admitted to the University Hospital Division of Neuro-
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surgery, with a diagnosis of cerebral AVM. Before study of platelet aggregation, all patients underwent four-vessel cerebral angiography and computerized tomography (CT) scanning to determine the size, location, and nature of the AVM. The technique of the radionuclide studies and the potential complications were explained to all patients prior to obtaining their written consent to undergo these tests. Blood analysis, including hemoglobin, white blood cell count, platelet count, and prothrombin and partial thromboplastin time, was obtained on all patients before the study.

Radionuclide Studies

Platelets were separated and labeled by a technique modified as described by Heaton, et al.,8,10 and as previously reported by us.28 Thirty hours after injection of the labeled platelet suspension, the patients were brought to the Nuclear Medicine Department where they underwent cranial and upper thoracic scanning to determine the distribution of 111In. The technique required the acquisition of pairs of separate images, one with data from the 111In window of the pulse-height analyzer and the other with data from the 99mTc window. This was necessary so that the scatter of the higher-energy 111In into the 99mTc window could be determined and used in the subtraction of the blood-pool activity at a later stage. Thus:

\[
\begin{align*}
\text{Isotope} & \quad \text{Window} & \quad \text{AVM} & \quad \text{Aortic Arch} \\
\text{In} & \quad \text{Tc} & \quad \text{In(BP + D)} & \quad \text{In(BP)} \\
\text{In} & \quad \text{In(BP + D)} & \quad \text{In(BP)},
\end{align*}
\]

where \( S = \) scatter, \( BP = \) blood pool, and \( D = \) deposition of radionuclides.

Red blood cells were labeled with 99mTc.24,28 The patients then underwent repeat scanning to obtain one further pair of images, with one image for each energy window, as described above:

\[
\begin{align*}
\text{Isotope} & \quad \text{Window} & \quad \text{AVM} & \quad \text{Aortic Arch} \\
\text{Tc} & \quad \text{Tc} & \quad \text{Tc + In(BP + D)} & \quad \text{Tc + In(BP)} \\
\text{In} & \quad \text{In(BP + D)} & \quad \text{In(BP)}.
\end{align*}
\]

In each case, two regions of interest were defined, the target (AVM) and a single reference (aortic arch). The AVM contained activity in the blood pool due to circulating platelets and possibly additional activity due to local platelet deposition, while the reference was assumed to contain blood-pool activity only.

As previously described,28 the blood-pool activity was subtracted through the equation:

\[
\frac{\ln(BP) \ AVM + \ln(D) \ AVM}{\ln(BP) \ AVM} = 1 + \frac{\ln(D) \ AVM}{\ln(BP) \ AVM},
\]

\[
\frac{\ln(D) \ AVM}{\ln(BP) \ AVM} = \frac{\ln(BP + D) \ AVM}{\ln(BP) \ AVM} - 1.
\]

where \( \ln(BP) \ AVM = \ln(BP) \) aortic arch \( \times \) volume correction factor (VCF). A ratio greater than 0 indicates indium deposition and therefore platelet aggregation.

Observations

Twenty patients were prospectively examined from January through June, 1984. Eleven males and nine females participated in the study. The mean patient age was 34 \pm 11 years (mean \pm standard deviation). Participants were categorized into Groups 1 and 2 on the basis of \( \ln(D)/\ln(BP) \) ratios; those allocated to Group 1 demonstrated \( \ln(D)/\ln(BP) \) ratios significantly greater than 0 (mean age 29 \pm 12 years), whereas Group 2 individuals failed to achieve ratios of significance (mean age 36 \pm 10 years). Hemoglobin, white blood cell count, platelet count, and prothrombin and partial thromboplastin times were found to be within normal limits for all patients, with no statistical difference between groups (\( p > 0.05 \)).

Group 1

The eight patients who demonstrated platelet aggregation comprised Group 1 (Table 1). The majority of these patients presented with a seizure disorder. In addition, hemiparesis and/or hemorrhage were frequently encountered. Exotropia, cardiac murmur, and hemianopsia were unusual clinical findings. Two patients had hemorrhagic episodes and one had previously undergone embolization, all at a time remote from the radionuclide study.

Radiographic visualization of AVM's by CT brain imaging revealed that the malformations were evenly distributed throughout the supratentorial compartment. Two of the AVM's were partly calcified. The CT criteria for acute hemorrhage were not in evidence; however, zones of cerebral hypodensity (compatible with chronic changes secondary to old hemorrhagic episodes) were present in two patients. All patients underwent four-vessel angiography, with all but one of the AVM's being larger than 7 cu cm. Multiple feeding and draining vessels were present in all of the malformations.

On pathological examination, all seven excised malformations consisted of multiple vascular channels within gliotic brain. Thrombosed vessels of variable age, focal intimal thickening, calcification, and hem siderin deposits were present in all specimens. Three specimens showed evidence of old or recent endovascular embolization.

The results of radionuclide isotope studies in Group 1 patients are shown in Table 2. The \( \ln(D)/\ln(BP) \) ratio was elevated in all cases, with a mean value of 0.71 \pm 0.36.

The following case of a 14-year-old boy who presented after two episodes of generalized convulsions illustrates the findings in Group 1 patients. A CT scan of this patient (Fig. 1) revealed a high-density right frontal lesion that, following injection of contrast medium, showed serpentine enhancement. Subsequent an-

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TABLE 1
Clinical, radiographic, and pathological findings in Group 1 patients (with platelet aggregation) *

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Clinical Features</th>
<th>Radiographic Findings</th>
<th>Pathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>generalized seizures</td>
<td>large rt frontal AVM</td>
<td>multiple vascular channels within gliotic brain; thrombosed vessels of variable age;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>focal intimal thickening; calcification; evidence of recent embolization</td>
</tr>
<tr>
<td>2</td>
<td>focal seizure disorder</td>
<td>large rt anterior midtemporal AVM</td>
<td>multiple vascular channels within gliotic brain; thrombosed vessels of variable age;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>focal intimal thickening; calcification; hemosiderin deposits</td>
</tr>
<tr>
<td>3</td>
<td>focal seizure disorder</td>
<td>large lt anterior midtemporal AVM</td>
<td>multiple vascular channels within gliotic brain; thrombosed vessels with many containing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a clear foreign substance; focal intimal thickening; calcification; foreign-body</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>giant-cell reaction</td>
</tr>
<tr>
<td>4</td>
<td>generalized seizures</td>
<td>small rt sylvian fissure AVM</td>
<td>same as in Case 2</td>
</tr>
<tr>
<td>5</td>
<td>generalized seizures, hemorrhage; lt hemiparesis</td>
<td>large rt frontal, partially calcified AVM; encephalomalacia</td>
<td>same as in Case 2</td>
</tr>
<tr>
<td>6</td>
<td>generalized seizures, hemorrhage; lt hemiparesis</td>
<td>large rt frontal, partially calcified AVM; encephalomalacia</td>
<td>same as in Case 2</td>
</tr>
<tr>
<td>7</td>
<td>rt eye exotropia; cardiac murmur</td>
<td>large thalamic midbrain quadrigeminal cistern AVM; aneurysmal dilatation of vein of Galen</td>
<td>same as in Case 1; recent hemorrhage</td>
</tr>
<tr>
<td>8</td>
<td>progressive lt spastic hemiparesis; lt homonymous hemianopsia</td>
<td>large rt basal ganglia thalamic AVM; large varix</td>
<td>AVM not excised</td>
</tr>
</tbody>
</table>

* AVM = arteriovenous malformation.

FIG. 1. Preoperative computerized tomography scan demonstrating the serpentine enhancement of a right frontal arteriovenous malformation.

angiography confirmed the large right frontal AVM with several feeding vessels arising from the anterior choroidal, middle cerebral, and anterior cerebral arteries. Multiple draining veins fed mainly into the superior sagittal sinus. Radionuclide studies (Figs. 2 and 3) showed platelet aggregation, with an In(D)/In(BP) ratio of 1.52 ± 0.31. Treatment consisted of staged endovascular embolization with isobutyl-2-cyanoacrylate occluding 40% to 50% of the nidus, followed by surgical

TABLE 2
Dual-isotope studies using 111In-labeled platelets and 99mTc-labeled red blood cells

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case No.</td>
<td>In(D)/In(BP) AVM*</td>
</tr>
<tr>
<td>1</td>
<td>1.52 ± 0.31</td>
</tr>
<tr>
<td>2</td>
<td>0.78 ± 0.27</td>
</tr>
<tr>
<td>3</td>
<td>0.52 ± 0.11</td>
</tr>
<tr>
<td>4</td>
<td>0.51 ± 0.21</td>
</tr>
<tr>
<td>5</td>
<td>0.61 ± 0.02</td>
</tr>
<tr>
<td>6</td>
<td>0.75 ± 0.22</td>
</tr>
<tr>
<td>7</td>
<td>0.67 ± 0.11</td>
</tr>
<tr>
<td>8</td>
<td>0.33 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>mean 0.71 ± 0.36</td>
</tr>
</tbody>
</table>

* In(D)/In(BP) = ratio of the indium deposited:the indium in the blood pool. For explanation see text. Values are mean ± standard deviation. AVM = arteriovenous malformation.
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Fig. 2. Dual-isotope images. The image on the left was obtained from the $^{99m}$Tc window of the pulse-height analyzer and the one on the right from the $^{111}$In window. Targets are placed over the arteriovenous malformation (AVM) and the aortic arch. The $^{99m}$Tc window contains both technetium activity and scatter from the higher-energy indium. The indium window contains blood-pool activity in the aortic arch and both blood-pool and deposition activity in the AVM.

excision. Pathologically, the lesion consisted of thick- and thin-walled vessels within gliotic brain. The histology showed thrombosis of variable age, focal intimal thickening, calcification, and evidence of recent embolization.

Group 2

Group 2 consisted of 12 patients in whom platelet aggregation was not demonstrated (Table 3). Clinical features in Group 2 patients were similar to those in Group 1, and consisted of seizures, hemorrhage, migraine, facial pain, and hemiparesis. Computerized tomography brain imaging demonstrated partial calcification in four patients with AVM's, and two had adjacent encephalomalacia indicative of previous intracerebral hemorrhage. All but one of the AVM's were noted to be supratentorial in location. Cerebral angiography showed that all of the AVM's were large (> 7 cu cm) and supplied by multiple feeding and draining vessels.

On pathological examination, four of the five excised malformations showed evidence of vascular thrombosis of variable age, focal intimal thickening, and calcification. Two were associated with hemosiderin deposition, and one had evidence of previous endovascular embolization.

The results of radionuclide isotope studies in Group 2 patients are presented in Table 2. The ln(D)/ln(BP) ratios were not elevated, the mean value being 0.02 ± 0.13.

Discussion

This prospective study of 20 patients with cerebral AVM's has demonstrated a high incidence of ongoing platelet aggregation within AVM's, as defined by dual-isotope scanning. Platelet function is known to be well preserved following in vitro indium labeling, with no alteration in platelet survival time or in the in vitro aggregation response induced by collagen. Since its introduction, the $^{111}$In-labeled platelet method has been
FIG. 3. In this dual-isotope image the blood-pool activity has been subtracted, leaving only excess indium activity within the arteriovenous malformation, reflecting platelet aggregation. The ratio \( \text{In(D)/In(BP)} \) was 1.52 ± 0.31 (mean ± standard deviation) (see text for explanation).

used to evaluate in vivo platelet aggregation related to catheter thrombogenicity, coronary artery bypass grafts, deep-vein thrombosis, carotid artery atherosclerotic disease, and giant intracranial aneurysms.

It is speculated that endothelial injury within the AVM secondary to turbulent blood flow would result in platelet adherence, shape change, prostaglandin and thromboxane synthesis, and the expulsion of vacuolar contents. This would induce further platelet aggregation and, together with an activated clotting cascade, would cause the formation of a stable platelet plug or thrombus. The release mechanism would liberate not only adenosine diphosphate, thus promoting aggregation, but also other biologically active materials, including serotonin, platelet factor IV, \( \beta \)-thromboglobulin, and platelet mitogenic factor. The platelet mitogenic factor stimulates the growth and migration of vascular smooth-muscle cells and fibroblasts. In addition, platelets release a collagenase, various lysosomal hydrolases, and several coagulation proteins including factors V and VIII and fibrinogen. Fibrin and its degradation products, possibly along with complement chemoattractants, recruit tissue macrophages and circulating monocytes to a wound site, and these cells, when stimulated, continue producing the necessary growth factors and chemoattractants until wound repair is complete.

Within an AVM a process of repeated hemodynamic injury and healing may be established, leading to the histological changes of wound healing (that is, vascular thrombosis of variable age with or without recanalization, focal intimal hyperplasia, and calcification). Our study supports this hypothesis through the demonstration of ongoing platelet aggregation and the histological findings of chronic wound healing in all but one of the excised malformations.

Our inability to demonstrate platelet aggregation in Group 2 patients may indicate the absence of recent endothelial injury or recent repair of exposed subendothelium. It must be appreciated that the study technique described here can only detect platelet aggregation within the AVM that is ongoing during the 30-hour period of study. In addition, the quantity of platelet aggregation would have to exceed the sensitivity of our method, which differentiates between blood pool and blood pool plus deposited indium. It should be noted that both patient groups were comparable in clinical presentation and in the size, type, and location of the AVM. The only small AVM, less then 7 cu cm, was found in a Group 1 patient. One patient in each group had undergone endovascular embolization 1 to 2 years prior to radionuclide studies. This therapeutic modality could certainly contribute to ongoing platelet aggregation. In view of the pattern of referral to our unit, all patients (in both groups) in whom hemorrhage had occurred were studied at a time remote from the ictus, thereby lessening the effect of this variable in our study.

Within the AVM complex, the degree of thrombosis induced by endothelial injury would be counterbalanced by removal of activated clotting factors, prostaglandins, and thromboxane in the passing circulation, and by the simultaneous activation of plasminogen to plasmin. In the presence of extensive endothelial injury, this balance could be offset toward thrombosis and therefore, in theory, lead to partial or even complete thrombosis of the AVM. Etiological factors that may produce extensive endothelial injury would include excessive turbulence, hemorrhage, radiation therapy, or endovascular embolization. This may, therefore, be the underlying pathophysiology in the reported cases of spontaneous thrombosis of cerebral AVM's, and the progressive thrombosis seen in association with either radiation therapy or endovascular embolization. Furthermore, organization within the thrombosed AVM could lead to recannulation and hence the angiographic reappearance of the lesion.

Conclusions

An elevated \( \text{In(D)/In(BP)} \) ratio as determined by dual-isotope radionuclide studies constitutes prima facie...
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**TABLE 3**

Clinical, radiographic, and pathological findings in Group 2 patients (without platelet aggregation)*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Clinical Features</th>
<th>Radiographic Findings</th>
<th>Pathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>focal seizures</td>
<td>large lt parieto-occipital AVM</td>
<td>multiple vascular channels within gliotic brain; thrombosed vessels of variable age; focal intimal thickening, calcification</td>
</tr>
<tr>
<td>2</td>
<td>focal seizures</td>
<td>large lt paracentral AVM</td>
<td>AVM not excised</td>
</tr>
<tr>
<td>3</td>
<td>focal seizures: rt hemispheric headache</td>
<td>large rt parietal occipital AVM</td>
<td>AVM not excised</td>
</tr>
<tr>
<td>4</td>
<td>focal seizure disorder; hemorrhage; rt hemiparesis</td>
<td>large lt posterior sylvian fissure AVM; encephalomalacia</td>
<td>AVM not excised</td>
</tr>
<tr>
<td>5</td>
<td>focal seizure disorder; subarachnoid hemorrhage</td>
<td>large rt parietal AVM; 1-cm aneurysm of the basilar bifurcation</td>
<td>same as in Case 1: foci of acute &amp; chronic inflammatory cell infiltration; hemosiderin deposits</td>
</tr>
<tr>
<td>6</td>
<td>hemorrhage; transient lt hemiparesis</td>
<td>large lt parietal AVM; encephalomalacia</td>
<td>same as in Case 6</td>
</tr>
<tr>
<td>7</td>
<td>subarachnoid hemorrhage</td>
<td>large lt parietal AVM</td>
<td>multiple vascular channels within gliotic brain; thrombosed vessels, many containing a clear foreign substance; focal intimal thickening; calcification; foreign-body giant-cell reaction</td>
</tr>
<tr>
<td>8</td>
<td>migraine; subarachnoid hemorrhage</td>
<td>large lt occipital AVM</td>
<td>AVM not excised</td>
</tr>
<tr>
<td>9</td>
<td>migraine</td>
<td>large rt parietal AVM</td>
<td>AVM not excised</td>
</tr>
<tr>
<td>10</td>
<td>migraine</td>
<td>large lt cerebellar AVM</td>
<td>multiple vascular channels within cerebellar tissue</td>
</tr>
<tr>
<td>11</td>
<td>trigeminal neuralgia</td>
<td>large lt frontal AVM</td>
<td>AVM not excised</td>
</tr>
<tr>
<td>12</td>
<td>transient lt hemiparesis; cardiac aneurysm</td>
<td>large lt parietal AVM</td>
<td>AVM not excised</td>
</tr>
</tbody>
</table>

* AVM = arteriovenous malformation.

cie evidence of platelet aggregation in cerebral AVM's. The hypothesis that these lesions have a dynamic pathophysiology is supported by the observed high frequency of ongoing platelet aggregation. Repeated endothelial injury with resultant platelet aggregation would explain the histological features of vascular thrombosis, focal intimal hyperplasia, and calcification seen almost universally in these lesions. Furthermore, the occurrence of extensive endothelial injury could, in theory, result in partial or complete thrombosis of the AVM.

Acknowledgments

The authors would like to acknowledge Mrs. Helen Sutherland for her technical assistance in preparing the indium-labeled platelets. They also thank Ms. Penny Frank for preparation of this manuscript.

References


Manuscript received August 29, 1986. Accepted in final form July 14, 1987.
Address reprint requests to: Garnette R. Sutherland, M.D., F.R.C.S.(C), Department of Surgery, Section of Neurosurgery, Health Sciences Centre F419, 820 Sherbrook Street, Winnipeg, Manitoba R3A 1R9, Canada.