Prospective Brain Imaging Evaluation of Children with Sickle Cell Trait: Initial Observations

**PURPOSE:** To determine whether sickle cell trait (hemoglobin AS) is associated with abnormalities in the brain of asymptomatic children.

**MATERIALS AND METHODS:** Magnetic resonance (MR) imaging and MR angiography were performed prospectively in 26 siblings (eight girls, 18 boys; mean age, 10.5 years) of patients with sickle cell disease. Two neuroradiologists, blinded as to whether a child had hemoglobin AS or AA, reviewed images obtained in siblings. With MR imaging, lacunae, loss of white matter volume, encephalomalacia, or leuкоencephalopathy was identified. With MR angiography, arterial stenosis, occlusion, or tortuosity was identified. Images with definite or possible abnormalities were mixed with randomly selected images and were referred to a third neuroradiologist for a completely blinded review. In cases in which all neuroradiologists concurred, a score was assigned that indicated the sibling had an abnormality. MR angiographic findings were assigned a score for tortuosity with a new quantitative scale.

**RESULTS:** Among 26 siblings screened, 21 children had sickle cell trait. Among these 21 children, two had mild abnormalities at MR imaging (sample prevalence rate, 10% [95% CI: 1%, 29%]), and four had arterial tortuosity (sample prevalence rate, 19% [95% CI: 5%, 42%]). When children with sickle cell trait were compared with 31 control subjects without the trait, arterial tortuosity was significantly more common in children with sickle cell trait (P = .014). Among children with sickle cell trait, percentage of hemoglobin S was significantly greater in children who had tortuosity than percentage of hemoglobin S in children who had normal blood vessels at MR angiography (P < .03).

**CONCLUSION:** Findings suggest that greater percentage of hemoglobin S is associated with mild vasculopathy. This vasculopathy may explain some of the excess risk of stroke among African Americans.

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The risk of stroke is well characterized among patients with sickle cell disease (SCD) (1–8). In some scattered reports, researchers also indicate that sickle cell trait, the heterozygous condition, can be associated with cerebrovascular complications including stroke (9–27). Yet, stroke is assumed to be a relatively rare complication in people with sickle cell trait (13,27), and the risk of stroke in African Americans with hemoglobin AS (sickle cell trait) is reported to be no greater than the risk of stroke in African Americans with normal hemoglobin AA (16).

There are essentially no data about magnetic resonance (MR) imaging findings in a sample of healthy individuals with sickle cell trait. Investigators in most prior studies of sickle cell trait included case histories of one or a few patients and did not assess the population prevalence of cerebrovascular abnormalities (24). Researchers in several case studies described findings in a pediatric patient with stroke who had hemoglobin AS (15,17,25,26), but researchers in none of these studies addressed the prevalence of risk...
factors associated with stroke. With several exceptions (14,16,17,22,25,26), investigators in prior studies of stroke in patients with sickle cell trait used autopsy material, with the inherent problem that such studies are neither prospective nor cross sectional. Furthermore, in many of the early reports, sickle cell trait was not diagnosed by using electrophoresis (9–11), and other tests used to diagnose sickle cell trait were often inaccurate (13). Consequently, researchers in some studies did not conclusively demonstrate that the index patient had sickle cell trait but rather assumed that the patient had the trait because there were sickled red blood cells in the vasculature, although the patient had no history of SCD (11). In one of the only studies in which researchers investigated the prevalence of cerebrovascular abnormalities in individuals with sickle cell trait, an autopsy study was performed for the evaluation of 1,248 general fatalities in Memphis, Tenn (13). In this study, a 2% prevalence (two of 120) of cerebral infarction was reported among patients with sickle cell trait who died of other causes (13). In another study, a 6% prevalence (11 of 175) of neurologic abnormalities was reported among patients with the trait, although none of the patients in this study had stroke (14).

The purpose of our study was to determine whether sickle cell trait is associated with abnormalities of the brain in asymptomatic children.

MATERIALS AND METHODS

Siblings of Patients with SCD

In this prospective study, we evaluated the brain in the siblings of patients with SCD by using MR imaging and MR angiography. The study was reviewed and approved by the institutional review board, and parents or guardians of all siblings signed an informed consent after the protocol was briefly described. We enrolled a total of 26 siblings of children with SCD since the protocol became available in March 1997. All siblings underwent imaging with a protocol identical to that used in patients with SCD. None of the siblings were sedated for their examination, nor was a contrast agent used. Hemoglobin phenotype and hemoglobin S quantitation were determined with high-performance liquid chromatography at a reference laboratory.

The mean age of the 26 siblings was 10.5 years ± 3.2 (SD), and there were eight girls and 18 boys. There were 21 siblings with hemoglobin AS and five siblings with hemoglobin AA. Among the 21 siblings with hemoglobin AS, the mean percentage of hemoglobin S was 37.4% ± 3.9.

The expected prevalence of hemoglobin AS among siblings of patients with SCD was calculated by assuming random mating of parents with genotypes AA, AS, and SS, with a distribution of 92.1%, 7.8%, and 0.1%, respectively (24). Healthy siblings of patients were assumed to come only from families with parental genotypes of (AS, AS) or (AS, SS), since a parental combination of (AA, SS) would not produce any children with SCD. The chance of a healthy sibling having AS is two out of three if the patient with SCD is from an (AS, AS) family, and it is two out of two if the patient with SCD is from an (AS, SS) family. The expected prevalence of AS in healthy siblings of patients with SCD is thus 67.5% overall.

MR Imaging

All imaging was performed at 1.5 T (Vision; Siemens Medical Systems, Iselin, NJ) with a standard quadrature head coil. Weekly quality-assurance monitoring of field homogeneity and eddy current compensation was performed, and image quality was monitored daily as a part of the clinical imaging program. A T1-weighted image set was acquired in the transverse plane with parameters as follows: repetition time msec/echo time msec/inversion time msec, 8,000/29/300; field of view, 17 × 23 cm; flip angle, 180°; matrix, 196 × 256; sections, 19; distance factor, 1.00; acquisitions, one in 3 minutes 53 seconds (sequence repeated again with 3-cm offset to image 100% of the brain volume). A T2-weighted image set was acquired in the transverse plane with parameters as follows: repetition time msec/echo time msec/inversion time msec, 3,500/17, 102 (three echoes per repetition time for each effective echo time); field of view, 17 × 23 cm; matrix, 190 × 256; sections, 19; distance factor, 1.00; acquisitions, one in 3 minutes 35 seconds (sequence repeated again with 3-cm offset to image 100% of the brain volume). A T2-weighted turbo spin-echo image set was acquired in the same orientation with parameters as follows: repetition time msec/echo time msec/inversion time msec, 3,500/17, 102 (three echoes per repetition time for each effective echo time); field of view, 17 × 23 cm; matrix, 190 × 256; sections, 19; distance factor, 1.00; acquisitions, one in 3 minutes 35 seconds (sequence repeated again with 3-cm offset).

In March 2000, we also added fluid-attenuated inversion recovery (FLAIR) imaging in the transverse orientation, with parameters as follows: 9,000/119/2,470; field of view, 17 × 23 cm; flip angle, 180°; matrix, 154 × 256; sections, 19; distance factor, 1.00; acquisitions, one in 3 minutes 27 seconds. This sequence was also repeated with a 3-cm offset to image 100% of the brain volume for image segmentation and classification.

Evaluation of MR Images

Images for all 26 siblings were reviewed by two neuroradiologists (J.W.L., K.J.H.), who achieved consensus in regard to all cases. Readers were blinded as to whether a child had AS or AA, but they knew that the children were siblings of patients with SCD. MR images obtained in children with any abnormalities were mixed with several randomly selected images and were referred to a third neuroradiologist (K.B.) for a completely blinded review. Only cases in which all three neuroradiologists concurred were reported here as those with abnormalities.

Standard criteria for abnormalities on T1-weighted MR images included lacunae, loss of white matter volume, encephalomalacia, or leukoencephalopathy. Criteria for abnormalities on T2-weighted images included small areas of high signal intensity (consistent with lacunae) or large diffuse areas of high signal intensity (consistent with demyelination of white matter). The criterion for abnormalities with FLAIR imaging was any area of high signal intensity within the brain parenchyma. We defined a lacuna as a shelled-out volume, usually in white matter, that must be visible on both T1- and T2-weighted MR images. Encephalomalacia was any other ischemic change, including atrophy, even if atrophy was present with no other apparent abnormality. Leukoencephalopathy was degeneration or demyelination of white matter, which was seen as abnormally high signal intensity on T2-weighted or FLAIR MR images.

MR Angiography

MR angiography was performed by using a time-of-flight sequence to obtain spoiled gradient-echo images of the brain in the transverse plane at 64 section levels (28–30). The volume of the MR angiogram was centered on the sella turcica. The following parameters were used: 34/5; field of view, 20 cm; flip angle, 20°; matrix, 192 × 256; effective section thickness, 1 mm; acquisitions, one in a total imaging time of 7 minutes.

Evaluation of MR Angiograms

All MR angiograms were evaluated by the same three neuroradiologists who evaluated the MR images, as described previously. Standard criteria for abnor-
malities on an MR angiogram included stenosis or apparent occlusion of a vessel or arterial tortuosity. Tortuosity is typically a subjective clinical impression, which is determined on the basis of the presence of several features. These features include dilatation (ectasia) of a vessel segment, abnormal increase in length of a vessel segment, and/or obvious bowing of an artery (28–30). These features are related in that ectatic vessels are likely both to bow and to be longer than normal (28).

In addition, we sought to standardize and simplify the definition of tortuosity to make it more objective and easier to apply. Standardization was achieved by an experienced reader (R.G.S.) who made caliper measurements on MR angiograms obtained in the patients and who was blinded to the results of the evaluation by the neuroradiologists. We defined tortuosity as bowing of both the basilar artery and either the middle cerebral artery or the anterior cerebral artery (Fig 1). Results of the quantitative assessment of tortuosity are reported here, although we have reported the prevalence of basilar tortuosity in healthy children, but results are available about the prevalence of vascular abnormalities on an MR angiogram.

We characterized basilar artery bowing on a coronal reconstruction of the basilar artery (28), with measurements referenced to the scale bar printed on the image. First, a basilar chord was established by drawing a line from the point of junction of the vertebral arteries to the point of bifurcation of the posterior cerebral arteries (Fig 1a). Then a perpendicular distance was measured from the basilar chord to a line drawn down the center of the basilar artery at a point where the artery was bowed farthest from the basilar chord. In healthy adult subjects (28), the mean distance is 1.7 mm ± 1.5, so the mean ± 2 SDs, which is equivalent to the 95% CI, is less than 5 mm in healthy subjects. If this distance was 5 mm or longer, a subject would be assigned a tortuosity score of 1, whereas a subject with a distance shorter than 5 mm was assigned a score of 0.

We characterized middle cerebral artery and anterior cerebral artery bowing by making measurements on a coronal reconstruction of the circle of Willis (30). A point was located at the confluence of the A1 segment of the anterior cerebral artery and the M1 segment of the middle cerebral artery on each side of the brain, and a line of reference was drawn through these points (Fig 1b). This compensates for head tilt, which could otherwise corrupt the measurement, in the subject. Then the perpendicular distance was measured from the line of reference to the midpoint of the artery (at the point of farthest bowing) of the A1 segment (right arrows) and M1 segment (left arrows) on both sides of the circulation.

MR Angiographic Control Data

To our knowledge, no published data are available about the prevalence of vascular tortuosity in healthy children, but we have reported the prevalence of basilar ectasia in children used as control subjects and in children with SCD (28). We reanalyzed our published data for 26 healthy control subjects of an age similar to that of the siblings of patients with SCD (age for all, >5 years old; mean age, 10.9 years ± 3.2) by using the criteria described previously. These data were pooled with findings from the five siblings with AA to form a composite control group.

Population Prevalence of Trait-related Imaging Abnormalities

Our data were combined with data available in the literature to estimate the
number of African Americans who would potentially show trait-related imaging abnormalities. The population prevalence of sickle cell trait (24) was multiplied by an estimate of the number of African Americans in the United States, obtained from census figures (31), to calculate the total number of people at risk. Then the minimum sample prevalence of imaging abnormalities (lower bound of the 95% CI) was multiplied by the total number of people at risk to calculate the number of African Americans who would potentially show trait-related imaging abnormalities.

Statistical Analysis

We used statistical software (StatExact 3 for Windows, version 3; Cytel Software, Cambridge, Mass) to calculate binomial distributions, probability values, and 95% CIs for the prevalence data. The minimum accepted value for significance was a \( P \) value less than .05 in all cases.

RESULTS

siblings of children with SCD

Roughly 81% (21 of 26) of our sample had hemoglobin AS, and the percentage of hemoglobin S was known in all siblings. The incidence of sickle cell trait in our sample was not significantly greater \( (P = .11) \) than the expected incidence of 67.5%.

MR Imaging Results

Two of 21 siblings with hemoglobin AS had abnormalities at MR imaging. Both of these children had a slight increase in signal intensity of the white matter on T2-weighted and FLAIR MR images (Fig 2). The sample prevalence of abnormalities at MR imaging in siblings with AS was 10% (two of 21), and the 95% CI for this estimate spans the range from 1.1% to 29.2%. This estimate is significantly greater than zero \( (P < .05) \), as shown by the fact that the 95% CI of the estimate excludes zero.

MR Angiographic Results

Three siblings were unable to complete the examination without sedation, so we lack MR angiographic data from three of the 26 siblings. None of the 23 siblings we examined had stenosis or occlusion of a cranial artery. However, tortuosity was a common finding (Figs 3, 4), which was present in four of 18 siblings with AS who were able to complete the examination. The Table shows that seven siblings had a tortuosity index of 1, including two subjects with hemoglobin AA, but arterial tortuosity (as we defined it) was seen only among subjects with hemoglobin AS.

The sample prevalence of abnormalities at MR angiography in 21 siblings with AS was 19% (four of 21), and the 95% CI for this estimate spans the range from 5.5% to 41.9%. Thus, the prevalence of abnormalities at MR angiography is significantly greater than zero \( (P < .05) \). Comparison of data for siblings with AS with data for the composite control group suggests that arterial tortuosity is significantly more common in children with the trait. None of the 31 control children had arterial tortuosity, whereas 19% (four of 21) of the siblings with AS had tortuosity, a difference that was significant by using the Fisher exact test \( (P = .014) \).

Among the four children with vascular tortuosity (tortuosity index of 2, Table), the mean percentage of hemoglobin S was 39.3 ± 1.8, and the mean percentage of hemoglobin S was 39.2 ± 3.0 among the five siblings with AS who had slight tortuosity (tortuosity index of 1). By contrast, the mean percentage of hemoglobin S was 34.8 ± 4.3 among the nine siblings with AS who had normal blood vessels at MR angiography (tortuosity index of 0). This trend is significant \( (P = .028) \), suggesting that tortuosity is more common among those siblings with AS who have a greater proportion of abnormal hemoglobin.

Population Prevalence of Trait-related Abnormalities

The sample prevalence of parenchymal abnormalities shown by using MR imaging was 10% (two of 21), and the minimal prevalence shown by using the lower cutoff of the sample 95% CI was at least 1%. There are 34.7 million African Americans (31), and it is anticipated that roughly 7.8% will have sickle cell trait (24,32,33), so there are approximately 2.7 million people with sickle cell trait in the United States. If the population prevalence of parenchymal abnormalities is at least 1% among these people, then we calculate that more than 27,000 African Americans in the United States may have trait-related abnormalities of the brain parenchyma.

Similarly, the sample prevalence of vascular abnormalities by using MR angiography was 19% (four of 21), and the minimal population prevalence shown by using the lower cutoff of the 95% CI is likely to be at least 5%. Thus, there may be more than 135,000 people in the United States with trait-related tortuosity. These estimates suggest that trait-related brain abnormalities could be an unrecognized public health concern in the United States.
We report an unexpected presence of abnormalities in the brain of children with sickle cell trait. The imaging changes that we describe are more subtle, but they could potentially have a negative effect on cognition and might predispose a patient to stroke. The vasculopathic changes that we describe are more equivocal in that we do not know the sequelae of vascular tortuosity. However, findings in a large retrospective study indicate that severe vasculopathy (broadly defined) was the most common cause of pediatric stroke and was responsible for roughly half (19 of 35) of all such strokes. Vasculopathy of a degree similar to what is shown here is a function of hyperemia, and arterial hyperemia may be a compensatory mechanism associated with diminished oxygen-carrying capacity of the blood. Whether the vascular abnormalities described here could lead to an increased risk of stroke remains to be determined.

The parenchymal abnormalities we describe are distinct from what has been described among children with SCD. The prevalence of abnormalities at MR imaging in our sample of siblings (two of 21 [10%]) is also considerably less than the prevalence of parenchymal abnormalities in children with SCD. In the largest study to date, which involved 215 children with hemoglobin SS disease, there was a 24% prevalence (52 of 215) of parenchymal abnormalities, which included infarction, ischemia, or atrophy. Here, we describe a 10% (two of 21) prevalence of leukoencephalopathy, which is a mild abnormality of white matter, seen as abnormally high signal intensity on T2-weighted or FLAIR MR images. This is a controversial finding, as high T2-weighted signal intensity in the terminal zone is recognized as a normal developmental variant that can persist into early adolescence. However, we report high signal intensity in two children who were both 16 years old, and the degree of signal intensity was too high to be a normal variant. Leukoencephalopathy in children receiving high-dose chemotherapy for leukemia has been appreciated only recently and is apparently related to the transient demyelination of white matter. It is not known whether leukoencephalopathy in children with hemoglobin AS is reversible, whether it puts a child at increased risk of stroke or cognitive deficit, or whether it is most likely to remain clinically silent.

The limitations of this study arise mostly from the small sample size. Because of this small size, the population prevalence estimates must be regarded as tentative and subject to correction when imaging has been performed in a larger sample of siblings. It has been far more difficult than anticipated to perform imaging in the siblings of patients; we be-

**Figure 3.** Time-of-flight MR angiograms (34/5; field of view, 20 cm; flip angle, 20°; matrix, 192 × 256) obtained in two boys with hemoglobin AS. (a) Transverse image obtained in a 10-year-old boy. This view is through a 64-mm-thick slab of tissue; stationary protons in the brain parenchyma are nulled out, but moving protons in the blood have high signal intensity. (b) Transverse image obtained in an 11-year-old boy. There is an unusually high degree of signal intensity in the distal vessels (arrows), and this degree of conspicuity suggests very rapid blood flow. (c) Coronal image of the middle cerebral arteries obtained in the child in a shows tortuosity (arrow) of the A1 segment. (d) Coronal image of the middle cerebral artery obtained in the child in b shows severe tortuosity (arrow) of the A1 segment on the left side of the patient.

**Figure 4.** Coronal time-of-flight MR angiograms (34/5; field of view, 20 cm; flip angle, 20°; matrix, 192 × 256) obtained in two girls with hemoglobin AS show basilar artery. (a) Image shows mild tortuosity (arrow) in a 12-year-old girl. (b) Image shows severe tortuosity (arrow) in a 15-year-old girl.
Radiology

gan trying to accrue these children 5 years ago, yet we can only report data from 26 completed examinations. Another problem is the subjectivity of the determination as to which siblings had abnormalities among the siblings we examined; this is why concurrence among three neuroradiologists was required for a child to be classified as showing signs of an abnormality by using MR imaging. Because MR angiographic examination findings were scored quantitatively, there is less subjectivity, but many radiologists may disagree as to whether the patients described had arterial tortuosity. Finally, it may be difficult to accept that the rather mild vasculopathy we report could be linked to an increase in stroke risk in later years. This link is speculative now, but it will be important to establish whether the vasculopathy we note here continues to evolve through late adolescence and into early adulthood. Our study was small and cross sectional and should be replicated with a prospective study of more children with sickle cell trait.

Our results suggest that the key risk factor for vasculopathy is not sickle cell trait per se but rather the proportion of hemoglobin S in the bloodstream. This tentative conclusion arises from the finding that siblings with AS who had tortuosity had a significantly greater percentage of hemoglobin S than did children with AS who did not have MR angiographic abnormalities. Because we lack data regarding the hematocrit level for most of the siblings in this study, we were unable to determine if there is a relationship between anemia and vasculopathy, as has been reported in children with SCD (28,29). Sickle cell trait is not associated with severe anemia (39–41), although children who have sickle cell trait may have a somewhat decreased hematocrit level, compared with children who have AA (42,43). We propose a hypothesis that hyperemesis is associated with vasculopathy because chronically high blood flow damages the endothelial lining and acts as a stimulus to vessel growth (28). We note that children in our study could have been anemic for reasons unrelated to sickle cell trait, such as chronic lead exposure (44), and that anemia is associated with stroke in the absence of any other medical condition (45).

Sickle cell trait has been associated with sudden death from unexplained causes (13,46–50), but children with sickle cell trait are apparently not at greatly increased risk of stroke (25). However, the long-term risk of stroke in adults with sickle cell trait is not known. Investigators in necropsy studies reported that trait-associated death occurs no earlier than does death in the African American population at large (13,51), but this type of study has a very low statistical power. Researchers in a retrospective study of 295 adult patients with stroke in Guadeloupe evaluated the proportion of patients with hemoglobin AS, AC, or AA, compared with the prevalence of these phenotypes in the population at large (52). Researchers in this study reported that the proportion of patients with hemoglobin AS was 10-fold greater than was expected in patients with hemorrhagic stroke, whereas the proportion of patients with AS was 15-fold smaller than expected in patients with ischemic stroke (52).

In a widely cited article (16), the researchers claim that there is no increase in risk of stroke for blacks with sickle cell trait, as compared with blacks without the trait. However, we believe that this work (16) is deeply flawed: First, although 16,701 men were included in the study, the phenotype of the study participants was never actually determined. Second, the control group was assumed to be free of sickle cell trait simply because they were free of clinical concerns. Third, only four subjects with AS actually had stroke, so the statistical power of this study is very low. Last, the age at stroke onset was never considered, although study data show that stroke occurred at an average age of only 38 years in the control group (16). These early results (16) could actually be used to argue that the excess risk of stroke among blacks in the United States is a result of sickle cell trait. The men in this early study were never tested for the trait, so it is likely that sickle cell trait was as prevalent in this group as it would be in any other randomly selected sample of blacks in the United States. If we assume that 7.8% of the men in the AA category actually

### Imaging Findings in Siblings of Patients with SCD

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* Tortuosity index was as follows: grade 0 = normal blood vessels, grade 1 = normal blood vessels, and grade 2 = tortuous blood vessels.
had the sickle cell trait (24,32,33), then there would have been 1,303 unidentified men with AS among the control subjects (16). If we further assume that the incidence of stroke in black veterans with hemoglobin AA is comparable to the incidence of stroke in white veterans with AA, then there were 107 excess strokes among the 1,303 blacks with AS who were misidentified as having AA. Thus, if the lifetime stroke incidence is just 8.2% greater than normal among blacks with AS, then the entire excess risk of stroke among blacks in this study (16) could be explained by the sickle cell trait.

Although we do not believe that sickle cell trait explains all the excess risk of stroke in African Americans (8,53–55), our findings suggest that sickle cell trait may be associated with an incremental increase in the risk of stroke. Such an increase in risk could go unrecognized, because the hemoglobin phenotype is unknown in many African Americans who die of stroke. Given that one-third of the differential stroke mortality between blacks and whites is currently unexplained by any known risk factors or socioeconomic influences (55), it is critically important to determine the population prevalence of trait-related brain abnormalities. In addition, it will be important to elucidate the relationship between various variants in childhood and the risk of stroke in adulthood. Although there are recognized pitfalls in labeling sickle cell trait as a disease (32,56,57), it must also be recognized that sickle cell trait is associated with an increased risk of morbidity and mortality with certain circumstances (13,27,46–50).

Acknowledgments: We thank Mary F. Fitchpatrick, Mary Jo Freeman, Crystal Manchester, Carolyn A. Phillips, and Charles M. Summers, who performed MR imaging, and Sylvia C. Harris, RN, and Gloria Brunson, who coordinated the sibling studies. In addition, we thank the families who dedicated their time and effort to this research.

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