Cerebrovascular Complications of Sickle Cell Anemia

DON H. WOOD, M.D.

IN THE PAST several years a resurgence of interest in sickle cell anemia has led to new information about its effects on the central nervous system. The literature has several extensive reviews of the various types of neurological complications observed in patients with this disorder. However, it remains unclear whether many of the complications reported are directly attributable to sickle cell disease or are incidentally associated. The majority of investigators, however, agree that the cerebral vascular complications are a direct result of pathophysiological abnormalities produced by the abnormal hemoglobin. The presence of S-hemoglobin appears to be a definite predisposing factor to the development of cerebral vascular disease, particularly in children. This is illustrated in a study by Solomon et al., whose investigations of infantile hemiplegia revealed that 7% were attributable to or associated with sickle cell disease.1

Incidence

Over the past 35 years there have been numerous anecdotal reports of an association between sickle cell disease and occlusive and hemorrhagic cerebral vascular disease. In addition, a number of investigations have reported the types and number of neurological complications observed, primarily in hospital-based patient populations with sickle cell disease. Unfortunately, there are no adequate epidemiological studies relative to the risk of cerebral vascular complications in a sickle cell population. Thus, the most basic questions are yet to be answered: What are the incidence and prevalence of ischemic and/or hemorrhagic cerebral vascular disease in a sickle cell population? What risk factors predispose to the development of ischemic and/or hemorrhagic cerebral vascular disease in patients with this disorder? Is the sickle cell patient who develops an initial stroke at greater risk for the development of another stroke? Does the risk of stroke vary with age, hemoglobin level, or other clinical or laboratory factors? Is the development of cerebral vascular complications dependent on or independent of the severity of the underlying disease? The current literature and investigations conducted at Howard University Hospital provide only partial answers to these questions.

The prevalence of cerebral vascular complications in groups of sickle cell patients varies from series to series. Greer and Schotland2 at Columbia reported a 13% prevalence rate of cerebral vascular complications which closely approximates the 17% reported by Portnoy et al. at Duke University3 and the 15% observed at Howard University Hospital. In contrast, Adeyole reported a 4% prevalence at the University of Ibadan Hospital in Nigeria.4 The reason for this apparent difference in prevalence between African blacks and African blacks is not readily evident. It may be that the reportedly lower prevalence in African blacks may be merely a reflection of a higher mortality rate, thus reducing the number of patients at risk for the development of acute stroke. However, since none of the aforementioned studies indicates the total sickle cell population from which the cases were drawn, no accurate estimate can be made about the frequency of cerebral vascular disease in a sickle cell population.

Risk Factors

In adults it has been well documented that hypertension, diabetes mellitus, age, and heart disease are factors which predispose to the development of acute cerebral vascular disease. However, in patients with sickle cell disease, there is a paucity of information relative to predisposing factors. Many of the studies reported have not addressed this specific problem and thus have provided little information from which to derive any pertinent knowledge.

Age may be one of the risk factors for the development of stroke in patients with sickle cell disease. A review of five major studies reveals that 80% of patients with cerebral vascular complications were 15 years of age or less. This figure closely approximates the 77% obtained from our series of 86 patients at Howard University. However, it is not safe to conclude that children under the age of 15 with sickle cell disease are at a greater risk for the development of cerebral vascular complications than older persons; the findings may only reflect a greater total sickle cell population at risk under age 15 than over age 15.

In our series of 86 patients with sickle cell disease, 41 were under age 15. Twenty-four percent of the sickle cell patients under age 15 had cerebral vascular complications, whereas only 6% of those over age 15 had experienced a cerebral vascular event. This difference was significant with a P value of <0.04.

In the group less than 15 years old, the average age of onset of cerebral vascular complications was six years. In another series the average age of onset was also six years.6 Thus, there is some evidence to suggest that sickle cell patients under age 15 are at greater risk of developing a cerebral vascular lesion than those over 15.
In light of these observations, it is interesting to note that in our series the average age of onset of symptoms referable to sickle cell disease was 40 months in patients under age 15 who had cerebral vascular complications and 17 months in a comparable group that had no evidence of cerebral vascular disease. Although patients with sickle cell disease are at a greater risk for the development of stroke at a relatively early age, those patients who ultimately develop cerebral vascular complications manifest the onset of their symptoms of sickle cell disease at a later date than those who do not have clinical cerebral vascular disease.

It is well documented that adult patients who have one stroke are at a greater risk for another stroke than an age- and risk-factor matched control group. It appears that this is also true in patients with sickle cell disease. Twenty per cent of the patients reported in the Duke study had recurrent strokes, whereas we observed recurrent strokes in 60% of patients under age 15. Other investigators also have observed a high recurrence rate of strokes in sickle cell patients in a comparable age group. Why sickle cell patients who sustain an initial stroke are prone to develop recurrent strokes remained somewhat of an enigma until the recent investigations by Stockman et al. and Russell et al.

In separate studies these investigators observed that a significant number of sickle cell patients manifesting cerebral vascular complications had angiographic evidence of progressive occlusive disease involving the internal carotid artery and large cerebral vessels. Russell and his colleagues further showed that patients receiving periodic exchange transfusions had a reduction in the recurrence rate of stroke, as well as angiographic resolution or amelioration of the occlusive vascular lesions. These observations not only have important therapeutic implications but also confirm observations of increased risk of recurrent stroke in sickle cell patients.

Although progressive occlusive disease of large vessels may be a mechanism for recurrent stroke, it remains unclear what factor or factors are responsible for the development of occlusive disease and why the majority of sickle cell patients apparently are not affected by this disorder. One explanation may be that those sickle cell patients who develop cerebral vascular complications have a more virulent disease. Portnoy et al., in comparing sickle cell patients who had central nervous system involvement with those who did not, noted no differences in average hematocrit values, average bilirubin values, average hemoglobin values, the presence of splenomegaly, or the average number of complications per patient. However, they did note a higher incidence of cardiomegaly in patients with neurological complications. In contrast, in the age group below 15 years, we observed that sickle cell patients with clinical evidence of cerebral vascular disease had lower average hemoglobin and hematocrits and higher reticulocyte counts than patients who had no evidence of cerebral vascular disease. In addition, 62% of patients with evidence of cerebral vascular disease had abnormal liver profiles, compared with 32% of patients without evidence of cerebral vascular disease. The average number of crises in patients who had no evidence of cerebral vascular disease was 9.3, whereas those with evidence of cerebral vascular disease experienced twice as many crises — an average of 18.6 per patient. There was also a significant difference in the incidence of concurrent infection between the two groups. Ninety per cent of the patients with cerebral vascular disease had an associated concurrent infection compared with a 40% incidence in others. This value was significant with \( P = 0.01 \). We also confirmed Portnoy's observations of a higher incidence of cardiomegaly in patients with cerebral vascular disease. Sixty-three per cent of these patients had cardiomegaly on chest X-ray, whereas only 31% of the others had chest X-ray evidence of cardiomegaly. Another indicator of severity of illness may be frequency of hospitalization. In sickle cell patients with cerebral vascular disease, the average number of hospitalizations was 6.54 per patient, whereas in the other group the average number of hospitalizations was 4.2. Thus, observations in our investigations are somewhat at variance with those reported by others. Our investigations indicate that patients with sickle cell disease who develop cerebral vascular complications do, indeed, appear to have a more severe or virulent disease.

Classification of Cerebral Vascular Lesions

The types of cerebral vascular lesions that may occur with sickle cell disease include ischemic and/or hemorrhagic infarction, intracerebral hemorrhage, cortical venous and/or sinus thrombosis, and subarachnoid hemorrhage. Cerebral infarction, the most common cerebral vascular lesion, was observed in over 75% of the patients reported in the three studies mentioned previously. Intracerebral hemorrhage was the next most common vascular lesion, occurring in approximately 20% of cases. Subarachnoid hemorrhage without focal neurological deficit occurred in only 1 to 2% of cases. It is important to note that several of the patients presenting with subarachnoid hemorrhage were found subsequently, usually at autopsy, to have an aneurysm. Therefore, patients who manifest this clinical state should be considered for angiographic evaluation.

Clinical Manifestations

In most instances the onset of the ictus is heralded by or associated with a thrombotic crisis characterized by fever, abdominal, bone, or chest pain, and meningismus. There is a high incidence of seizures at the time of ictus. Seventy per cent of the sickle cell patients presenting with a stroke in our series had generalized or focal seizures at the onset. Subsequently, the majority of these patients developed a chronic seizure disorder requiring long-term anticonvulsant therapy.

It also should be emphasized that not only can ischemic lesions occur in the brain and brain stem, they can also develop in the spinal cord. In our series there was one patient who appeared to have an ischemic infarction of the spinal cord producing an acute myelopathy. In many instances, however, the only manifestation of a crisis may be the sudden development of a focal neurological deficit with or without seizures.

Patients admitted in coma usually have an associated subarachnoid hemorrhage or intracerebral hemorrhage. The combination of coma and subarachnoid hemorrhage is associated with a high mortality (50 to 70%).

Many of the patients with recurrent strokes developed a pseudobulbar palsy-like picture associated with difficulty in speaking, swallowing, and ambulation. Of patients with
ischemic infarctions 60 to 70% demonstrated substantial improvement, but significant residual neurological deficits persisted in many.

In addition to the cerebral alterations, ocular and cranial nerve dysfunctions have been described in patients with sickle cell disease. The ocular manifestations include retinal and vitreous hemorrhages, central artery occlusion, and finally, retinal vascular proliferation with subsequent retinal detachment and secondary glaucoma. These ocular manifestations usually occur independent of clinically demonstrable cerebral vascular disease. Optic atrophy and other isolated cranial neuropathies have also been described.

Pathology

When red blood cells containing hemoglobin S are exposed to a low oxygen tension, the abnormal hemoglobin forms tactoids, causing subsequent jelling of the hemoglobin in the red blood cell which alters the shape of the cell. This change results in an increase in blood viscosity with secondary arteriolar, capillary, and venous stasis leading to small vessel occlusion. In addition, autopsy data have shown endothelial proliferation in small arteries and arterioles. Rarely has pathological evidence of abnormalities in major cerebral arteries been reported.

However, large vessel involvement, including occlusion, has been demonstrated angiographically. It has been postulated that the occlusive lesions result from proliferation of the intima and media consequent to ischemia of the blood vessel wall produced by occlusion of nutrient arteries and/or vasa vasorum.

The subarachnoid and intracerebral hemorrhage may be related to ischemic changes in the walls of capillaries and arterioles which lead to diapedesis of red blood cells into the subarachnoid space and into the surrounding cerebral tissue.

Treatment

Unfortunately, there is no effective therapeutic agent presently available that will reverse or modify the pathophysiological events that produce cerebral ischemia in this disorder. Various modes of therapy have been attempted, such as intravenous bicarbonate, urea, and cyanate to decrease the sickling, but presently there is no definitive evidence of beneficial effects. The most effective therapy is adequate hydration, correction of electrolyte imbalance, and an assiduous search for and treatment of any associated underlying infection. Patients with altered states of consciousness should have an adequate airway established, careful monitoring of arterial gases, and administration of oxygen, if indicated. Exchange transfusions with fresh whole blood have been attempted, but their effectiveness in reversing or modifying the acute illness is yet to be demonstrated. Seizures should be treated vigorously with barbiturates and/or diazepam. There is evidence to suggest that prophylactic partial exchange transfusions by phlebotomy and the infusion of fresh red blood cells may prevent recurrent strokes. If angiography is indicated, exchange transfusions to lower the amount of sickle hemoglobin to less than 20% by electrophoresis should be accomplished prior to angiography. An active rehabilitation program should be instituted early in the convalescent phase of the illness.

Conclusions

There is evidence to suggest that children under the age of 15 with sickle cell disease are at greater risk of developing cerebral vascular disease than those over age 15 with sickle cell disease. In addition, there is strong evidence that patients who sustain an initial stroke are more likely to have recurrent strokes. Since there is some evidence that recurrent strokes may be partially prevented by periodic exchange transfusions, children demonstrating clinical evidence of cerebral vascular disease should probably receive this therapy. However, it is unclear at present how often and for what length of time treatment should be given. Hopefully, continued research in this disorder may provide a more specific therapeutic approach.

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Stroke. 1978;9:73-75
doi: 10.1161/01.STR.9.1.73

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