The Natural History of Stroke In Sickle Cell Disease

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The occurrence and progression of strokes in patients with sickle cell disease and the resultant structural and functional defects were investigated by an in-depth study of 35 patients, 32 of whom are part of a natural history study of 537 patients. The relative frequency for all ages is 6 per cent. Strokes are predominantly seen in patients with sickle cell anemia (33 with sickle cell anemia and two with heterozygous hemoglobin S and C (SC) disease). Twenty-five of the patients were less than 20 years old at the time of the first stroke—9.1 per cent of all patients observed during this age range. The actuarial or predictive risk of an initial stroke during the first two decades is 0.761 episodes per 100 person years whereas after age 20 the risk is 0.524 episodes per 100 person years. Children significantly at risk (p < 0.01) for cerebral infarction have a mean age at onset of 7.7 years (modal age of 5 years). Contrarily, adults have a significant risk for Intracranial hemorrhage (p < 0.05). Five of the 23 patients who had a cerebral infarct died. No predictive factors such as prior illness rate, hemoglobin level, fetal hemoglobin content or previous neurologic symptoms identified the patient "at risk" prior to the first stroke. Follow-up of the patients with cerebral infarction for a mean observation time of nine years revealed a reoccurrence rate of 67 per cent. Temporal clustering of the recurrence within 36 months is the outstanding clinical feature of this group of patients, and 80 per cent of subsequent strokes occurred before 36 months. Each patient who survived showed a functional neurologic improvement immediately after the stroke but never regained the intellectual or neurologic status they had before the stroke. Residual neurologic deficit increased with each reoccurrence and 11 of the patients have permanent paralysis. Computerized tomography demonstrated structural damage with low density areas in all patients with cerebral infarcts. These patients were not treated with a transfusion program of antiscickling agents. Subarachnoid or intracerebral hemorrhage occurred in 11 young adults ages 14 to 36 years, all with SS. Six of the 11 died, and structural vascular defects such as aneurysms were found in four. The susceptible person with SS experiences a definitive period of risk marked by recurrent stroke episodes following which no further strokes are likely to occur. Factors contributing to this cessation are unknown.

The most dramatic and debilitating complication of sickle cell disease is the occurrence of a stroke in a bright and active youngster. Sydenstricker et al. [1] first reported the association of cerebral infarction and the sickling syndrome in a male five year old in 1923.
Other early workers [2,3] reported a number of cases demonstrating both cerebral microinfarcts and major vessel occlusion in patients with sickling disorders. Following the advent of hemoglobin electrophoresis, many case reports and several large series of patients with sickle cell disease and neurologic manifestations appeared [4,5]. Angiographic studies were not commonly used because of evidence that radiographic dyes may enhance intravascular sickling [6]. This cautious approach was reinforced by a report of two patients who suffered strokes immediately after angiography; death occurred in one patient [7]. However, in 1972 Stockman et al. [6] demonstrated the occlusion of large cerebral vessels in six of seven patients with neurologic manifestations, using cerebral angiography without notable adverse effects. All these patients had received repeated transfusion one to three weeks prior to the procedure, or exchange transfusions immediately before the study, so that the hemoglobin S comprised less than 20 per cent of the total hemoglobin present. This was assumed to reduce the risk of intravascular sickling. This report challenged the then prevailing concept that multiple microinfarcts were the sole cause of cerebral vascular accidents in patients with sickle cell disease.

Recently, increased interest in prolonged transfusion therapy for cerebral infarction has been supported by the work of Russell et al. [9] who published the results of prolonged transfusion therapy in three children with sickle cell anemia who had suffered strokes. These patients were maintained at a hemoglobin concentration above 10 g/dl with hemoglobin S levels of less than 30 per cent. Angiographic abnormalities resolved or lessened after one year of transfusion therapy. Two patients not treated with transfusions had angiographic evidence of progressive disease after one year. Lusher et al. [10] reported on a remarkable series of 15 patients who were treated by a prophylactic transfusion program; there were only two treatment failures (one of which was thought to be related to lack of compliance).

To date, no one has described the long-term outcome in patients with sickle cell disease who had stroke. In this review we summarize our experience with 35 patients in an attempt to delineate the natural history of the patient with sickle cell disease who has had a stroke and to define possible predictors of impending stroke. An understanding of the natural progression of this complication should be a prerequisite for the evaluation of any proposed therapeutic program.

MATERIALS AND METHODS

Thirty-five patients who had one or more strokes were identified with the aid of a computer retrieval system which selected any patient with a sickling disorder and a clinical diagnosis of stroke. Included are patients with cerebral infarction, subarachnoid hemorrhage, intracerebral hemorrhage, and embolism. The natural history demographic study of sickle cell disease currently in progress at the Los Angeles County-University of Southern California Comprehensive Sickle Cell Center consists of a cohort of 537 registered patients. The combined cumulative person years of observation provide a significant data base allowing risk rates and actuarial calculations to be determined. Thirty-two of the 35 patients reported on are part of this cohort group and are the base from which risk rates have been determined. The other three patients were brought to our attention through requests for consultative advice.

In the majority of instances, the clinical manifestations of the stroke are obvious, with severe neurologic deficits clearly evident. The diagnosis has been supported by the following studies: lumbar puncture, computerized tomography (CT) scan, brain scan, electroencephalogram, psychologic testing or autopsy. A firm diagnosis cannot always be made. We have encountered some youngsters in whom neurologic findings were sufficient to require the battery of laboratory studies but in whom an unequivocal diagnosis could not be established. This diagnostic problem has occurred in both the potential new case, in the suspected repeater or in those with a transient ischemic attack. One patient had pneumococcal meningitis three years prior to his first stroke but had no apparent residua from this infection, whereas another patient had a subsequent fatal bacterial meningitis. The clinical course of the other 33 patients was not complicated by any central nervous system infections.

Diagnosis of the underlying hemoglobinopathy is based on the presence of a chronic hemolytic anemia with morphologic evidence of the sickling phenomena in association with the mobbility pattern of the abnormal hemoglobin on cellulose acetate electrophoresis at pH 8.4 and citrate agar electrophoresis at pH 6.0. Further specific studies included microcolumn A2 determinations and column chromatography on selected cases. Fetal hemoglobin has been studied using four distinct methods: Betke alkali denaturation, microcolumn F on DEAE Sephadex, gamma chain isoleucine residues and the histochemical staining of Kleinbauer. In none of the 12 patients who died was there a complete biochemical evaluation of fetal hemoglobin distribution.

The therapy employed during the acute stages of the cerebral vascular accident included supportive care and intravenously administered hypotonic electrolyte fluids. Most patients received blood transfusion during the acute phase of illness, but none received a complete exchange transfusion, prolonged hypertransfusion therapy or antisickling agents. This is, in effect, a natural history study.

RESULTS

The patient's age at the time of the first stroke ranged from 29 months to 36 years. The age, hemoglobinopathy distribution and classification of cerebral vascular accidents are shown in Table I. Thirty-three of the 35 patients had sickle cell anemia (SS) whereas two were SC. Of the 537 patients registered in this natural history study, there are 1,383 person years of observation in the first decade of life, 1,639 during the second decade.
TABLE I Cerebral Vascular Accidents: 35 Patients with Sickle Cell Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients (no.)</th>
<th>Hemoglobin Type</th>
<th>Mean Age at Initial (yr)</th>
<th>Death as a Result of Stroke (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction</td>
<td>23</td>
<td>SS</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Intracranial hemorrhage, subarachnoid and intercerebral embolism</td>
<td>11</td>
<td>SC</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Embolism</td>
<td>1</td>
<td>Epi# &amp;?</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>33</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

and 1,717 person years after age 20. In this series, 32 of 537 patients suffered strokes, representing a relative frequency of 6 per cent. Of these, 30 had SS and two SC compared to the entire group which contains 397 with SS, 99 with SC and 41 with S other (combinations of hemoglobin S with other hemoglobinopathies). This is 7.56 per cent of the patients with SS and 2.02 per cent of those with SC. The patient with SS has a statistically significant increased risk (p < 0.05). Twenty-five of the 35 patients in this series were less than 20 years old at the time of their first episode. This includes 22 of 23, all with SS, who had cerebral infarcts but only two of 10 with subarachnoid or intracerebral hemorrhages and the single patient with a bone marrow infarct. The calculated actuarial risk for the first two decades of life is 0.761 per 100 person years whereas the actuarial risk after age 20 is 0.524 episodes per 100 person years. In order to determine statistically valid risk rates, person years must be used because of the wide variation between individual patients in the length of survival or time in the study. Although the risk appears greatest during the first two decades of life, when strokes occur 1.7 times more frequently than after age 20, this is not statistically significant.

The hospitalization rate of the 32 patients was compared to an age-matched demographic cohort group; we were unable to demonstrate any difference in the rate or severity of illness when patients with SS who had and who had not suffered strokes were compared by age prior to the first stroke. Following the neurologic insult there was an increase in hospitalizations and clinic visits, not only for stroke-related rehabilitation but also for pneumonia, priapism, pyelonephritis and sickle cell crisis. Neither of the two patients with SC had been seriously ill prior to the stroke.

Hemoglobin levels ranged from 6.1 g/dl to 8.4 g/dl and did not differ from the age-matched cohort group. Following the strokes, fetal hemoglobin determinations were repeated using several methods. Levels varied widely from 2 per cent to 21 per cent. Somewhat higher hemoglobin F levels were seen in the younger children, but these levels tended to decrease and reach the steady state level after five years of age following the usual pattern in sickle cell anemia. Fetal hemoglobin was heterogeneously distributed among the red cells in 12 study patients who survived. There was no difference in the concentration of fetal hemoglobin between those who had strokes and age-matched cohorts who did not. Two patients had concomitant glucose 6-phosphate dehydrogenase deficiency. Blood pressure measurements for the younger children, obtained before the stroke, are not available, but blood pressure measurements for all patients who survived are within normal limits. We have observed two families in which siblings with SS have had cerebral infarctions.

Neither "soft neurologic signs" nor other neurologic illness was detected prior to the first stroke. Since some patients had their first stroke a number of years ago, a routine search for these signs by current standards was not made. In an attempt to identify children "at risk", routine electroencephalograms have been performed on many children with SS who had no evidence of neurologic disease during the last 12 year period. Only two of the 25 children (less than 20 years of age) had electroencephalographic examinations prior to the first stroke. One was within normal limits whereas the other was clearly abnormal and will be discussed later. Several children with SS who have abnormal electroencephalograms have no clinical neurologic symptoms to date.

Cerebral Infarction. Cerebral infarction occurred in 23 patients. All had lateralized neurologic deficits of greater than 24 hours' duration without evidence of intracranial hemorrhage. Aphasia was a frequent finding; coma was less common. Of the 23 patients, five died and two were lost to follow-up. There is one recent case in which there is a short post-stroke follow up period. There are 15 long-term survivors with a mean observation time of nine years after the first cerebral infarction. Their clinical courses and follow-up status are outlined in Table II.

Patients with cerebral infarction displayed three distinctive features. First, there was an overwhelming predominance of SS hemoglobinopathy (22 with SS and one with hemoglobin SC), significantly greater than other subgroup sickle cell hemoglobinopathies (p < 0.05). Second, patients with cerebral infarction were young, with a modal age at onset of five years and a mean age of 7.7 years. The risk of occurrence of a cerebral infarct is significantly increased during child-
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Each Episode</th>
<th>Presenting Neurologic Symptoms</th>
<th>No of CVAs</th>
<th>Residual Deficit</th>
<th>CT scan</th>
<th>Hoemoglobin (g/dl) at Time of CVA Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 yr 8 mo</td>
<td>R hemiparesis</td>
<td>4</td>
<td>Spastic quadraplegia, severe mental retardation, seizure disorder, requires custodial care</td>
<td>7.0</td>
<td>Transfusions given from 4/69 thru 4/71 and intermittently thereafter. G-6-PD deficiency</td>
</tr>
<tr>
<td>2</td>
<td>9 yr 1 yr 6 mo</td>
<td>5 yr 4 yr 5 yr 9 yr 12 yr 12 yr 7 yr 8 yr 11 mo</td>
<td>1 1 1 1 1 1</td>
<td>R hemiparesis, mental retardation, Peabody picture I.Q.: 53 to 70 in 1 yr, severe behavioral problems, hyperkinetic, convulsion</td>
<td>7.6</td>
<td>Functioning well in regular school; sibling had CVA</td>
</tr>
<tr>
<td>3</td>
<td>5 yr 4 yr 6 mo</td>
<td>L hemiparesis, Homonymous hemianopsia</td>
<td>1</td>
<td>L facial weakness</td>
<td>8.2</td>
<td>1/73: Brain scan: localized decreased uptake in R occipital parietal areas; functioning in school</td>
</tr>
<tr>
<td>4</td>
<td>5 yr 4 yr 6 mo</td>
<td>L hemiparesis, gait abnormality, Peabody picture I.Q.: 49, mental retardation seizure disorder</td>
<td>3</td>
<td>Patchy low density area in R frontal parietal and high posterior occipital regions with R lateral ventricular dilatation</td>
<td>7.7</td>
<td>10/72: Brain scan: decreased flow entire R anterior hemisphere</td>
</tr>
<tr>
<td>5</td>
<td>5 yr 4 yr 6 mo</td>
<td>R hemiparesis, seizures</td>
<td>4</td>
<td>R hemiparesis, mental retardation Peabody picture I.Q.: 42, seizure disorder</td>
<td>6.9</td>
<td>S pneumoniae meningitis 1963 with no neurologic residual; sibling had CVA</td>
</tr>
<tr>
<td>6</td>
<td>5 yr 4 yr 6 mo</td>
<td>R hemiparesis, seizures defect, obtundation</td>
<td>1</td>
<td>Solzuro disorder, borderline mental retardation, marked personality change with irritability and temper tantrums</td>
<td>6.1</td>
<td>11/74: Brain scan: normal 11/74: EEG slow waves L frontal merging into spike wave discharges; functioning in school</td>
</tr>
<tr>
<td>7</td>
<td>5 yr 4 yr 6 mo</td>
<td>R hemiparesis, seizures, aphasia</td>
<td>4</td>
<td>L hemiparesis</td>
<td>7.1</td>
<td>15 yr interval between CVA episodes</td>
</tr>
<tr>
<td>8</td>
<td>5 yr 4 yr 6 mo</td>
<td>R hemiparesis, seizures</td>
<td>2</td>
<td>R hemiparesis, monoparesis</td>
<td>7.6</td>
<td>Functioning well in regular school; sibling had CVA</td>
</tr>
</tbody>
</table>

**Continued**
### TABLE II (Cont'd)  Cerebral Infarction in 15 Long-Term Survivors (Patients with Sickle Cell Anemia)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Eposle</th>
<th>Presenting Neurologic Symptoms</th>
<th>No. of CVAs</th>
<th>Residual Deficit</th>
<th>CT scan</th>
<th>Hemo- globin (g/dl) at Time of CVA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>8 yr 9 mo R hemiparesis, aphasia 9 yr 10 mo R hemiparesis, coma seizure</td>
<td>2 R hemiparesis, mental retardation, expressive aphasia, requires custodial care</td>
<td>G-G-PO deficiency; functioning in school</td>
<td>Large low density area in L parietal temporal area with shift of ventricles toward L</td>
<td>7.3</td>
<td>2/68: Brain scan: decreased flow in L parietal area</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5 yr Seizures with paralysis of legs</td>
<td>4 R hemiparesis, expressive aphasia, agaphia, seizure disorder</td>
<td></td>
<td>Large low density area in L parietal area; ventricular dilatation; prominent sulci with evidence of generalized atrophy</td>
<td>8.5</td>
<td>9/73: Brain scan: decreased flow in bilateral middle cerebral vessels</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>10 yr 10 mo R hemiparesis 13 yr R hemiparesis, blurred vision, aphasia</td>
<td>2 R hemiparesis Peabody picture I.Q.: 67</td>
<td></td>
<td>Low density area L mid parietal area; generalized ventricular dilatation; prominent sylvian fissures</td>
<td>6.9</td>
<td>I.Q. improving; functioning in school</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>14 yr R hemiparesis</td>
<td>1 R hemiparesis, mild mental retardation, Peabody picture I.Q.: 67; seizure disorder</td>
<td>Prominent sulci, prominent low density areas in periphery of frontal lobes</td>
<td></td>
<td>7.8</td>
<td>11/72, 1/73, 10/73 had TIA with seizures; I.Q. improving</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>6 yr L hemiparesis 7 yr 8 mo L hemiparesis, aphasia 8 yr R hemiparesis</td>
<td>3 Spastic quadriplegia, expressive aphasia, Peabody picture I.Q.: 54</td>
<td>Large low density area R frontal parietal region; patchy low density in L parietal occipital area</td>
<td></td>
<td>7.4</td>
<td>I.Q. Improving</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4 yr R leg weakness, ataxia, 11 yr 2 mo nuchal rigidity 11 yr 6 mo L hemiparesis 11 yr 10 mo L hemiparesis 12 yr L hemiparesis L hemiparesis</td>
<td>5 L hemiparesis with spasticity, mental retardation, Peabody picture I.Q.: 48</td>
<td>Low density area R parietal area. Loss of substance R frontal lobe, ventricular system shifted to right</td>
<td></td>
<td>7.3</td>
<td>Sibling had CVA</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** L = left; R = right; G-6-PD = glucose-6-phosphate dehydrogenase; EEG = electroencephalogram; SS = sickle cell anemia; CVAS = cerebrovascular accidents.
hood (p < 0.01) whereas the adult patient will have an intracranial bleed (p < 0.05). Third, among the 15 long-term survivors whose life table is shown in Figure 1, recurrent episodes were seen in 10, a recurrence rate of 67 per cent. The incidence of a second cerebral infarction was independent of the age at onset. Temporal clustering of the recurrences within 36 months is the outstanding clinical feature of this group of patients. Fourteen of 21 repeat episodes occurred before 24 months. The mean interstroke interval was 28 months with 80 per cent of the subsequent strokes recurring before 36 months as shown in Figure 2. The susceptible person appears to experience a definite period of risk marked by recurrent stroke episodes following which no further stroke episodes occur. Factors contributing to this cessation are unknown.

Results of follow-up neurologic examinations are given in Table II. Each patient showed considerable neurologic improvement during the year immediately following the stroke. With two exceptions, the children were eventually able to return to school. Neurologic deficit increased in severity with each reoccurrence of cerebral infarction. In seven of the 15 survivors a seizure disorder, for which they require medication, followed the stroke and their seizures have been difficult to manage. Eleven have permanent motor disability, four have recovered essentially normal motor function.

Psychologic testing was performed in 10 of the 15 survivors. Four of the five not tested were so neurologically handicapped that testing could not be carried out. A child psychologist administered the following standard tests: W.I.S.C., Peabody Picture Vocabulary Test and Hooper Visual Organization Test. These tests were given at variable intervals after the stroke but well after the acute symptoms had subsided. Some intellectual impairment was seen in all patients; seven of 10 exhibited significant mental retardation with an I.Q. of less than 70. Two of the patients did demonstrate improving I.Q. scores with the passage of time.

CT scans were obtained on 13 of the 15 survivors (Table II) and on all patients with recent cases during both the acute episode and in follow-up. The major findings included low density areas in the region of the infarct with ventricular dilatation and shifting of the ventricular system towards the involved area. Prominent sulci over the infarcted area were often seen. The CT scans have proved useful in the differentiation of the extent of involvement resulting from old and sometimes repeated episodes. The structural deficits demonstrated on CT scan correlate well with the functional deficits found on neurologic examination. The CT scan performed at 40 hours after the stroke revealed low density in both hemispheres in a seven year old boy who died with his first stroke (Figure 3). Autopsy findings correlated exactly, demonstrating total right hemisphere and left frontal parietal area infarctions. Another patient (Case 10) had large low density areas in both hemispheres after his fourth infarction (Figure 4). He now has a seizure disorder characterized by prolonged seizure activity followed by altered sensorium always raising the question of recurrent ischemia. A repeat CT scan after one such convulsive episode showed no increase in the area of infarction.

Five of 23 patients with cerebral infarction died. One, whose CT scan is shown in Figure 4, died four days after the onset of neurologic symptoms. Another, a four year old child with SS, had an episode of weakness in the
lower right extremity which lasted for one week with complete resolution. Six months later he had a massive fatal infarction. A two year old girl died after a six month hospital course characterized by multiple strokes. At autopsy she was found to have severe encephalomalacia with both recent and old areas of infarction in both hemispheres. A woman with SS suffered two cerebral infarctions in 1952 and 1953 which resulted in permanent right hemiparesis. She had no further strokes but died 20 years later in renal failure. The only patient with SC who had a cerebral infarct had an episode of left hemihypesthesia one year before she died after sustaining head trauma with a subacute subdural hematoma. In addition to the subdural hematoma, the autopsy revealed an area of porencephaly in the right cerebral hemisphere.

**Subarachnoid and Intracerebral Hemorrhage.** Eleven patients with SS had an acute episode of subarachnoid or intracerebral hemorrhage. All 11 manifested severe headache, nuchal rigidity, coma or focal neurologic deficits in association with bloody xanthochromic spinal fluid. Table III shows the categorical breakdown of these bleeding episodes. A representative CT scan is shown in Figure 5. The age at the time of the hemorrhages ranged from 14 years to 36 years, mean age 25 years. No patient was known to have had hypertension prior to the hemorrhage. Six of the 11 died as a direct result of the neurologic insult. Two patients who survived were diagnosed as having intracerebral bleeding on the basis of bloody spinal fluid associated with focal neurologic deficits. No ancillary studies were performed, and the

| Table III: Spontaneous Intracranial Hemorrhage in 11 Patients with Sickle Cell Disease |
|-----------------------------------------------|------------------|
| Ruptured aneurysm                              | 3                |
| Vascular malformation                          | 1                |
| Heparin toxicity                               | 1                |
| Primary intracerebral hemorrhage (autopsy)     | 4                |
| No associated condition demonstrated—alive     | 2                |

**Figure 3.** CT scan performed 40 hours after cerebral infarct showing simultaneous involvement of the entire right hemisphere and segmental infarction on the left.

**Figure 4.** CT scan from an 18 year old boy with four episodes of cerebral infarction and residual right hemiparesis, spasticity and mental retardation. Note the large low density area in the left parietal region representing the old infarct. There is a shift of ventricular system towards the left.

**Figure 5.** Computerized tomography scan demonstrating a massive intracerebral and subarachnoid intraventricular hemorrhage taken at three days after onset of the stroke.
exact site of their hemorrhage remains unknown. Neither has a functional deficit at this time.

In three patients, cerebral angiography demonstrated the presence of one or more aneurysms. One patient presented with nuchal rigidity and obtundation which progressed to coma. Cerebral angiography revealed multiple aneurysms of the posterior cerebral arteries as well as one involving the left middle cerebral artery. Because of the multiplicity of lesions, she was not considered a surgical candidate and died two years later following another subarachnoid hemorrhage during the last trimester of her first pregnancy. Another patient had a potentially correctable aneurysm but did not undergo surgery. An aneurysm of the superciliary branch of the left internal carotid artery was demonstrated in a 29 year old man with SS. The patient became totally comatose for several hours immediately after the cerebral angiogram despite the fact that an exchange transfusion had reduced the hemoglobin S to 34.6 per cent. Subsequently, the aneurysm was surgically repaired and the patient made an uneventful recovery.

Fat Embolization. One patient with SC hemoglobinopathy died following bone marrow infarction with subsequent fat embolism to the lungs, kidneys and brain. At autopsy, fat globules and hematopoietic tissue including megakaryocytes were found in the small vessels of the cerebral parenchyma. This patient was 14 years old and had not been hospitalized or seriously ill prior to her death.

COMMENTS

Strokes occur with an alarming frequency in the sickling disorders. In a review of the English language medical literature in which the specific hemoglobinopathy diagnosis is based on electrophoresis, 102 cases were found [4,6,8-17]. Not included in this number is a general discussion of 86 patients from Howard University [5]. However, many unreported cases are known to exist in several centers throughout the United States. Various stroke syndromes occur with sickle cell disease, including cerebral infarction, subarachnoid and intracerebral hemorrhage, and bone marrow infarction with subsequent fat embolism. Ten of 257 (4 per cent) Nigerians hospitalized with sickle cell disease had strokes [13]. Thirty-three of 537 of our total demographic patient population had strokes. However, the actuarial risk of stroke is not different at different ages. There is a clearcut statistically significant difference between the type of stroke observed during childhood and that observed during adulthood. No factors have been identified that explain prevalence of infarcts in the younger age group. We know of no other clinical situation in which one type of stroke occurs in the young and another in older patients, all of whom have the same underlying disease.

As with "acute hemiplegia of childhood" [18], onset of strokes in children with SS is marked by acute hemiparesis and seizures, and younger children have a poorer prognosis. Long-term residual hemiparesis, mental retardation and a poorly controlled seizure disorder are the usual outcome. Cerebral infarction is not usually associated with immediate death. However, in our study, more than half of the patients with intracranial hemorrhage died immediately as a direct result of the neurologic insult. Hypertension is not a feature of stroke in sickle cell disease, either as a precipitating factor or as a complication after stroke.

In three reports in which angiography was performed to investigate the cause of cerebral infarction [8,9,13], 12 of 15 patients manifested partial or complete occlusion of major cerebral vessels. The reason why major vessels are involved remains unclear. Stockman et al. [8] suggested that intravascular sickling in the vasa vasorum of these arteries might damage the arterial wall leading to eventual vascular occlusion. Boros et al. [16] described a child with SS who had four cerebral infarcts between 8 and 13 years of age and who died at 18 with a massive intracerebral hemorrhage, demonstrating the age relationship to the type of stroke in a single patient. Angiographically, there were multiple stenotic lesions of large cerebral vessels which were documented at autopsy as severe fibrotic endarteritic changes. It has been hoped that the benefits of hypertransfusion therapy could be objectively demonstrated by angiography as originally suggested by Russel et al. [9]. However, angiography performed on hypertransfused patients during recent follow-up has failed to regularly demonstrate vascular improvement. Several patients have been seen in Chicago and New York who have had "striking progression" of the angiographic abnormalities in the face of improving clinical neurologic status. These findings suggest to us that the cerebral infarcts were caused by multiple large and small vessel disease involving the vascular supply to both hemispheres.

Subarachnoid and intracerebral hemorrhage are by no means rare in sickle cell disease and have been the subject of numerous reports [7,14,19,20,21]. However, it is not universally correct to assume that the cause of the hemorrhage is the sickling disorder. Confirming an observation of Wood [5] we have found that one must consider the possibility of an aneurysm or other arteriovenous malformation. In the cooperative study by Locksley [22], 51 per cent of the subarachnoid hemorrhages in the general population were related to the presence of an underlying aneurysm. The prevalence of ruptured aneurysms at autopsy has been reported by various investigators to be in the range of 0.6 per cent to 1.5 per cent [22-27], whereas unruptured aneurysms are thought to be present in as many as 3.1 per cent of the general population [28]. We speculate that the combination of a structural malformation of the...
cerebral vasculature in a patient with the sickling disorder would result in an added rheologic insult to already damaged red cells increasing risk of a stroke. This is supported by evidence that mechanical damage of red cells containing SS hemoglobin induces the sickling phenomena in vitro [29]. Included in the study is the first reported successful surgical correction of a cerebral aneurysm in a patient with SS.

Fat embolization to the brain following bone marrow infarction has been reported on several occasions in sickling disorders [30–35]. In life, bone marrow biopsy reveals areas of necrosis with replacement of normal hematologic precursor cells by an eosinophilic-staining amorphous material. One should suspect bone marrow embolism when a patient with a bone marrow infarct begins to have dyspnea and a change in his level of consciousness. The diagnosis is usually confirmed at autopsy with demonstration of fat particles and hematopoietic tissue in the cerebral vessels. Based on the paucity of reports in the literature and from our own experience, this appears to be a rare event. It should be noted that the one patient in our series with fat embolism had SC hemoglobinopathy as have several patients in the reported cases.

**Predictor of Impending Stroke.** Clearly, we have not found reliable and objective indicators of impending stroke. The frequent assumption that the clinical severity of the sickle cell anemia prior to the stroke is a consistent indicator of risk is not borne out by this study. Fetal hemoglobin levels vary widely among our patients with SS occasionally reaching levels of up to 20 per cent. A stable level of fetal hemoglobin may not be obtained until a child is five years old. The higher fetal hemoglobin levels observed during infancy and early childhood clearly do not protect the child from cerebral infarction. One half of the children with cerebral infarction were less than five years of age at the time of their first stroke.

Just as there are no certain hematologic predictors, there are no sure neurologic predictors. A history of transient mild motor or sensory loss may presage a more serious ischemic event. An example is the patient who was hospitalized with fever and mild nuchal rigidity in whom a severe left hemiparesis and hemianopsia developed during the electroencephalogram. On careful questioning, the parents recalled that the youngster had had a transient weakness two weeks prior to admission. Careful multiple neurologic examination looking for mild reflex asymmetries, visual field deficits, hemisensory changes or weakness may demonstrate evidence of a prior clinically insignificant stroke.

We have recently initiated routine CT scanning on minimal indication because of the suggestion that patients with SS may suffer "silent" cerebral infarcts. We believe that regular CT scans performed on neurologically asymptomatic patients with SS might reveal previously unsuspected cerebral insults since CT scans can identify the presence of small lesions [36–39]. With sufficient clinical suspicion, transfusions followed by angiography may be undertaken in order to detect vessel stenosis. Flow studies with radioisotopes have not been rewarding due perhaps to the multiplicity of lesions or the hyperdynamic circulatory state of the patient with SS.

The electroencephalograms which have been carried out routinely in some of our children with sickle cell anemia have not been a useful predictor of susceptibility to strokes. The electroencephalogram recorded in one patient after he had had his stroke episode, showed an abnormality in the area corresponding to the area of infarct, but while reviewing this patient's previous electroencephalograms we found that the abnormality had been present 18 months before. Whether the abnormality on the electroencephalogram was an indicator of stroke susceptibility remains questionable in view of the fact that similar recordings have been observed in children with sickle cell anemia without strokes.

**Therapeutic Implications.** The compelling nature of the problem of strokes in patients with sickle cell disease has resulted in an aggressive therapeutic philosophy. There is an evident willingness to take large therapeutic risks in desperation because of the currently discouraging results. Hypertransfusion with normal red cells in order to reduce the hemoglobin S concentration to 20 or 30 per cent is being investigated by several centers [9, 10]. Results have been encouraging, and there are now a number of children who are being so treated and who have not had a recurrence of their strokes. However, we would like to point out an unexpected observation in our series of 15 long-term cerebral infarct survivors. As demonstrated in Figure 1, the most recent recurrence among our surviving group occurred in one patient three years ago. Had we decided during the last three years to begin a prophylactic therapeutic regimen of any sort, we would have clearly demonstrated a lack of recurrence in all patients, spuriously suggesting therapeutic efficacy. The majority of our patients have shown significant clinical improvement with a program of supportive neurologic rehabilitation. In addition, one-third of our children have had no further strokes, and these children showed spontaneous improvement in both neurologic and intellectual function. If the Los Angeles patients can be considered a control group for the Detroit study [25], no benefit from long-term transfusion therapy can be claimed; however, variability in clinical expression of sickle cell anemia makes evaluation of treatment a difficult problem in small groups of patients observed for a limited period of time.

Long-term transfusion in sickle cell anemia has added another category of problems to the patient. Rare anaphylaxis and a minimal risk of hepatitis is expected.
with the use of buffy coat-poor frozen blood from volunteer donors. More importantly, iron overload of already compromised cardiac and hepatic tissues will necessitate early institution of iron chelation therapy. A high rate of transfusion-induced irregular isoimmune antibodies will result in a progressive increased difficulty in obtaining appropriate blood.

The best therapy would be an antisickling agent that could be used both intravenously and orally in the long-term patient. At the time of this writing, no such agent having an acceptable therapeutic index has been identified. Several agents are under investigation and may prove useful. However, we know of no attempts at drug therapy in patients with strokes.

This natural history study suggests that since 80 per cent of repeat cerebral infarctions occur within three years of the previous stroke, therapy aimed at prevention of recurrence should be initiated at the time of the stroke and continued for a minimum of three years. The pattern of temporal clustering clearly indicates that there is little rationale for beginning an "antistroke" therapeutic regimen at some delayed indeterminate time after the stroke episode, particularly if the time elapsed is more than two years. In view of the rarity of cerebral infarction and the paucity of natural history studies, historic controls have limited validity. Efficacy of therapy must be evaluated on a national multi-institutional basis.

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REFERENCES

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