Cerebrovascular Disease in Sickle Cell Anemia: A Clinical, Pathological and Radiological Correlation

Kurt H. H. Merkel, M.D., Paul L. Ginsberg, M.D., Joseph C. Parker, Jr., M.D., and M. Judith Donovan Post, M.D.

SUMMARY An opportunity to study cerebrovascular changes in sickle cell anemia (SCA) presented itself when a black child with this disorder died of hemiplegia. Autopsy demonstrated severe occlusive vascular disease involving primarily the circle of Willis and major bifurcations of both internal carotid arteries. Collateral circulation to the distal branches of the internal carotid arteries occurred through transdural anastomoses from the external carotid system and via the leptomeningeal route. Perfusion of the basal ganglia was accomplished by vessels arising from the proximal internal carotid arteries. These changes resembled those of Moyamoya disease. Autopsy showed old and recent cerebral infaracts. Two vascular processes were responsible for the arterial occlusions: (1) exuberant intimal hyperplasia, and (2) old and recent thrombi with partial recanalization. The former has been described only once before in SCA. Small vessels in the basal ganglia were exceptionally numerous and dilated. We conclude that intimal hyperplasia within large cerebral arteries may be responsible for infarction and small vessel proliferation in basal ganglia in patients with SCA.

Clinical Features

A 7-year-old black boy was admitted to Jackson Memorial Hospital with an acute alteration of consciousness. The patient was originally diagnosed as having sickle cell anemia at the age of 7 months. Originally he had edema of both hands and feet, was anemic, and had a positive sickle cell preparation. Subsequently, he had several hemolytic crises. Seven months before this last admission, the child developed a right hemiparesis with hemianesthesia and Broca's aphasia. This was accompanied by focal myoclonic seizures involving his right arm and the right side of his face. He was given phenytoin and improved, but 4 months later he suffered a similar episode, which left him with moderately severe expressive aphasia. A Tc-99 (Technetium) brain scan was diagnostic for occlusion of the left middle cerebral artery. His hemoglobin ranged between 6–8 gm/dl, and his reticulocyte count between 10–40%. Prior to his last admission he had been irritable and was found comatose. In the emergency room, he was stuporous, and had right spastic hemiparesis, a right gaze preference and right-beating jerk nystagmus. His hemoglobin was 6.9 gm/dl, with a white cell count of 17,400 per mm³ and 16% reticulocytes. The cerebrospinal fluid contained 11 white blood cells per mm³, 45% granulocytes. He was treated with phenobarbital and diazepam and became more alert. Subsequently, an EEG revealed bilateral slowing, more marked on the left. Three days later, he became febrile (102.4°F) and more lethargic. Examination revealed nuchal rigidity and a positive Brudzinski sign. A second spinal tap showed 6850 red cells and 340 white cells per mm³ with 55% granulocytes and a protein of 322 mg/dl; CSF glucose levels were normal. Cultures of spinal fluid, blood and urine were all negative. A brain scan (Tc99) showed another area of increased uptake in the posterior right hemisphere. The child was treated with penicillin and a transfusion of 1000 ml packed cells after which he improved slightly. Hemoglobin electrophoresis showed only hemoglobin A and S. Three days later he became comatose with bilateral hyperreflexia, Babinski signs, a right gaze preference with nystagmus, bilateral decerebrate posturing.
and irregular respirations. His pupils were 3 mm in diameter and sluggish. Emergency electroencephalography did not show any paroxysmal activity, but the maximum focus of disorganization had shifted to the right hemisphere. His hemoglobin was now 14.2 gm/dl. A transfemoral bilateral carotid arteriography was done (see below). The patient subsequently developed gastrointestinal bleeding, bradycardia and hypotension. At no time did his level of consciousness improve. He required a tracheostomy and a respirator, and died 19 days after admission.

**Angiography**

The right common carotid injection revealed an abrupt occlusion of the supraclinoid portion of the right internal carotid artery (ICA) just distal to the origin of the anterior choroidal artery (figs. 1, 2). Injection of the opposite carotid artery demonstrated occlusion of its proximal intracavernous segment (figs. 3, 4). Multiple collateral vessels reconstituted portions of the intracranial circulation of both hemispheres. Transdural anastomoses were present between the external and internal carotid arteries, a pattern often referred to as rete mirabile. In addition, leptomeningeal channels between cortical branches of the anterior and middle cerebral arteries existed bilaterally. Finally, communication was established with the deep basal ganglia by numerous small perforating vessels arising from the proximal internal carotid and anterior choroidal arteries (fig. 2). Since the vertebral arteries were not injected, the presence of collateral vessels from the posterior circulation could not be determined.

**Pathologic Examination**

1. **General Findings**

The heart was dilated and markedly hypertrophied, weighing 195 gm. The myocardium was flabby, light brown and showed viral myocarditis characterized by scattered lymphocytes, plasma cells, histiocytes, a few granulocytes and eosinophilic intranuclear inclusions in myocardial cells. These inclusion bodies were also seen in epithelial cells of the esophagus and trachea, which were superficially ulcerated. The lungs weighed 540 gm and possessed recent thrombo-
II. Neuropathologic Findings

The fresh brain weighed 1170 gm. The superior sagittal and right transverse sinuses were occluded by recent thrombi. The leptomeninges covering the left cerebral hemisphere and right occipital pole were opaque and brown, made so by fibrosis and hemosiderin. The surface of the remaining right cerebral hemisphere was green-yellow and showed acute meningitis. The left cerebral hemisphere was smaller than the right, with a shrunken frontal pole. The left frontal gyri and anterior cingulate gyrus showed marked cortical atrophy; the left posterior temporal and parietal lobes were less involved. The occipital lobe was spared. Coronal sections of this hemisphere revealed a 4 x 3 x 2.5 cm old infarct in the frontal and parietal lobes. The right cerebral hemisphere was soft, dusky, swollen and exhibited a recent anemic infarct in the distribution of the middle cerebral artery (fig. 5). The midbrain, pons, medulla, cerebellum and spinal cord were essentially normal. There were no herniations.

The arterial system was normally formed without congenital abnormalities and had both old and recent extensive occlusive disease (fig. 6). The intracranial portions of both ICA's were totally occluded by gray tissue. The proximal portions of the right anterior, middle and posterior communicating cerebral arteries had thickened blue-gray walls with total occlusion by soft, brown material. On the left side the proximal portions of the anterior, middle and posterior communicating cerebral arteries were thinner than on the right and totally occluded by white tissue. In addition, a recent thrombus occluded the distal lumen of the left middle cerebral artery. Both posterior cerebral arteries, the basilar and vertebral arteries appeared normal.
Two processes were responsible for the occlusion of the large cerebral arteries: segmental thickening of the vessel wall with total occlusion in some areas due to an exuberant intimal hyperplasia and recent and organizing thrombi. The intima in these areas showed proliferation of fibroblasts and smooth muscle cells as well as focal splitting or clumping of the internal elastic lamina. The media showed focal atrophy and fibrosis in these regions. The adventitia was prominent (fig. 7). There were no inflammatory cells, macrophages, lipids, hemosiderin or small vessels in these thickened intimal zones (fig. 8). The recent and old thrombi overlying segmental zones of intimal fibroplasia would indicate in some instances that the thrombi were younger than the thickened intima (fig. 9). For that reason the intimal proliferation was considered the likely primary event which may have led to the formation of thrombi. The small intraparenchymal vessels in the basal ganglia were congested and numerous.

Discussion

A review of the literature concerning pathologic changes in SCA yielded several patterns of involvement (table 1). Small and large vessels may be involved in the pathologic process causing strokes.3-12, 16 Accepting these reports as cases of SCA, despite the absence of hemoglobin electrophoresis in some, the question remains: why does thrombosis of large cerebral arteries occur in this disease? It is unlikely that stasis at the capillary level causes thrombus formation in the large arteries since in many patients this is the only finding, and in other cases of large vessel thrombosis, stasis in the capillary bed was absent. Evidence to support the hypothesis of Murphy and Shapiro,8 that capillary stasis leads to a hypercoagulable state, has been advanced by Leslie et al.12 who showed that patients with SCA had low Factor V and plasminogen levels and high fibrin degradation products. Furthermore, intravascular coagulation has been demonstrated after brain injury,13-15 and it is conceivable that, on the basis of microinfarcts in sickle cell crises, the hypercoagulable state causes thrombosis in large vessels. A third possible mechanism for large strokes in SCA is endarteritis of large cerebral arteries, as found by Bridgers.16 Stockman17 described angiographic occlusion of large cerebral arteries in patients with SCA due to thrombus formation.

Our patient resembles Bridgers' first case with exuberant intimal hyperplasia occluding the vessel lumen. However, recent and old thrombi were also present. Normally, the cerebral arterioles and arteries possess a well developed internal elastic lamina, a thin media, and no external elastic lamina.16, 19 The internal elastic lamina may show the first signs of degeneration, that is, splitting, in early childhood.20 Ultrastructural analysis has recently shown basement membrane abnormalities even in infancy.21 Degeneration of the internal elastic lamina and intimal proliferation is a fairly nonspecific finding. Vaso-vasorum in cerebral arteries are never,21 or only rarely observed.18, 19 We...
did not find any. Therefore, occlusion of these hypothesized minute vessels could not account for the intimal proliferation, as has been proposed. This process of intimal proliferation or fibroplasia may well have arisen from the bifurcation sites of the large extracerebral arteries, since we found this process only in proximal portions of arteries and at sites of bifurcation.

As has been known for years, cerebral arteries possess
bifurcation cushions which are similar to those in the renal, pulmonary and coronary arteries. They are present in childhood, enlarge with growth of the vessel lumen and undergo typical ageing changes. Reactions of these cushions to different kinds of irritation include edema, sclerosis and proliferation of fibroblasts and smooth muscle cells. In our case, the sludging of erythrocytes in recurrent sickle cell crises may have repeatedly altered the nutrition of the inner portion of the vessel wall resulting in endothelial irritation, intimal edema and proliferation. We also relate the development of thrombi in the large extracerebral arteries to the above mentioned process and to the state of hypercoagulation in sickle cell crises.

The angiographic pattern of the cerebral vessels of our patient reveals an extensive collateral network due to bilateral internal carotid artery occlusions, resembling the situation in Moyamoya disease. This pattern consists of (1) bilateral occlusions of the intracranial segment of the internal carotid arteries, (2) a well developed rete mirabile and (3) numerous perforating vessels supplying the deep portions of the brain giving rise to a "puff of smoke" appearance rendered in Japanese as Moyamoya. The first description of this disease entity is attributed to Takeuchi, though this syndrome was fully elaborated by others. Originally felt to be confined to the Japanese, reports have appeared describing this syndrome in Occidentals. The anastomoses of the cerebral vessels are generally inadequate in cases of sudden, large blood flow disturbances, but potential collaterals are present in the circle of Willis, deep perforators to the basal ganglia (Moyamoya pattern), extracranial to intracranial anastomoses via a rete mirabile and leptomeningeal collaterals among the large cerebral arteries. The appearance of these potential collateral vessels especially the deep perforators to the basal ganglia, in our case must mean that features and mechanisms similar to those of Moyamoya disease were operative. Most likely, these factors include the youth of the patient and the progressive occlusion of the large cerebral arteries by ex-

TABLE 1  Literature Review of Cerebrovascular Pathology in CSA

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of cases</th>
<th>Age/Sex</th>
<th>Central nervous system pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridgers</td>
<td>2</td>
<td>4Y/F</td>
<td>Obliterative endarteritis of large cerebral arteries. Few inflammatory cells in vessel wall. Intraparenchymal perivascular hemorrhage and small infarcts. Engorged capillaries with hyaline bodies.</td>
</tr>
<tr>
<td>Hughes, et al</td>
<td>2</td>
<td>6Y/M</td>
<td>Recent thrombosis of peripheral LMCA* and small intraparenchymal vessels. Endothelial proliferation in region of infarct.</td>
</tr>
<tr>
<td>Connell</td>
<td>1</td>
<td>20Y/F</td>
<td>Recent thrombosis of LMCA*. Recent and old infarcts. Endothelial proliferation and hyalinization in arterioles.</td>
</tr>
<tr>
<td>Wertham</td>
<td>5</td>
<td>28Y/F</td>
<td>Small and large infarcts; thrombosed capillaries and venules; adventitial fibrosis; endothelial thickening of arterioles.</td>
</tr>
<tr>
<td>Tomlinson</td>
<td>11</td>
<td>8Mths-18Y</td>
<td>Congested small vessels with perivascular fibrosis; endothelial swelling and proliferation. Occasional petechial hemorrhages.</td>
</tr>
<tr>
<td>Kimmelstiel</td>
<td>1</td>
<td>11Y/F</td>
<td>Disseminated microinfarcts; exceptional capillary thrombosis.</td>
</tr>
</tbody>
</table>

*LMCA = left middle cerebral artery.
uberrant intimal hyperplasia and secondary thrombosis.

Postmortem examinations of only a few patients with Moyamoya disease have been described in the literature.\textsuperscript{38-46} (table 2). Reviewing these reports it becomes apparent that thrombi.

\begin{table}
\centering
\caption{Literature Review of Cerebrovascular Pathology in Moyamoya Disease, Postmortem Findings}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
Author & Case & Parenchymal lesions & Arteries & Intimal fibroplasia & Thrombotic lesions & Medial fibrosis & Medial atrophy & Adventitial fibrosis & Thrombi \\
\hline
Kawakita & 12Y/F & Infaracts; Hemorrhages & ICA,ACA’s & + & Thickening & 0 & 0 & 0 & + \\
(1965) & & & MCA,PCA’s & + & & & & & \\
& & & Poom. A’s & + & & & & & \\
Suzuki & 10Y/F & Hemorrhages & ICA’s & + & 0 & 0 & 0 & 0 & 0 \\
(1965) & & & MCA’s & + & 0 & 0 & 0 & 0 & 0 \\
Maki & 9Y/F & Subdural Hematoma & Arteries & Circle of Willis & + & 0 & 0 & 0 & 0 \\
(1965) & & & & & & & & & \\
Moriyasu & 55Y/F & Multiple Infarcts & ACA,MCA’s & + & Ruptured & 0 & 0 & 0 & 0 \\
(1966) & & & Poom. A’s & + & . & 0 & 0 & 0 & 0 \\
Ando & 43Y/F & Subarachnoid hemorrhage & ICA,ACA’s & + & Undulation & 0 & 0 & 0 & + \\
(1966) & & & MCA’s & + & . & 0 & 0 & 0 & + \\
& & & Poom. A & + & + & 0 & 0 & 0 & + \\
Vuia & 44Y/M & Cerebral Hemorrhage & ICA’s & + & 0 & 0 & 0 & 0 & 0 \\
(1970) & & & MCA’s & + & 0 & 0 & 0 & 0 & 0 \\
& & & ACA’s & + & 0 & 0 & 0 & 0 & 0 \\
Carlson & 2Y/M & Cerebral infaracts & ACA’s & + & Absent & 0 & 0 & 0 & 0 \\
(1973) & & & MCA’s & + & hypoplastic & 0 & 0 & 0 & 0 \\
& & & ACA’s & + & & 0 & 0 & 0 & 0 \\
Mastri & 30Y/F & Recent Infaracts & ICA’s & + & Fragmentation & + & 0 & 0 & 0 \\
(1973) & & & MCA’s & + & . & 0 & 0 & 0 & 0 \\
& & & LACA & + & + & 0 & 0 & 0 & 0 \\
& & & BA,VA & Mild & + & 0 & 0 & 0 & 0 \\
Pila & 16Y/M & Recent Infarct & RACA & + & Fragmentation Dissection & + & + & + & + \\
(1976) & & & MCA,PCA & + & . & + & + & + & + \\
Merkel & 7Y/M & Infaracts & ICA’s & + & Splitting & + & + & + & + \\
(1977) & & & ACA,MCA’s & + & clumping & 0 & 0 & 0 & 0 \\
& & & Poom. A’s & + & . & 0 & 0 & 0 & 0 \\
& 22Y/F & Infaracts & ICA’s & + & Split & 0 & 0 & 0 & 0 \\
& & & ACA’s & + & + & 0 & 0 & 0 & 0 \\
& & & MCA’s & + & + & 0 & 0 & 0 & 0 \\
& & & Poom. A & + & + & 0 & 0 & 0 & 0 \\
\hline
\end{tabular}
\footnotesize{ICA’s = Internal carotid arteries; ACA’s = Anterior cerebral arteries; MCA’s = Middle cerebral arteries; PCA’s = Posterior cerebral arteries; PcomA’s = Posterior communicating arteries; VA = Vertebral arteries; BA = Basilar artery; + = Present; O = Absent.}
\end{table}

References
11. Connel JH: Cerebral necrosis in sickle cell disease. JAMA 114-123, 1942
17. Stockman JA, Nigro MA, Mishkin MM et al: Occlusion of large
Vascular Spasm in Cat Cerebral Cortex Following Ischemia

MICHAEL NOEL HART, M.D., MARTIN D. SOKOLL, M.D., LOYD R. DAVIES, and EDUARDO HENRIQUEZ, M.D.

SUMMARY The reaction of brain parenchymal vessels in areas of no-reflow following ischemia in cats was evaluated. A method was devised by which brain biopsies following ischemia were quickly frozen at \(-17^\circ\)C, sections were cut and stained and vessel internal and external diameter measured. Vessels in the no-reflow areas had smaller internal and external diameters and thicker walls when compared to adjacent reflow areas as well as to normal control animals. By utilizing a 2-way analysis of variance in which reflow versus no-reflow vessel diameters were compared by region the differences were found to be statistically significant (p < 0.05). The data raise the possibility that there may exist normal regional differences in the size of cerebral vessels.

FOLLOWING EXPERIMENTAL cerebral ischemia, the failure to perfuse random areas of the brain after circulation has been re-established is a well-known phenomenon variously referred to as no-flow or no-reflow state. The cause of no-reflow is generally ascribed to blockage of the cerebral vessels in sickle cell anemia. N Engl J Med 287: 846-849, 1972

The smaller internal and external diameters and thicker walls when compared to adjacent reflow areas as well as to normal control animals. By utilizing a 2-way analysis of variance in which reflow versus no-reflow vessel diameters were compared by region the differences were found to be statistically significant (p < 0.05). The data raise the possibility that there may exist normal regional differences in the size of cerebral vessels.

stagnation of hematopoietic elements have not been ruled out as contributory causes, however.

One of the major criticisms of the no-reflow observations is that they do not coincide with patterns of ischemic brain lesions in humans. However, we have observed perivascular patterns of necrosis in human cerebral cortices following ischemia combined with serum hyperosmolality. Upon re-examination of that material we concluded that the focal ischemic areas were associated with penetrating vessels large enough to contain significant amounts of smooth muscle in their walls. This observation raised the question of whether spasm of intraparenchymal cerebral vessels could occur and if it could be contributory to post-ischemic no-reflow in the
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