Sickle cell disease affects many organ systems, but one of the major morbidities is brain disease, especially stroke. In this paper, the etiology, diagnosis, treatment, and prevention of clinical stroke, as well as so-called “silent stroke,” are examined. Risk factors, diagnostic tools, and data from prevention and treatment studies as well as issues pertaining to neuropsychological function, especially in younger patients, are discussed and current best options for treatment considered.

I. DIAGNOSTIC TESTING, MIMICS OF STROKE AND STROKE PREVENTION

Robert J. Adams, MS, MD*

Diagnostic Testing:
Ischemic Stroke versus Hemorrhage
Patients presenting with neurological symptoms and the diagnosis of sickle cell disease (SCD) are often assumed to have stroke because it is very common. This is not an unreasonable assumption as long as other diagnoses are considered and a thorough evaluation is performed. Ischemic stroke most often presents with focal signs and symptoms especially hemiparesis, hemisensory deficits and complaints, focal seizures or visual disturbances.1 Severe headache and altered level of consciousness are more typical of intracranial hemorrhage. Generalized seizures and/or syncope may accompany any stroke but are more common with subarachnoid hemorrhage.2,3 Bilateral hemiparesis is uncommon in sickle cell disease because the blood supply to the brain stem is less often affected by occlusive vasculopathy than the carotid systems.4
The presence of fever, antecedent symptoms and other risk factors for stroke should enter into the diagnostic consideration. Some causes of stroke that are not specifically related to SCD such as endocarditis, drug abuse, anticardiolipin antibody syndrome, carotid or vertebral artery dissection and cerebral venous thrombosis are important causes of stroke in young people generally and should be entertained.

Brain Parenchymal Imaging
After physical and neurological examination is performed, the most common next step is a cranial computerized tomography (CT) scan without contrast. This test is sensitive for intracranial hemorrhage and will show brain ischemia after 2-3 hours as well as important alternative diagnoses such as subdural hematoma due to trauma, brain abscess or tumor and some kinds of central nervous system (CNS) infections.

Cranial magnetic resonance imaging (MRI) is usually the next step to accomplish one of several objectives. The following techniques are useful to define important pathology:
• Diffusion weighted imaging (DWI)5 can produce a very sensitive map of areas of acute (less than 1 hour) ischemia and verify that the symptoms in question are indeed ischemic. In some cases it can show multiple areas, not suspected clinically, that can aid in determining the cause of the stroke syndrome.
• Routine T1 and T2 weighted imaging produce sensitive and specific brain images that show gray and white matter contrast, borderzone lesions that are especially prone to insult in SCD, cerebrospinal fluid (CSF) spaces, intracranial blood, edema and mass lesions to full advantage.6,7
• Magnetic resonance angiography (MRA) is based on the movement of blood through the arteries during each MRI pulse sequence and has been shown to correlate reasonably well in some studies with conventional angiography.8 It can detect large vessel disease in the internal carotid and middle cerebral arteries at least when it is severe, and can detect large aneurysms and vascular malformations.

Cranial Arterial Imaging
The presence of an infarction is detected by parenchymal imaging, but the status of the vessels provides other related important information regarding the risk of future stroke. Although there is little prospective angio-
graphic data because patients are usually symptomatic when studied, it is reasonable that patients with extensive arterial disease evident on arterial testing have a greater chance of having stroke than those with normal appearing vessels. Four techniques are used to assess the cerebral vasculature: cerebral catheter angiography, MRA, CT angiography, and Transcranial and extracranial Doppler and ultrasound imaging.

Angiography has largely been supplanted by non-invasive techniques but it is still the best way to clearly visualize the lumen and vascular morphology. It is the best way to detect cerebral aneurysms that can cause fatal subarachnoid hemorrhage. In cases with intracranial hemorrhage cerebral angiography it is advisable to rule out lesions that should be treated with surgery. Hydration and reduction of Hb S to < 30% prior to angiography is the usual method for preparation, and there have been few (if any) reports of stroke complications since this practice was initiated. Angiography in SCD patients who have symptoms of ischemia often shows stenotic lesions or occlusions in the internal carotid artery (ICA) or middle cerebral arteries (MCA) but seldom in the vertebrobasilar or extracranial carotid systems. Angiography to investigate brain ischemia is usually not needed. MR angiography has been compared to conventional angiography in SCD. Kandeel and colleagues reported that MRA is 85% accurate when compared to conventional angiography. In a study of 22 SCD patients, an MRA abnormality in a long segment (6 mm) with reversed, arterial dilatation is reversed based on MRA. The abnormality in MRA was in part reversible that this dilatation is inversely proportional to the hematocrit. The higher blood flow is related to anemia and the resulting hyperemia affects the vasculature. Arterial dilatation has also been reported by others on cerebral angiography. Once the anemia and hyperemia are reversed, arterial dilatation is reversed based on MRA.

These findings are of interest but as yet do not dictate a specific treatment strategy. Also, there is little to suggest that stenotic lesions will reverse with treatment.

In addition to providing an assessment of the arteries the technique can be used to look for two other conditions that might be present in unusual cases: arterial dissection due to trauma and venous thrombosis, which has been reported in SCD. An MR venogram must be specially requested if cerebral venous thrombosis is suspected. Such cases present with headache, seizure, increased intracranial pressure and possibly cerebral hemorrhage and are usually anticoagulated until resolution of the venous clot on imaging.

CT angiography requires intravenous contrast and is not yet widely available. The published pictures appear to provide greater detail than MRA, and series in non-SCD patients comparing CT angiography to conventional angiography have been published. The technique has the disadvantage of requiring a contrast agent. Ultrasound techniques have been used for decades to image the carotid arteries (carotid Doppler) in the neck and more recently the extracranial vessels (TCD). Since there is very little documentation of extracranial artery disease in SCD this review will focus on TCD. TCD detects stenositis by indicating regions of the circle of Willis vessels at the base of the brain that show higher than expected arterial flow velocities. Higher velocities indicate either elevated cerebral blood flow, in which case the TCD shows widespread increases in velocity, or an area of reduced arterial diameter, or stenosis, in which case there is a focal increase in velocity. There are two variations on the technique: TCD, which has come to imply Doppler only, with no imaging component, and TCDI (imaging), which combines Doppler and ultrasound color imaging of vessels based on flow.

The images are not useful for reading stenositis but provide a visual map to help the operator place the Doppler sample volume for velocity recording. TCD has been used since 1986 in children with SCD, and three independent, prospective series have demonstrated that elevated velocities in the segments most likely to have vasculopathy in SCD predict future stroke. TCD readings are given in cm/sec values. In normal children the velocity is in the range of 90 cm/sec in the middle cerebral artery. In children with SCD the velocity is higher overall due to anemia and in the range of 130-140 cm/sec in the absence of increased risk. Above 170 cm/sec, which is about 1.5 standard deviations above the mean, stroke risk increases. Over 200 cm/sec the risk of stroke rises from the baseline rate of .5-1%/year to the range of 10-13%/year. Values in between 170 and 200 indicate intermediate risk not well characterized from these studies.

These benchmark velocities are what are called...
“time averaged maximal mean” velocities rather than peak systolic or minimum diastolic velocities. The different velocities that are used are a source of confusion. Generally, when Doppler is used in other diseases only the peak is reported. It is thus necessary when interpreting TCD to be sure one knows what vessel velocity is being reported and the type of velocity reading. The Clinical Alert from National Heart Lung and Blood Institute (NHLBI; see below), which called for TCD screening and consideration of chronic transfusion to prevent first stroke in children with SCD, bases selection for treatment on a cutoff of 200 cm/sec time averaged maximal mean, recorded on two different occasions. In most cases a time averaged maximal mean of 200 cm/sec will be associated with a peak systolic of 280-300 cm/sec.

The addition of imaging may shorten training time by allowing the operator to visualize the approximate location of the vessels, but studies indicate that the velocities measured are somewhat lower than those recorded by TCD using Doppler alone.27,28 The reasons for this are not clear but the difference is about 10-15%, which implies that the treatment cutoff may need to be moved down to 185 cm/sec although as yet there are no firm recommendations in this regard.

**Perfusion Imaging and Blood Flow**

Cerebral blood flow (CBF) is increased by 68% in SCD patients as compared to age matched controls29 as demonstrated in a study of 67 patients with SCD using Xenon inhalation techniques. Other CBF studies confirm the hyperemia.30 Positron emission tomography (PET) studies also confirm that both CBF and cerebral blood volume (CBV) are increased in SCD but with no change in oxygen extraction fraction,31 although the number of patients studied with PET has been small. This increase in blood flow is directly related to cerebral blood volume and inversely related to Hct. Transfusion therapy normalizes the findings. The change seems to be related primarily to normalization of the Hct but is at least in part determined by the replacement of Hb S with Hb A.20,32 SCD is a hyperemic, hypervolemic state probably related to both the anemia and the abnormal red cell type. Since patients with SCD develop distal field insufficiency, some of the infarcts in SCD are probably related to an inability to improve circulation to vulnerable areas of the brain in times of stress because of diminished cerebrovascular reserve.

Perfusion can also be assessed using MR33 and PET techniques.31,34-36 In a study using perfusion magnetic resonance (dynamic susceptibility contrast MRI) with a contrast agent (gadolinium-DTPA), perfusion abnormalities were associated with neurological symptoms (strokes, TIAs, seizures, headaches) in children with SCD. Abnormal perfusion studies and neurological symptoms often persisted despite transfusion therapy. In addition, three sickle cell patients with TIAs presented with abnormal perfusion MRs, but no abnormality was found in other neuroimaging techniques (MRI, DWI, MRA, TCD). This study suggested that perfusion MR can help to guide individual management of patients with SCD at risk of stroke or stroke recurrence.33 However, in most clinical settings it is not clear how perfusion or blood flow measurements should specifically alter therapy and more study is needed.

Magnetic resonance spectroscopy (MRS) and PET are techniques that probe brain physiology. There has been one study using MRS,37 which showed metabolic abnormalities in areas of ischemia, but the clinical utility of MRS remains to be established.

PET studies31,34-36 that have been done in patients with SCD have shown a variety of abnormalities including hypometabolism in frontal areas of the brain and areas of low perfusion that appear normal on MRI. The study of Powars et al36 suggested that few patients with SCD have normal PET studies and areas of hypometabolism in brain regions with normal MR appearance are not uncommon. The authors suggested that PET could be used to select patients for treatment. Although the natural history of PET abnormalities is not known in detail, four patients showed partial reversal of abnormalities (improvement of glucose metabolism and perfusion) with transfusion treatment. The most powerful predictor of ischemia in other applications of PET is an increased oxygen extraction fraction (OEF) and this has been evaluated in only one small study of SCD, that found OEF was not increased. PET is not widely available, and the clinical applicability of this approach remains to be established.

Electroencephalography (EEG). There is no specific role for EEG unless clinical or subclinical seizures are suspected.

Specialized laboratory testing. Screening for hypercoagulability including homocysteine levels and anticardiolipin antibodies should be considered in all SCD cases with stroke because of reported associations of these abnormalities with SCD and neurological complications.34-40

Mimics of Stroke

While none of these are specific to SCD, the following should all be considered in the differential of SCD patients presenting with neurological complications:

- Seizures—with postictal paralysis
- Encephalopathy
- Increased intracranial pressure (secondary to cerebral venous or sinus occlusion)
- Head trauma
- Meningitis
- Metabolic causes of altered mental status
- Peripheral neuropathy

**Stroke Prevention**

**Primary Stroke Prevention**

*STOP paradigm for children:* The only strategy for prevention of stroke, either primary or secondary, in SCD that has been tested in a randomized clinical trial in SCD is the one based on the Stroke Prevention Trial in Sickle Cell Anemia (STOP study). In this study, about 2000 children age 2-16 years with SCD but no clinical evidence of stroke were screened with TCD. About 9% were found to have high risk TCD (> 200 cm/sec in either the MCA or ICA) on one or both sides. Bilateral high velocities were found in about 40% of the high risk cases, and the velocities ranged from 200 cm/sec to 317 cm/sec. Patients were randomized to standard care (episodic transfusions only) and a regimen of regular blood transfusions intended to reduce the Hb S to < 30%. Children on average received transfusion about every fourth week. The trial was halted when 11 strokes were observed in the standard care arm (intention to treat analysis) and one in the transfusion arm, and a Clinical Alert was issued to advise screening of children with TCD and consideration of transfusion. Acceptance of transfusion continues to be incomplete due to the rigors and side effects of transfusion despite its demonstrated efficacy in the STOP study. The risk of 10% per year justifies prophylactic transfusion in some peoples minds and in others not. Whether hydroxyurea is a viable alternative remains to be tested. Research is ongoing to determine if transfusion can be safely halted after a period of treatment during which the TCD reverts to low risk. TCD surveillance is a critical part of this protocol.

*Ischemic stroke prevention in adults:* There have been no trials assessing primary prevention treatments for adults. Some clinicians recommend transfusion while others recommend using antiplatelet agents or anticoagulation. A small number of patients have received a form of bypass surgery used in patients with Moyamoya syndrome. There were too few strokes in the adult trial of hydroxyurea to prevent painful crises to assess its impact on stroke.

*Hemorrhage:* It is not known if transfusion prevents recurrent hemorrhage. Patients with any form of intracranial bleeding, excepting subdural from trauma, need evaluation for a surgically correctable aneurysm even if the bleeding appears to be primarily intracerebral. If there is no aneurysm then transfusion for at least a year is often recommended, but it is not clear if this helps. Recurrent hemorrhage is less common than recurrent ischemic stroke, partly because more of the first events are fatal.

**Secondary Prevention**

There have been no randomized trials testing preventive treatment after the first stroke. However, a number of case series and a more recent review have reported that the risk reduction appears to be substantial, reducing at least the recurrence in the first few years from over 50% to around 10%.

Transfusion is usually continued for at least 2-3 years, and small series have differed on whether the risk after withdrawal is low and acceptable or high and unacceptable, but a randomized trial of either withdrawal or modification of therapy after years of treatment has not been done. Case series showing reductions in transfusion intensity or conversion to hydroxyurea have resulted in encouraging but not definitive data on how to modify or limit the need for long term transfusion.

Bone marrow transplantation (BMT) appears to arrest cerebrovascular disease, at least based on follow up of several years. The use of BMT for primary prevention is currently under debate and consideration.

II. CLINICALLY EVIDENT STROKE IN SICKLE CELL DISEASE: RISK FACTORS, PRESENTATION, TREATMENT, AND OUTCOME

*Kwaku Ohene-Frempong, MD*

The clinical pathology of SCD stems from the combined effects of two phenomena, chronic hemolytic disease and vasoocclusion. Chronic hemolysis leads to anemia and tissue hypoxia, while vasoocclusion diminishes or blocks tissue blood supply and can also lead to tissue ischemia and infarction. The system in which sickling-related vasculopathy has been best demonstrated is the cerebrovascular system. Sickle cells damage both small vessels in the arteriole-capillary-venule beds and vessels as large as the internal carotids and those of the circle of Willis. Large vessel disease is easily demonstrated by angiography, but small vessel damage is inferred largely from the distribution of cerebral infarcts or perfusion studies. The combined effects of vasoocclusion and severe anemia may lead to ischemic damage to brain tissue, silent infarcts and abnormalities in neurocognitive function. Less frequently, the ischemia affects motor areas, or vascular damage causes hemorrhage resulting

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in acute clinical stroke. The extensive vascular and parenchymal brain damage that can result from SCD has been demonstrated in pathological specimens.1-3

Stroke as a complication of SCD was first reported by Sydenstricker et al in 1923, some 13 years following the publication in 1910 of the first description of SCD in modern medicine.4 In 1935, Arena described another case and later (in 1939) suggested that cerebrovascular disease and thrombosis were the cause of stroke in SCD.5,6 Stroke did not attract attention as a major complication of SCD until the 1970s when standard cerebral angiography was used to demonstrate the extent of cerebrovascular disease in SCD, and it was reported that chronic transfusion therapy (CTT) can prevent the recurrence of stroke.7,9 The seminal report on the natural history of stroke and its high frequency of recurrence was made by Powars et al in 1978.10 Since then the attention of clinicians has focused on the prevention of recurrent stroke through chronic transfusion therapy.

Cerebrovascular disease and resultant parenchymal pathology in SCD have been studied using a variety of techniques. Some techniques such as standard angiography and MRA detect vascular disease. Others such as CT,11-13 and MRI14,15 show infarcts and ischemic changes, while single photon emission computerized tomography (SPECT),16 xenon-133 inhalation,17 PET,18,19 and MRS20 provide data on regional metabolism and/or blood flow. A recent addition to this armamentarium is TCD.21-23 TCD has proven to be a technique reliable in predicting high risk of first stroke in SCD and a useful tool for selecting patients for intervention to prevent first stroke.24,25 (See Section I.)

Both small and large vessels are involved in the pathogenesis of stroke in SCD. The caliber of these small vessels is typically beyond the resolution of standard or MRA.26 Infarcts in arterial borderzones suggest loss of distal small vessels.15 Larger arteries, particularly those of the circle of Willis, internal carotids, and the vertebral-basilar system may show stenosis and occlusion.7,8 Moyamoya disease, the formation of a mass of small friable blood vessels in response to severe stenosis or occlusion of major intracranial vessels, is frequently seen in SCD.27-30 The vascular pathology in the large vessels appears microscopically as intimal hyperplasia with internal encroachment of the lumen. The internal elastic lamina also shows fragmentation and duplication.31 Cerebral vessels, particularly those of the circle of Willis, also show increased formation of aneurysms in older SCD patients.30-32 Rupture of these aneurysms is the usual cause of hemorrhagic stroke. The hemorrhage is typically subarachnoid but may be intraventricular or parenchymal.33 Bleeding may also result from rupture of Moyamoya vessels. There is evidence to suggest that cerebrovascular disease responsible for infarctive strokes may progress and lead to hemorrhagic stroke at a later age.34

Definition of Stroke in Sickle Cell Disease
Stroke is defined by clinical criteria despite the myriad of sophisticated neuroimaging and electrophysiologic measurements currently available for the study of brain pathology. The definition of stroke tends to ignore subtle, non-physical changes in behavior, memory, or personality that may be signs of cerebrovascular disease. This is an important issue in young children, since stroke in SCD affects children at ages when their ability to verbalize physical or mental difficulties may be limited. The Cooperative Study of Sickle Cell Disease (CSSCD) defined stroke as “an acute neurologic syndrome due to vascular occlusion or hemorrhage in which neurologic symptoms lasted more than 24 hours.”35 By the inclusion of “vascular occlusion or hemorrhage,” the CSSCD definition implied the need for neuroimaging. Typically, the diagnosis of stroke is made on the bases of physical findings supported by the demonstration of vascular or parenchymal abnormalities on neuroimaging studies. Moreover, neurologic symptoms suggestive of stroke are typically those manifested as focal motor deficits. However, it is clear now that abnormal neuroimaging studies that show vascular occlusion and/or parenchymal infarcts may be found in SCD patients without obvious neurologic symptoms.36,37 The term “silent infarct” has been coined to describe a condition in which infarction of brain tissue is found on imaging studies in the absence of a history of neurologic symptoms.38-40 Patients with “silent infarcts” are usually not managed as having had a stroke. In addition, neurologic symptoms lasting less than 24 hours are considered to be the result of a transient ischemic attack (TIA). Patients with TIA whose symptoms are recognized and reported are likely to undergo neuroimaging studies. If the results of these studies show infarcts or hemorrhage, the patients are usually classified as having had a stroke. Patients presenting with a history consistent with a TIA but whose neuroimaging studies are normal are not usually managed as stroke patients. In summary, having neurologic symptoms without positive imaging study or a positive imaging study without symptoms is currently not considered a stroke.

A definition of stroke that included all objective evidence of infarct of brain tissue would provide justification for routine brain imaging in patients with SCD and would lead to increased reporting of stroke in SCD. This would be analogous to the increased discovery of pulmonary lesions when chest x-rays are obtained as a routine part of evaluating febrile young children with SCD who may show no obvious signs of respiratory illness. (The subject of “silent infarcts” and their clinical significance are discussed in the Section III.)
Incidence and Prevalence of Stroke

The CSSCD determined prevalence and incidence rates of stroke based on data from 4,000 patients followed for up to 10 years from 1978 to 1988. Overall prevalence of stroke in all forms of SCD was 4%; it was 5% in those with homozygous SCD (SCD-SS). First stroke occurred in all age groups of the CSSCD cohort except for children under one year of age. The annual incidence of first stroke was approximately 0.6 per 100-patient years in SCD-SS (Table 1). However, the highest incidence occurred in the first decade of life with rates of 1.02 per 100-patient years in SCD-SS patients 2-5 years and 0.8 in those 6-9 years of age. The cumulative risk of first stroke in SCD-SS patients was 11% by age 20 years, 15% by age 30, and 24% by age 45. The combined incidence of hemorrhagic and ischemic strokes in a general sample of American children through 14 years of age was reported as 3.3/100,000/year or, 0.0033 per 100-patient years. The incidence rates of ischemic and hemorrhagic strokes in the first decade in children with SCD-SS are approximately 300 times those for all children in the US.

Reliable reports of the incidence of stroke in SCD populations from other countries are scanty. The Jamaican Cohort Study reported that 17 (5.5%) of 310 children with SCD-SS had had a stroke by age 14 years. Twenty (6.7%) of 299 SCD-SS patients, mostly of African origin with a mean age of 10.1 ± 5.8 years, enrolled by the French Study Group had had a stroke, a prevalence similar to that found by the CSSCD. Stroke is reported infrequently as a major complication SCD in reports from Africa and appears to be rare in Saudi Arabian SCD patients.

The types of stroke differ between adults and children with SCD. Infarctive strokes are relatively more common in children than in adults while the reverse is true for hemorrhagic stroke. In the CSSCD report, while 5 (9.6%) of 52 first strokes in SCD-SS patients less than 20 years of age were hemorrhagic, 14 (52%) of 27 first strokes in those over 20 years of age were hemorrhagic. The risk of hemorrhagic stroke (0.44 per 100-patient years) was highest in the 20-29 year group.

In the CSSCD, stroke occurred less frequently in the other common genotypes of SCD. Age-adjusted prevalence rates of stroke at study entry were 2.43% for Sβ thalassemia (SCD-Sβ), 1.29% for Sβ thalassemia (SCD-Sβ), and 0.84% for SCD-SC. Seven of 873 SCD-SC patients had a stroke by the time of entry into the CSSCD, and another 7 had their first stroke on study. Three of the 14 (21%) SCD-SC patients who had a stroke were under 10 years old compared to those with confirmed SCD-SS and stroke among whom 58 of 187 (31%) were under 10.

Risk Factors for Stroke

Stroke affects only a minority of SCD patients. Moreover, since its incidence does not increase with age, stroke cannot be attributed simply to progressive cerebrovascular damage. If stroke in SCD were attributable to SCD-related factors alone, it would be expected that factors related to overall disease severity would be associated also with stroke. The fact that the highest incidence of stroke is seen in the first decade of life makes it likely that other risk factors, perhaps unrelated to SCD in origin, place some children with SCD at a higher than average risk for stroke.

The CSSCD examined disease-associated risk factors for stroke in its cohort. Infarctive and hemorrhagic strokes were evaluated separately since they may have different pathogenesis and pathophysiology. TIA was included as a possible risk factor for completed infarctive or hemorrhagic stroke although it may have been managed as a stroke. Gender, α-thalassemia (presence of < 4 α-globin genes), systolic blood pressure, Hb F level, mean steady-state Hb level, leukocyte and platelet counts; history of meningitis; presentation for seizure, surgery, priapism, acute anemia, acute chest syndrome, and transfusion within two weeks prior to the first stroke event; and rates of acute chest syndrome and painful episodes were included as potential covariates. In the multivariate analysis, prior TIA, steady-state Hb level, systolic blood pressure, acute chest syndrome within two weeks of the stroke event and rate per year of acute chest syndrome were found to be significant risk factors for infarctive stroke. Low steady-state Hb levels and high leukocyte counts were found to be significant risk factors for hemorrhagic stroke. The multivariate analysis was repeated adjusting for age, sex, and prior acute chest syndrome. The results were similar, and no significant risk factors were identified.

Table 1. Incidence of first stroke on study (Cooperative Study of Sickle Cell Disease) by age and Hb genotype

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>SS</th>
<th>SC</th>
<th>Sβ*</th>
<th>Sββ</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>0.13* (1)**</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.08 (1)</td>
</tr>
<tr>
<td>2 - 5</td>
<td>1.02 (20)</td>
<td>0.27 (2)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.75 (22)</td>
</tr>
<tr>
<td>6 - 9</td>
<td>0.79 (15)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.55 (15)</td>
</tr>
<tr>
<td>10 - 19</td>
<td>0.41 (15)</td>
<td>0.09 (1)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.30 (16)</td>
</tr>
<tr>
<td>20 - 30</td>
<td>0.52 (14)</td>
<td>0.16 (1)</td>
<td>0.46 (1)</td>
<td>0.43 (1)</td>
<td>0.45 (17)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>0.59 (8)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.39 (8)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>0.74 (3)</td>
<td>1.01 (2)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.76 (5)</td>
</tr>
<tr>
<td>50 -</td>
<td>1.28 (2)</td>
<td>0.76 (1)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.91 (3)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>0.61 (78)</td>
<td>0.17 (7)</td>
<td>0.11 (1)</td>
<td>0.10 (1)</td>
<td>0.46 (87)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.61</td>
<td>0.15</td>
<td>0.09</td>
<td>0.08</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Number Per 100 Patient-Year followup; **Number of cerebrovascular accidents

factors for hemorrhagic stroke in the multivariate analysis. Table 2 summarizes the results of the final multivariate analyses of SCD-related risk factors for first stroke. The coinheritance of α-thalassemia and SCD has been shown to reduce the risk of stroke.50,51 The CSSCD analysis showed that the protective effect of the presence of fewer than the normal number of alpha genes on the incidence of stroke in SCD-SS was due largely to the improvement in steady-state Hb level.

The degree of anemia in SCD is, in general, one of the most reliable indicators of disease severity. The CSSCD did not find any correlation between acute anemia and stroke although, others have reported such an association. It is presumed that in patients with existing cerebrovascular disease, cerebral hypoxia induced by acute severe anemia may precipitate a stroke event. The positive correlation between stroke and acute chest syndrome within two weeks prior to the stroke event also suggests the possibility of hypoxic injury to the brain. The association of the frequency of acute chest syndrome with stroke is less easy to explain other than the fact that it may be a good indicator of overall disease severity.

The frequency of painful episodes is regarded as another measure of severity of SCD. However, the CSSCD did not identify the rate of severe pain as a risk factor for stroke, which suggests that painful episodes and stroke differ in pathogenesis. Alternatively, the definition of painful events used by the CSSCD may have introduced a bias since only episodes of pain presenting to medical institutions were tabulated. Increased Hb F levels improve overall clinical course of SCD and has been reported to reduce the risk of stroke.10,42 Surprisingly, the CSSCD did not find an association between low Hb levels and stroke. The CSSCD did not address the association of recent priapism and exchange transfusion with stroke, although this sequence had been reported in a few cases.52,53

Genetic factors unrelated to SCD that may increase the risk for stroke in patients with SCD have also been examined. Although there are anecdotal reports of familial aggregation of stroke in SCD,54 the CSSCD did not report such an association, and no strong genetic linkage for stroke has been found in SCD patients. An association between stroke and β-globin haplotypes was found in some studies but not in others.55,56 Higher homocysteine levels have been associated with stroke in SCD in one report.57 In another study, homocysteine levels and the frequency of homozygosity for the common mutation (C677T) in the gene for methylenetetrahydrofolate reductase (MTHFR), which is associated with elevated homocysteine levels, were compared among controls and SCD patients with and without stroke.58 No differences were found in either homocysteine levels or the frequency of the MTHFR gene mutation among the three groups. Genetic predisposition to stroke in SCD was supported by a study of HLA Class I and II typing of 53 patients with SCD-SS.59 Differences in Class I HLA-B, Class II HLA-DRB1 and DQB1 between 22 SCD patients with cerebral infarction detected by MRI and 31 with normal MRI examination were consistent with different risks for stroke. Factor V Leiden, known to be less common in people of African descent, was not a risk factor for stroke in patients with SCD.60

Table 2. Results of analyses of risk of first stroke in homozygous sickle cell disease (SS) patients: Data from the Cooperative Study of Sickle Cell Disease (CSSCD).

A. Infarctive Stroke
Final multivariate model: Five predictors significant at p < 0.05

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior transient ischemic attack</td>
<td>56.0</td>
<td>(12.0, 285)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(TIA)</td>
<td>1.85 per 1 g/dL</td>
<td>(1.32, 2.59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline Hb (g/dL) decrease</td>
<td></td>
<td>7.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute chest syndrome within</td>
<td></td>
<td>2.39 per</td>
<td>0.005</td>
</tr>
<tr>
<td>previous two weeks</td>
<td></td>
<td>event /yr</td>
<td></td>
</tr>
<tr>
<td>Acute chest syndrome rate</td>
<td></td>
<td>1.31 per</td>
<td>0.033</td>
</tr>
<tr>
<td>Systolic blood pressure rise</td>
<td></td>
<td>10 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

B. Hemorrhagic Stroke
Final multivariate model: Two predictors significant at p < 0.05

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Hb (g/dL) decrease</td>
<td>1.61 per 1 g/dL</td>
<td>(1.11, 2.35)</td>
<td>0.013</td>
</tr>
<tr>
<td>WBC (1x10^9/L) increase</td>
<td>1.94 per 5x10^9/L</td>
<td>(1.73, 2.18)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval   Source: Ohene-Frempong et al. Blood. 1998;91:288-294
Presentation of Stroke

Stroke in SCD presents in ways similar to that in the general population except for its predilection for young children. Infarctive strokes present usually with hemiparesis, aphasia, monoparesis, or seizure while hemorrhagic stroke often presents with severe headache.10,61 Rarely, a patient presents in coma. Subtle motor changes and transient episodes of weakness or numbness are likely to be missed in young children. A painless limp in a young child may be misdiagnosed as a sign of painful episode unless careful physical examination fails to elicit local pain. Non-motor signs of stroke are reported less frequently, although infarcts of non-motor areas of the brain are common in both those with and those without a history of overt stroke.37,62

The diagnosis of stroke is often confirmed with an imaging study following presentation with an abnormal neurological examination or a recent history of a neurological event. Early use of imaging studies is critical in the detection of hemorrhage that may require surgery or different medical management. Often the physical symptoms of stroke may be resolved by the time the patient reaches medical professionals. In such cases, investigations need to be performed to establish the presence of anatomic changes consistent with a possible stroke. MRI, particularly diffusion weighted, is a sensitive method for the detection of cerebral infarction and ischemia and has become the method of choice for the confirmation of stroke.14,15,63 MRA has largely replaced standard angiography as the technique of choice for localizing the vessel(s) involved in the stroke process.26,36 While metabolic or perfusion studies can provide information on the degree of tissue hypoxia,16,64 computerized tomography is sensitive for the detection of hemorrhage but may not detect infarct for several days following the acute event.12 Transcranial Doppler ultrasonography has been useful for the determination of risk for overt stroke, but it has not been employed in the diagnosis of stroke. Routine application of neurocognitive studies and selected imaging studies can help guide clinicians in their selection of patients in whom stroke prevention measures may be necessary.

Stroke in SCD has a high tendency to recur. In untransfused patients there is a 67% recurrence rate with 70% of the recurrent strokes occurring within the first three years following the initial stroke.10

Treatment of Stroke

Acute infarctive stroke in SCD is managed differently from that in other patients. While thrombolytic therapy has become the mainstay of early management of stroke in the general population, it has not been tested in SCD. Initial management of acute stroke includes studies to rule out hemorrhage, stabilization of vital signs, careful use of hydration, and red cell transfusion. SCD patients who develop stroke are usually anemic; therefore, correction of anemia with red blood cell transfusions, with the hope of improving tissue perfusion and oxygenation and limiting or reversing tissue damage, is the goal of early therapy for stroke. Exchange transfusion allows further reduction of the percentage of Hb S-containing cells. Treatment centers where manual or automated exchange transfusion is available employ these methods in the early management of stroke in SCD. A study comparing the value of simple versus exchange transfusion or evaluating the value of any transfusion in acute stroke has not been conducted.

Long-term management of stroke is aimed at preventing recurrence. The most effective way to prevent recurrence of infarctive stroke in children is through chronic transfusion therapy (CTT), although the success rate is not complete.8,9,54,65,66 The standard recommendation is to maintain Hb S (and presumably Hb S-containing cell) percentage at less than 30% for the initial 3 years following the acute event. This goal typically requires transfusion every 3 to 4 weeks with red cells that do not contain Hb S. After 3 years the Hb S level to be maintained can be raised safely to less than 50% if the patient has remained neurologically stable.67

CTT demands careful donor selection, frequent monitoring of Hb and Hb S levels, and regular evaluation for and management of complications such as infection, alloimmunization, and iron overload.68 The management of transfusion and iron overload in SCD has been reviewed recently.69,70 CTT in children with SCD has been effective in reducing the frequency of recurrent stroke to about 10% or less, although it has never been tested in a controlled trial.34,66 In addition, the therapy has not been applied regularly to adult patients, and it is unclear how effective it is in preventing recurrence of hemorrhagic stroke. Transient neurologic events and progression of cerebrovascular disease have occurred in some patients on CTT despite the maintenance of low Hb S levels.54,71

The duration of transfusion therapy that assures long-term prevention of stroke is indeterminate. The risk of recurrence is unlikely to be the same for every patient since the extent of pathology underlying the initial stroke differs among patients. Moreover, the risk factors for recurrence of stroke in patients on CTT are unclear. Stroke has recurred following cessation of 1-12 years of CTT.72,73 However, many patients transfused for several years at pediatric centers have discontinued transfusion therapy after transition to adult care centers. Some of these patients have had recurrent stroke with devastating consequences, but others have been free of stroke for several years. Reliable objective data to support safe cessation of CTT need to be developed. Until then, CTT remains an open-ended intervention as long as preven-
tion of stroke remains the therapeutic goal.

An alternative therapy for the prevention of recurrent stroke is currently undergoing evaluation. Hydroxyurea therapy has been shown in a preliminary report to reduce recurrence rate to about 19% in patients in whom CTT was discontinued for various reasons. The recurrence rate in this small uncontrolled trial is better than that for untransfused patients but may be worse than that for those managed by CTT. However, hydroxyurea therapy may be the best choice left for patients for whom CTT is no longer a viable option. None of 9 patients with a history of stroke or TIA treated with hydroxyurea for an average of 4 years had a recurrence in a French study. A case of recurrent and fatal stroke has been reported in a patient with a previous long history of CTT and iron overload who was receiving hydroxyurea therapy.

Treatment of hemorrhagic stroke in SCD is not uniform. Patients with bleeding aneurysm have been managed acutely with craniotomy and clipping of the aneurysm. Endovascular coil embolization has also been employed. CTT has been used to manage children with hemorrhagic stroke, but it has not been reported as a widespread practice in adult patients.

While it is not a specific therapy for stroke, stem cell transplantation has been applied in the overall treatment of SCD in patients who have had a stroke. In the US, stroke or cerebrovascular disease is the most commonly used clinical eligibility factor for bone marrow stem cell transplantation in SCD. Post-transplant intracranial hemorrhage and/or seizures have been reported in a few patients. However, neurologic outcome in stroke patients who have undergone successful transplantation has been stable with few post-transplant neurologic events following modification of transplant-related chemotherapy.

**Outcome of Stroke**

Most SCD patients who develop focal motor symptoms of stroke recover with no obvious motor deficits. Children under 5 years of age were more likely to have permanent motor deficits compared to older children in one report. Aside from motor deficits, patients experience deterioration in neuropsychological function that may be long lasting despite CTT.

Stroke in SCD as in the general childhood population is associated with a high mortality. In the CSSCD, overall mortality due to stroke was 10%. No death was associated with infarctive stroke while 25% of those with hemorrhage died. In the Jamaican cohort study, 6 (40%) of 15 children with presumed infarctive stroke died while 1 of 2 children with hemorrhagic stroke died. Overall, cerebrovascular disease and stroke are major complications of SCD that can alter the clinical course, quality of life, and mortality rate in people with SCD. Early detection of cerebral pathology and pursuit of measures to prevent overt stroke are important goals in the comprehensive management of SCD. Aggressive therapy to prevent recurrence of stroke and further deterioration of neuropsychological function in those who have had a stroke must also be part of the care of SCD patients.

**III. Sickle Cell and the Brain: Cognitive Deficits and “Silent” Brain Infarction**

*Winfred Wang, MD*

Although an initial report in 1963 indicated normal intellect in children with SCD, a series of single institution studies in the late 1980s and early 1990s found neuropsychological deficits in school-aged children with SCD when compared with siblings or race and age-matched peers. Interpretation of these findings is limited by several factors, including (1) the limited number of subjects, (2) differences in control populations, (3) variability in test instruments used to measure neurocognitive performance, and (4) insufficient information regarding the possible presence of infarctive brain lesions on magnetic resonance imaging (MRI). Nevertheless, these studies, which exclude patients with overt stroke, suggest that sickle cell disease is associated with deficits in neurocognitive function in the school-aged child.

Recently, much larger multi-institutional prospective studies of the CNS status of children with sickle cell disease have been performed in the US (by the Cooperative Study of Sickle Cell Disease (CSSCD)) and in France. Prospective evaluation of the CNS was performed by serial MRI of the brain and neuropsychometric testing over a 10-year period in the CSSCD and by cross-sectional measurement of TCD, MRI, and neuropsychometric testing in the French study. Recent associations of the anatomical sites of CNS lesions and specific areas of neurocognitive dysfunction have been described by DeBaun and colleagues and in the CSSCD.

The following definitions have been used by the CSSCD:

1. **Stroke**: acute neurologic syndrome secondary to occlusion of an artery (or to hemorrhage) with resultant ischemia and neurologic symptoms.

2. **Transient ischemic attack (TIA)**: completed infarctive stroke with neurologic deficit lasting less than 24 hours.

3. **“Silent” infarct**: area of abnormally increased signal on intermediate and T2-weighted pulse se-
Armstrong including assessment of global intellectual performance were reported by patients with lesions. Simultaneously obtained studies patients with lesions had more lesions than did younger age, although affected older this age range, the prevalence of silent infarction did not increase significantly with age, although affected older patients with lesions had more lesions than did younger patients with lesions. Simultaneously obtained studies of neuropsychometric performance were reported by Armstrong including assessment of global intellectual functioning and specific academic and neuropsychological functions. Children with silent infarcts performed significantly more poorly than children with no MRI abnormality on tests of arithmetic, vocabulary, and visual-motor speed and coordination.

These studies set the stage for an ongoing evaluation of the significance of silent brain infarcts in children with sickle cell disease. Some of the questions that are currently being addressed are: (1) What is the extent of neurocognitive compromise related to silent infarcts? (2) How does the location of these lesions affect performance? (3) How early in life do silent infarcts develop? (4) What are predictors of silent infarcts? (5) What do these lesions themselves predict (i.e., what is the “natural history” of silent infarcts)? (6) What interventions are appropriate in the prevention or management of silent infarcts?

Comparison of Strokes and Silent Infarcts
Silent infarcts are more prevalent than overt strokes in children with SCD. In children with Hb SS, stroke occurs in 11% below age 20, whereas the prevalence of silent infarcts is 17% between ages 6 and 12. Thus, the overall risk for stroke or silent infarct in childhood is approximately 30%. In Hb SC disease, there is a 1% risk of overt stroke and 3% risk of silent infarct.

The risk factors for infarctive stroke and silent infarct have been analyzed in the CSSCD. These risk factors, which are based on multivariate analyses of both clinical and laboratory parameters, are summarized in Table 3. It is of interest that the two sets of factors are distinct from each other.

Strokes and silent infarcts differ in location and size. Both occur with roughly equal frequency in the frontal, parietal, and temporal lobes of the brain. However, strokes are much more likely to affect the basal ganglia/thalamus (69%) than silent infarcts (11%). Strokes affecting the frontal lobe typically involve both the cortex and deep white matter (71%), whereas silent infarcts are less extensive and are usually confined to deep white matter. Strokes are usually associated with more and larger lesions (75% > 1.5 cm in diameter). By contrast, only 11% of silent infarcts are > 1.5 cm, whereas 28% are < 0.5 cm in diameter.

In the CSSCD, sufficient numbers of patients were studied to allow comparison of neuropsychometric performance in those with overt stroke, silent infarcts, and normal MRI (Table 4). Neuropsychometric testing included the Wechsler Intelligence Scale for Children–III [full scale IQ (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ) subscales] and the Woodcock-Johnson Achievement Tests for Mathematics and Reading. Because the CSSCD did not include control subjects, data from an external population of similar age, gender, race, and socio-economic status (kindly provided by Drs. Jeff Schatz and Joel Kramer) were obtained.

Patients with normal MRI scored significantly higher than those with silent infarcts (p < 0.05) in FSIQ, VIQ, Math achievement, and Reading achievement, and higher than patients with stroke in PIQ and Math achievement. Furthermore, there were no significant differences between the scores of patients who had overt strokes and those who had silent infarcts. In comparison with the ad

<table>
<thead>
<tr>
<th>Problem</th>
<th>Clinical Predictors</th>
<th>Laboratory Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarctive stroke</td>
<td>Acute chest syndrome (recent or frequent)</td>
<td>Decreased hemoglobin</td>
</tr>
<tr>
<td></td>
<td>Increased blood pressure (systolic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior TIA</td>
<td></td>
</tr>
<tr>
<td>Silent infarct</td>
<td>Prior seizures</td>
<td>Increased WBC (&gt; 11.8 x 10^9/L)</td>
</tr>
<tr>
<td></td>
<td>Decreased pain event rate</td>
<td>SEN (β globin haplotype)</td>
</tr>
</tbody>
</table>

Table 3. Comparison of risk factors for infarctive stroke and silent infarct.

Table 4. Neuropsychometric performance in children with Hb SS in the Cooperative Study of Sickle Cell Disease (CSSCD).

<table>
<thead>
<tr>
<th>Test</th>
<th>Stroke</th>
<th>Silent Infarct</th>
<th>Normal MRI</th>
<th>Controls†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>43</td>
<td>122</td>
<td>45</td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.5</td>
<td>12.8</td>
<td>12.4</td>
<td>12.3</td>
</tr>
<tr>
<td>Full Scale IQ*</td>
<td>76.9</td>
<td>77.2</td>
<td>84.8</td>
<td>91.8</td>
</tr>
<tr>
<td>Verbal IQ*</td>
<td>79.9</td>
<td>77.1</td>
<td>85.3</td>
<td></td>
</tr>
<tr>
<td>Performance IQ*</td>
<td>77.3</td>
<td>81.1</td>
<td>86.7</td>
<td></td>
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<tr>
<td>N</td>
<td>23</td>
<td>49</td>
<td>122</td>
<td>45</td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.0</td>
<td>12.7</td>
<td>12.4</td>
<td>12.3</td>
</tr>
<tr>
<td>WJ – Math*</td>
<td>77.3</td>
<td>82.0</td>
<td>90.7</td>
<td></td>
</tr>
<tr>
<td>WJ – Reading*</td>
<td>84.6</td>
<td>81.8</td>
<td>93.9</td>
<td></td>
</tr>
</tbody>
</table>

* Woodcock-Johnson Achievement Tests for Mathematics and Reading
† Wechsler Intelligence Scale for Children-III
‡ data from Schatz and Kramer; see text.
hoc matched-control population, FSIQ was lower in sickle cell patients with normal MRI, indicating the presence of a neuropsychometric deficit in children with SCD even when they do not have infarctive lesions seen on MRI of the brain. This important finding will need to be confirmed, but it is consistent with the French study, which showed that FSIQ < 75 was independently associated with low hematocrit (< 20%) and thrombocytosis (platelet count > 500 x 10^9/L).

Comparison of Silent Infarcts and Transcranial Doppler Abnormalities
To compare the significance of MRI of the brain and TCD ultrasonography in school-aged children with SCD, data were analyzed from 78 children (mean age 11 years) who participated in both the CSSCD and the Stroke Prevention Trial in Sickle Cell Anemia (STOP). Patients who had experienced an overt stroke were excluded. MRI findings were classified as normal or silent infarct; TCD results were classified as normal, conditional, or abnormal based on the time-averaged maximum mean flow velocity in the proximal middle cerebral and distal internal carotid arteries. Of 61 patients who had a normal MRI examination, 11 (18%) had either conditional or abnormal TCD results (Table 5). Of 17 who had a silent infarct on MRI exam, only 5 had either an abnormal or conditional TCD result. Thus, TCD and MRI examinations were often discordant and probably reveal different aspects of the pathophysiology of CNS injury in SCD. Although an abnormal TCD is predictive of overt stroke, this lack of concordance between TCD and MRI findings suggests a need to develop more sensitive and specific indicators of early CNS pathology.

Anatomic Location and Infarcts
To gain a better understanding of the effects of brain infarcts, recent analyses of the relationship between the location of these infarcts and neuropsychological deficits have been conducted. Data from the CSSCD have been analyzed to test the hypotheses that (1) children with anterior (frontal) lesions have deficits in attention and memory, (2) children with left hemisphere lesions have problems with verbal skills, and (3) children with diffuse lesions have visual-spatial deficits. Analyses were performed in children with Hb SS who had silent infarcts (n = 58) and stroke (n = 21). Neuropsychometric evaluations included the Wechsler Intelligence Scale for Children, the Woodcock-Johnson Tests of Achievement in Math and Reading, the Beery Test of Visual-Motor Integration, the Purdue Pegboard Test and the Tactile Form Perception Test. Results were scored in accord with scales and subscales that measured attention and short-term memory (hypothesized to be associated with anterior lesions), verbal and language abilities (left hemisphere lesions) and visual-spatial abilities (diffuse lesions). A complex set of data analyses are summarized in Table 6.

This study has led to the conclusions that children with Hb SS and silent infarcts in the anterior brain perform more poorly on measures of perceptual organization and executive function and those with lesions in the left hemisphere perform more poorly on verbal comprehension and reading tasks. Thus, the anatomic locations of silent infarcts are associated with distinct areas of neurocognitive dysfunction, indicating a need for targeting interventions to specific deficits.

Neurocognitive Development in Preschool Years
Although neurologic events are among the most devastating complications of SCD and occur throughout childhood, most studies of the CNS have been performed in school-aged children and adolescents. However, there is increasing evidence that injury to the CNS occurs in children less than 5 years of age.

The risk of stroke in the preschool population is significant. In the CSSCD, the prevalence of cerebrovas-
cular accidents (CVA) in children with Hb SS between 2 and 5 years of age was approximately 2.3%. The incidence of first stroke in children with Hb SS was 0.13/100 patient-years in children less than 2 years of age and 1.0/100 patient-years in children 2-5 years of age. At St. Jude Children’s Research Hospital (SJCRH), CNS imaging has been performed in 42 children with Hb SS between the ages of 7 and 60 months (median 30 months) (updated). Three of these patients had a history of seizures. The overall prevalence of silent infarct was 8/42 (19%) and magnetic resonance angiography (MRA) abnormalities were seen in 3/40 (7.5%). TCD performed in the screening phase of the STOP revealed abnormally increased velocities in 10.9% of children 2-8 years of age, a slightly greater frequency than that seen in older children.18

Data regarding developmental and neuropsychometric testing in the preschool population are limited. The Denver Developmental Screening Test performed in children in the CSSCD younger than 6 years of age revealed scores in the questionable range in 6.4% and normal range in 1.5%.19 Questionable or abnormal scores were more common in children 3-5 years of age than in younger children. At SJCRH, 24 patients had developmental testing with the Bailey and McCarthy Scales at a median age of 34.5 months (updated). The mean Developmental (Cognitive) Index was 89.3 (range 65-121); two had scores < 70.

To examine this question pragmatically, we recently analyzed the performance of children with SCD on the Developmental Skills Checklist, a kindergarten readiness test given to determine educational needs and abilities.20 This test, which includes subtests for mathematics, language, memory, and auditory discrimination, is administered to all children entering kindergarten in the Memphis City School System. Sickle cell patients (n = 32) scored significantly below controls (n = 64) in auditory discrimination (p < 0.01), indicating that they were less able to identify likenesses and differences among sounds, a skill essential for phonic instruction and for reading. These deficits could not be attributed to school absence because children were tested during the first two weeks of kindergarten. Although this information is preliminary, it suggests that SCD affects the CNS status of preschool children and may then impact subsequent school performance.

At least two factors underscore the need for more extensive study of the CNS in preschool children: (1) There is an improving capacity to predict children who are at high risk for serious complications of SCD (including stroke), as exemplified by the recent “severity index” from the CSSCD.21 (2) There is increasing success with various therapeutic interventions for SCD, including chronic transfusion, stem cell transplantation, and pharmacologic manipulation with drugs such as hydroxyurea.22-24

Silent Infarcts—Prognosis and Intervention
Silent infarcts may indicate an increased risk for stroke or for new and more extensive silent infarcts.25,26 Recent data from the CSSCD25 indicate that children with Hb SS and a silent infarct have an increased incidence of new stroke (0.9/100 patient-years) and of new or larger silent infarcts (7.1/100 patient-years). These rates were greater than the overall incidence of stroke in the cohort (0.35/100 patient-years), but much less than the risk for recurrent stroke in children who are not provided chronic transfusion therapy following a stroke. In another analysis of CSSCD data,26 5/62 (8.1%) patients with silent infarcts had strokes (mean age 8.3 years, mean follow-up 5.2 years), compared with 1/186 (0.5%) patients without silent infarcts. These data indicated a 14-fold increase in the risk for stroke in children who have silent infarcts (p = 0.006).

What are the therapeutic implications of this risk?
Several approaches are being considered. The National Stem Cell Transplant Consortium has proposed that silent infarction be an eligibility criterion for patients to receive non-myeloablative (presumably, less toxic) “mini-transplants” with a goal of achieving stable mixed chimerism and an asymptomatic clinical state. Another large multi-institutional trial proposes a randomization of patients with silent infarcts to receive chronic transfusion versus standard care (i.e., observation). A third approach might involve the drug hydroxyurea. Hydroxyurea and phlebotomy have been used to prevent secondary stroke in patients who have already suffered an initial stroke and who are unable to receive standard management with chronic transfusion.27 However, although the use of hydroxyurea might be the least toxic approach, there is no direct evidence to support its efficacy in the management of silent infarcts.

Conclusions
Overt strokes have a significant detrimental effect on neuropsychometric performance and secondary strokes following a primary event need to be prevented. Silent infarcts may have an effect on neurocognitive function that is comparable to that of overt strokes. In addition, it is likely that sickle cell anemia is associated with compromised neuropsychometric performance even in the absence of infarcts visible on MRI of the brain.6 A risk factor, which may be a common denominator for these events, is hypoxia (acute, recurrent, or chronic), as suggested by the associations of increased CNS events with acute chest syndrome and severe anemia.

The likelihood of damage to the CNS appears to be significant even before children begin school. However,
the most appropriate interventions for the prevention and management of silent infarcts are uncertain. There is an absence of literature regarding cognitive or educational rehabilitation of children with SCD who have compromised neurocognitive abilities due to stroke or to silent infarcts. Well-planned, well-controlled, and well-conducted clinical trials are needed.

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