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Short report

Large cerebral vessel disease in sickle cell anaemia

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SYNOPSIS An 18 year old male with documented sickle cell disease was admitted to the hospital for the final time in coma. Cerebral angiography revealed multiple stenotic lesions of the large cerebral vessels. The pathology of this large vessel involvement is demonstrated and the potential contribution of large as opposed to small cerebral vessel disease in the neurological manifestations of sickle cell anaemia is discussed.

The association between sickle cell anaemia and acute neurological deficits was first recorded in 1923 with a report of convulsions, rigidity, and hemiplegia in a 5 year old boy with sickle cell disease (Sydenstriker *et al.*, 1923). Since that time, numerous attempts have been made to define the relationship between vascular insults in the central nervous system and sickle cell anaemia. The pathogenesis is believed to involve *in vivo* sickling as the initial insult. This leads to increased blood viscosity, stasis, hypoxia, thrombosis, and infarction causing damage in the lung, liver, spleen, eye, and other organs (Armaly, 1974; Bromberg, 1974; Konotey-Shuler, 1974). The widespread concept of small vessel intracerebral disease to explain acute neurological deficits in young patients with sickle cell anaemia (Arena, 1939; Diggs and VanderBuegge, 1954; Baird *et al.*, 1964) has been challenged by the angiographic demonstration of large vessel occlusions in this syndrome (Stockman *et al.*, 1972). The identification of patients whose neurological symptomatology can be attributed to large as opposed to small vessel disease may have therapeutic implications since there is some evidence that the large vessel lesions may be reversible (Russell *et al.*, 1974a,b).

CASE REPORT

This was the final hospital admission for an 18 year old male with homozygous haemoglobin S disease. Between age 8 and 13 years he experienced four separate episodes of acute left hemispheral dysfunction which culminated in a residual right hemiparesis and nonfluent aphasia. He had no further neurological deficits until the night of admission when he was found in deep coma with episodic spontaneous decerebrate posturing. A right carotid angiogram, after partial exchange transfusion, showed a 4 to 5 mm shift of the midline structures from right to left and a moderately dilated right lateral ventricle. There was marked stenosis of the anterior and middle cerebral arteries just distal to their origin with retrograde filling of several frontal branches of the middle cerebral artery. The lenticulostriate vessels were enlarged and tortuous with telangiectasia. Collateral vessels from the posterior cerebral artery filled right anterior and middle cerebral artery branches in a retrograde fashion.

A left carotid angiogram revealed complete occlusion of the left internal carotid artery immediately distal to the origin of the ophthalmic artery. There was faint visualisation of the left anterior cerebral artery and a frontal branch of the left middle cerebral artery through ophthalmic and meningeal collaterals (Fig. 1). Death occurred on the sixth hospital day.

Necropsy revealed the brain to be soft and friable, consistent with autolysis seen in patients with prolonged respirator dependence. There were no large areas of infarction. However microinfarcts were scattered throughout both cerebral hemispheres. A massive intracerebral haemorrhage in the left hemisphere had ruptured into the left lateral ventricle. No aneurysms were identified. The smaller cerebral vessels showed engorgement with sickled erythrocytes and an occasional capillary was hyalinised. An endarteritic process totally occluded the lumen of the left internal carotid artery (Fig. 2). Van Geison and trichrome stains demonstrated that the tissue medial to the internal elastic lamina was composed of fibrous

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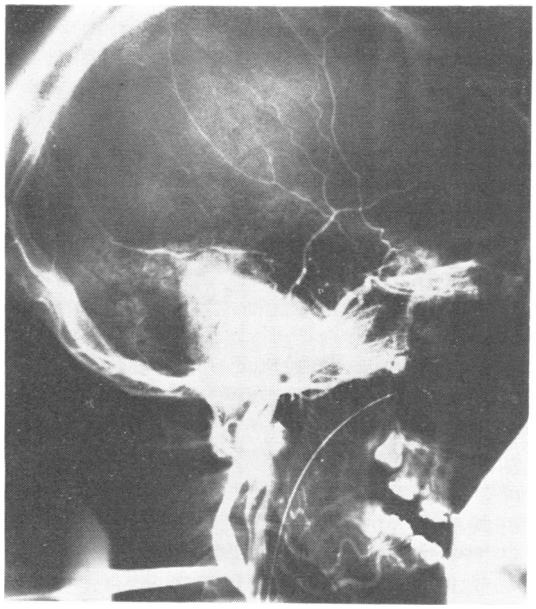

FIG. 1 *Left carotid angiogram demonstrating complete occlusion of internal carotid artery distal to ophthalmic artery.*

bands and fibroblasts. No capillary spaces were identified and there was no recanalisation within the proliferating fibrous tissues. Endothelial cells could not be identified. The right internal carotid artery was partially occluded by an identical process. The end-arterial changes extended into the proximal portions of the middle and anterior cerebral arteries. The basilar artery was patent with no significant changes on microscopy.

DISCUSSION

Acute central nervous system abnormalities are a significant and common complication in sickle cell disease. In fact, neurological involvement is exceeded only by painful crisis and cardiomegaly as the most common clinical findings in this syndrome (Greer and Schotland, 1962; Portnoy and Herion, 1972).

Neuropathological changes in patients with sickle cell anaemia can take many different forms including small vessel occlusion (Seeler, 1972), massive intracranial haemorrhage (Baird *et al.*, 1964; Adeloye *et al.*, 1970), large vessel occlusion (Greer and Schotland, 1962), subarachnoid, subdural, or epidural haemorrhage (Hughes *et al.*, 1940), leptomeningitis, encephalomalacia (Bridges, 1939), and ruptured aneurysm (Cheatham and Brackett, 1965). In spite of the early recognition of these complications, little has been written to define the aetiology of central nervous system abnormalities in sickle cell anaemia. In 1964 Baird *et al.* summarised earlier work suggesting that small vessel occlusion by sickled erythrocytes caused infarction and haemorrhage. It was suggested that this process, which involved the capillaries and pre-capillary arterioles, caused the central nervous system symptoms. Stockman *et al.* (1972) highlighted a new dimension by demonstrating angiographic occlusion of large cerebral vessels in six patients with sickle cell

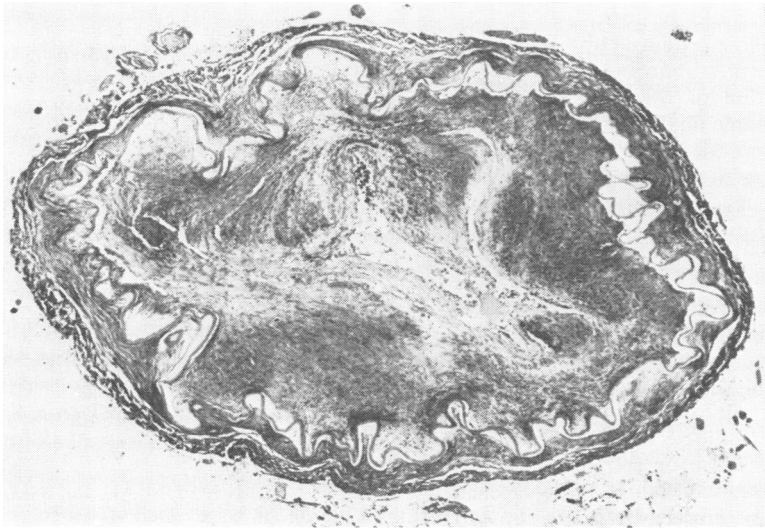

FIG. 2 *Cross-section of left internal carotid artery. Note marked endarteritic process nearly totally occluding vessel lumen (H and E, ×25).*

disease and acute neurological disorders. This report has led to renewed interest in attempting to define the contribution of large cerebral vessel occlusion to the clinical spectrum of disease observed in these patients.

Only incomplete descriptions of the large vessel abnormalities are available (Bridges, 1939; Hughes *et al.*, 1940; Wertham *et al.*, 1942). In 1939 Bridges *et al.* described the pathological changes seen in a child with medium-sized cerebral vessel occlusions. There was endothelial proliferation, fibroblastic reaction, hyalinisation and occasional loss or fragmentation of the internal elastic lamina. They postulated that the process leading to occlusion was endarterial intimal proliferation and not thrombosis. The following year, Hughes *et al.* (1940) confirmed the pathological findings and described fresh and organising thrombi in the narrowed vessel lumen. Significantly, they also saw instances of thrombosis without associated vessel wall abnormalities. They concluded that the arterial wall changes were secondary to chronic stasis and diminished blood volume leading to capillary and venous thrombosis. Stockman *et al.* (1972), without necropsy data, postulated yet a third process. They suggested that sickled erythrocytes occlude the vasa vasorum of large blood vessels causing ischaemic damage and leading to progressive intimal and medial proliferation with eventual obliteration of the lumen. This controversy, as it applies to large and medium sized vessels, is unresolved.

In the patient presented here, the stenotic lesions demonstrated on the arteriogram correspond to the severe, fibrotic endarteritic changes. We were unable to demonstrate a thrombotic process or to identify the vasa vasorum. It seems reasonable to suggest that the transient and permanent neurological deficits were caused by episodic occlusion of cerebral vessels. The primary pathological process could be intraluminal with damage to the endothelium produced by either the sludging sickled cells or by flow abnormalities. On the other hand, destruction of the vasa vasorum could also have led to the same final picture of fibrotic obliteration.

An important question remains as to whether the aetiology of the multiple cerebral vessel occlusions affects the choice of therapy. Indeed, response to specific therapy may distinguish patients with sickle cell disease from those with large vessel occlusion due to other or no known causes (Suzuki and Takaku, 1969; Solomon *et al.*, 1970). Russell *et al.* (1974a,b) have preliminarily reported that, in children with sickle cell disease who had angiographically demonstrated stenotic large vessel lesions, chronic transfusion therapy could reverse the vascular pathology. In children who were not transfused there was progression of vascular disease in follow-up angiography. It is possible that transfusion therapy may offer new hope for patients with sickle cell disease and large cerebral vessel occlusion.

REFERENCES

Adeloye, A., Ogbeide, M. I., and Odeku, E. L. (1970). Massive intracranial hemorrhage in sickle cell anemia. *Neurology (Minneap.)*, **20**, 1165–1170.

Arena, J. M. (1939). Cerebral vascular lesions. *Journal of Pediatrics*, **14**, 745–751.

Armaly, M. F. (1974). Ocular manifestations in sickle cell disease. *Archives of Internal Medicine*, **133**, 670–679.

Baird, R. L., Weiss, D. L., Ferguson, A. D., French, J. M., and Scott, R. B. (1964). Studies in sickle cell anemia. XXI. Clinico-pathologic aspects of neurological manifestations. *Pediatrics*, **34**, 92–100.

Bridges, W. M. (1939). Cerebral vascular disease accompanying sickle cell anemia. *American Journal of Pathology*, **15**, 353–362.

Bromberg, P. A. (1974). Pulmonary aspects of sickle cell disease. *Archives of Internal Medicine*, **133**, 652–657.

Cheatham, M. L., and Brackett, C. E. (1965). Problems in management of subarachnoid hemorrhage in sickle cell anemia. *Journal of Neurosurgery*, **23**, 488–493.

Diggs, L. W., and VanderBuegge, C. F. (1954). Vascular occlusive mechanisms in sickle cell disease. *Journal of the National Medical Association*, **46**, 46–49.

Greer, M., Schotland, D. (1962). Abnormal hemoglobin as a cause of neurologic disease. *Neurology (Minneap.)*, **12**, 114–123.

Hughes, J. G., Diggs, L. W., and Gillespie, C. E. (1940). The involvement of the nervous system in sickle cell anemia. *Journal of Pediatrics*, **17**, 166–184.

Konotey-Shuler, F. I. D. (1974). The sickle cell diseases. *Archives of Internal Medicine*, **133**, 611–619.

Portnoy, B. A., and Herion, J. C. (1972). Neurologic manifestations in sickle cell disease: with a review of the literature and emphasis on the prevalence of hemiplegia. *Annals of Internal Medicine*, **76**, 643–652.

Russell, M. O., Goldberg, M. I., and Friedman, S. (1974a). Improvement of cerebral vascular disease in sickle cell anemia. *Pediatric Research*, **8**, 134.

Russell, M. O., Goldberg, M. I., and Friedman, S. (1974b). Reversal of arterial changes in sickle cell anemia with prolonged transfusion therapy. *Proceedings of the 1st International Symposium on Sickle Cell Disease*, Washington, D.C. OHEW Publ. (NIH) 75–723; Bethesda, MD.

Seeler, R. A. (1972). Death in children with sickle cell anemia: a clinical analysis of 19 fatal instances in Chicago. *Clinical Pediatrics*, **11**, 634–637.

Solomon, G. E., Milal, S. K., Gold, A. P., and Carter, S. (1970). Natural history of acute hemiplegia of childhood. *Brain*, **93**, 107–120.

Stockman, J. A., Nigro, M. A., Mishkin, M. M., and Oski, F. A. (1972). Occlusion of large cerebral vessels in

sickle cell anemia. *New England Journal of Medicine*, **287**, 846–849.

Suzuki, J., and Takaku, (1969). Cerebral 'Moyamoya' disease: disease showing abnormal net-like vessels in the brain. *Archives of Neurology (Chic.)*, **20**, 288–299.

Sydenstriker, V. P., Mulherin, W. A., and Huseal, R. W. (1923). Sickle cell anemia: report of two cases in children, with necropsy in one case. *American Journal of Diseases of Children*, **26**, 132–154.

Wertham, F., Mitchell, N., and Angrist, A. (1942). The brain in sickle cell anemia. *Archives of Neurology and Psychiatry (Chic.)*, **47**, 752–767.

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