Background and Purpose—Brain imaging abnormalities were reported in up to 44% of children with sickle cell disease (SCD). The prevalence of neuroimaging abnormalities in adult patients with SCD and their relationship to transcranial Doppler is still unclear. Our objectives were to study the frequency of MRI and MR angiography abnormalities in adults with SCD and to define what transcranial Doppler velocities are associated with intracranial stenoses detected by MR angiography.

Methods—We examined all adult patients (>16 years) with SCD followed in the hematology outpatient clinic at our university hospital with MRI, MR angiography, and transcranial Doppler.

Results—We evaluated 50 patients. The overall prevalence of MRI abnormalities was 60%. Abnormal MRI findings were more frequent when vessel tortuosity or stenoses were present on MR angiography ($P<0.01$). Patients with intracranial stenoses had significantly higher time-averaged maximum mean velocities ($P=0.01$). A time-averaged maximum mean velocity of 123.5 cm/s allowed the diagnosis of middle cerebral artery or internal carotid artery intracranial stenosis with sensitivity of 100% and specificity of 73% with an area under the receiver operator characteristic curve of 0.91 (CI, 0.79 to 1.00).

Conclusions—The frequency of brain imaging abnormalities detected by MRI/MR angiography in adults with SCD was higher than that described for children. Transcranial Doppler velocities in adult patients with intracranial stenoses were lower than those described for the pediatric population with SCD. (Stroke. 2009;40:00000.)

Key Words: magnetic resonance imaging ■ sickle cell anemia ■ stroke ■ transcranial Doppler ultrasonography

Stoke occurs in 11% of children with sickle cell disease (SCD) before the age of 20 years.1 Cerebrovascular disease is also common in adults with SCD, with an incidence 10 times greater than that of stroke in blacks without SCD.1,2

Ischemic strokes in SCD are usually the result of fibrous proliferation of the intima, leading to intracranial artery stenoses, which can be detected by transcranial Doppler (TCD).3,4 In neurologically asymptomatic children with SCD, the combination of increased TCD velocities and presence of intracranial stenosis detected by MR angiography (MRA) leads to the highest risk for stroke.5

TCD is the key test for determining the need for prophylactic blood transfusion in children with SCD.6 In adults, however, TCD velocities that predict the presence of intracranial stenosis have not been determined. TCD velocities in adults with SCD are lower than those observed in children with SCD but still higher than velocities found in an adult control population.7,8 Therefore, TCD velocity criteria of stenoses in adults with SCD remain to be established.

Silent infarcts detected by MRI have been reported in as many as 22% of neurologically asymptomatic children with SCD.5,9–11 The prevalence of silent infarctions is higher among older children, which is consistent with an effect of age on cerebrovascular disease in SCD.5,12 In adult patients with SCD, the frequency of MRI and MRA abnormalities and the relationship between MRI/MRA and TCD findings are not known. Our objectives were to study the frequency of MRI and MRA abnormalities in adults with SCD and to define what TCD velocities are associated with intracranial stenoses detected by MRA.

Patients and Methods

We evaluated all patients with hemoglobin SS disease >16 years followed in the outpatient clinic of the Department of Hematology at our University Hospital. The TCD characteristics of this population were previously published.7 The diagnosis of SCD was confirmed by hemoglobin electrophoresis on cellulose acetate. Data were prospective and systematically collected, including demographic features, presence of stroke risk factors, history of stroke, and fetal hemoglobin levels. The diagnosis of a previous stroke was based on clinical history (focal neurological deficit of vascular origin persisting for >24 hours) confirmed by neuroimaging at the time of the symptoms.
The protocol received Institutional Review Board approval. All participants gave written informed consent for participation in the study.

Transcranial Doppler Ultrasonography

TCD examinations were performed and reviewed by the same author (G.S.S.) using a 2-MHz pulsed Doppler ultrasonograph (Model EME TC 2000; Nicolet, Madison, Wis) according to the Stroke Prevention Trial in Sickle Cell Anemia (STOP) protocol.6 Time-averaged mean velocities were recorded bilaterally in the distal internal carotid artery, middle cerebral artery (MCA), anterior cerebral arteries, posterior cerebral arteries, bifurcation of the internal carotid arteries, and vertebral and basilar arteries. The TCD operator was unaware of neuroimaging results. The highest value of either right or left MCA, distal internal carotid artery, or bifurcation of the internal carotid artery was taken as the time-averaged maximum mean (TAMM) velocity for each patient. We also analyzed the frequency of flow velocity asymmetry (interhemispheric flow velocity difference of ≥30 cm/s between segments in the MCA) and of focal flow velocity changes (difference of ≥20% in neighboring segments in the same artery).13,14 Complete blood count was performed on the same day as TCD examination.

Magnetic Resonance Imaging

Brain MRI was performed on a 1.5-T device (Sonata Maestro Class; Siemens Medical Systems) using a standard head coil. The protocol included: sagittal T1-weighted images (TR/TE=420/13 ms, field of view=24 cm, matrix 256x256, slice 5.5 mm), axial T1-weighted images (TR/TE 422/13 ms, field of view=25 cm, matrix 320x240, slice=5.0 mm), turbo spin echo T2-weighted images (echo train=11, TR/TE 3300/84 ms, field of view=25 cm, matrix=320x260, slice=5.0 mm), and axial fluid-attenuated inversion recovery (TR/TE 8500/107 ms, inversion time=2500 ms, field of view=25 cm, matrix 173x256, slice=5.0 mm). MRA was performed using a 3-dimensional time-of-flight technique (TE=4.47 ms, TR=36 ms, matrix 512x512, effective section thickness=0.9 mm). Sections were reconstructed using a standard maximum intensity projection algorithm. All portions were photographed in sequence and were large enough for the vascular anatomy to be worked out when maximal intensity projections raised questions. MR images were evaluated by 2 neuroradiologists unaware of the TCD results. Discordant readings were resolved by consensus.

Lesions were defined to include lacunar infarction, encephalomalacia, leukoencephalopathy, and atrophy according to the classification previously published by Steen and collaborators.12 A lacune was defined as a shelled-out volume in the white matter that was visible with T1-weighted, T2-weighted and fluid-attenuated inversion recovery sequences in the absence of ipsilateral large artery stenosis. Encephalomalacia was defined as any other ischemic change seen as a high-intensity signal on a T2-weighted or fluid-attenuated inversion recovery sequence. Atrophy was defined as loss of brain tissue volume (lobar asymmetry, open sulci, or ventricular dilatation). Leukoencephalopathy was defined as degeneration or demyelination of white matter seen as abnormally high signal intensity on T2-weighted or fluid-attenuated inversion recovery images (Figure 1). T1-weighted images were used to confirm encephalomalacia, leukoencephalopathy, lacune, and atrophy.

MRA abnormality criteria included stenosis or apparent occlusion of any vessel and arterial tortuosity according to criteria previously published.15 Stenosis was defined as obvious narrowing or focal signal dropout in a major artery (MCA, anterior cerebral artery, posterior cerebral artery, distal internal carotid artery, and basilar artery). We did not make a distinction between stenosis and occlusion. Diagnosis of tortuosity was based on the presence of dilation of a vessel segment, abnormal increase in length of a vessel segment, or obvious bowing of an artery11 (Figure 2).

Statistical Analysis

Descriptive analyses, including means and SDs, were used to describe patients’ characteristics. Independent samples t tests were used to compare means between groups. Categorical variables were compared with χ² or Fisher exact test. We generated a receiver operator characteristic curve with TAMM velocity as a predictor of intracranial stenosis detected by MRA and calculated sensitivity and specificity at the chosen cutoff value. We used multiple linear regression analysis to investigate the influence of intracranial stenoses of the anterior circulation on TAMM velocities with adjustment for hematocrit values. A 2-tailed P<0.05 was considered statistically significant. Statistical analysis was performed with SPSS 15.0 software (Chicago, Ill).

Results

Of the 56 patients with SCD followed in the adult outpatient clinic, 6 patients were excluded from the study due to inability to undergo MRI/MRA, 3 due to presence of metal prostheses and 3 due to claustrophobia. Fifty adult patients with SCD (mean age 26.8±10.1 years) were studied. In all patients, the TCD was performed before the MRI (mean time interval: 3±1 month). History of stroke was documented in 4 patients (Table). Three patients had ischemic strokes and one a subarachnoid hemorrhage.

TCD Findings

The mean TAMM velocity was 116.9±21.0 cm/s. One patient (2%) had TAMM velocity >170 cm/s. No velocities >200 cm/s were obtained. Eight patients (16%) had flow velocity asymmetry and 6 (12%) had focal flow velocity changes (Table). Hematocrit was negatively correlated with TAMM velocities (P<0.01). Only one patient had an inadequate transtemporal ultrasound bone window.

Figure 1. MRI abnormality criteria. (A) Leukoencephalopathy; (B) encephalomalacia; (C) brain atrophy; and (D) lacunar infarction.
MRA Findings
The interobserver agreement for the diagnosis of MRI and MRA abnormalities was good (kappa=0.83). MRA was abnormal in 72% of patients; intracranial stenoses were observed in 16% and arterial tortuosity in 64% of the patients (Table). Patients with abnormal MRA had significantly lower levels of fetal hemoglobin, hemoglobin, and hematocrit than patients with normal MRA (P=0.03, 0.02, and 0.05, respectively).

TCD and MRA Correlation
Patients with MCA or internal carotid artery intracranial stenoses had significantly higher TAMM velocities (P=0.01; Figure 3). The only patient with an inadequate transtemporal bone window had a right internal carotid artery intracranial stenosis by MRA and was excluded from the TCD/MRA comparison. The highest TAMM velocity found in patients with intracranial stenoses on MRA was 175 cm/s. Focal flow velocity changes were more common in patients with intracranial stenoses (P=0.04). A TAMM velocity of 123.5 cm/s allowed the diagnosis of MCA or internal carotid artery intracranial stenosis with sensitivity of 100% and specificity of 73% with an area under the receiver operator characteristic curve of 0.91 (CI: 0.79 to 1.00; Figure 4). TAMM velocities were 34.6±9.8 cm/s higher in patients with anterior circulation stenoses when compared with patients without stenoses (P=0.001; Figure 3). After adjusting for hematocrit values, this difference was 29.8±9.0 cm/s (P<0.01).

MRI Findings
The overall frequency of lacunar infarction, encephalomalacia, leukoencephalopathy, or atrophy was 60%. Leukoencephalopathy was the most common finding (48%). Lacunes were identified in 4% of the patients, encephalomalacia in 6%, and atrophy in 28% (Table). MRI abnormalities were identified in all patients with a history of stroke. Atrophy and encephalomalacia were more frequent in the group with previous stroke (100% versus 21%, P<0.01, and 50% versus 2%, P=0.01, respectively). Abnormal MRI findings were more frequent in patients with vessels tortuosity or stenoses on

| Table. Demographic, TCD, and MRI/MRA Characteristics of Adult Patients With SCD |
|-----------------|-----------------|-----------------|
| Age, years      | 26.8±10.1       | 26.8±10.1       |
| Females, %      | 60%             | 60%             |
| Previous stroke, % | 8%             | 8%             |
| Hematocrit, %   | 23.6±3.1        | 23.6±3.1        |
| TAMM velocity, cm/s | 116.9±21        | 116.9±21        |
| FV asymmetry    | 16%             | 16%             |
| Focal FV        | 12%             | 12%             |
| MRI abnormality | 30 (60%)        | 30 (60%)        |
| Lacune          | 2 (4%)          | 2 (4%)          |
| Leukoencephalopathy | 24 (48%)    | 24 (48%)        |
| Encephalomalacia | 3 (6%)         | 3 (6%)          |
| Atrophy         | 14 (28%)        | 14 (28%)        |
| MRA abnormality | 36 (72%)        | 36 (72%)        |
| Stenoses        | 8 (16%)         | 8 (16%)         |
| Tortuosity      | 32 (64%)        | 32 (64%)        |

FV indicates flow velocity.
MRA than in patients with normal MRA (69.4% versus 35.7%, \( P < 0.01 \)). Patients with intracranial stenoses had a higher frequency of encephalomalacia (\( P < 0.01 \)).

**Discussion**

In the present study, we reported the frequency of brain imaging abnormalities in adults with SCD and their correlation with TCD findings. We found that TAMM velocities in adults with SCD were higher in patients with intracranial stenoses than in patients without stenoses, albeit lower than the velocities described in children with SCD and intracranial stenoses.\(^3,6\) We also found a high frequency of brain MRI abnormalities, especially when compared with the frequency described for the pediatric population.\(^12,15\)

Our study indicated that TCD was able to identify patients with intracranial stenoses with good sensitivity and specificity. In our adult patient population with SCD, intracranial stenoses confirmed by MRA led to TAMM velocities that would be classified as normal according to the STOP study criteria. In children with SCD, a TAMM velocity of <170 cm/s is considered low or average stroke risk, 170 to 199 cm/s is termed “conditional,” leading to increased TCD surveillance, and >200 cm/s, “abnormal or high risk,” leading to treatment with periodic transfusions.\(^3,4,6\) Adams and coworkers, in collaboration with our group, described that the frequency of conditional and abnormal TAMM velocities in adults with SCD is lower than in the pediatric population.\(^7,8\)

In these studies, however, neuroimaging was not performed. In the present study, we confirmed that the lack of abnormal TAMM velocities in adults with SCD does not indicate absence of intracranial stenoses, and, more importantly, we showed that it was possible to define cutoffs for TCD velocities that allowed for the prediction of the presence of intracranial stenoses.

The lower TAMM velocities observed in adults with SCD with intracranial stenoses when compared with children may be associated with changes in cerebrovascular hemodynamics such as decreased cerebral blood flow due to decreased metabolic demand or lower cardiac output.\(^16,17\) A mild increase in vessel diameter with age could also explain, at least in part, the lower velocities observed in adults when compared with children with SCD.\(^18\)

We found an overall prevalence of 16% of intracranial stenoses detectable by MRA. In neurologically asymptomatic children with SCD, the frequency of stenoses detected by MRA is similar to our findings.\(^12,19,20\) Children with intracranial stenoses are at highest risk for developing a stroke and are usually maintained on prophylactic blood transfusion on a long-term basis.\(^9,21\) In adults with SCD, the natural history of intracranial stenoses, including the risk of stroke, is still unclear.

Using the TAMM velocity threshold of 123.5 cm/s, we identified all anterior circulation intracranial stenoses in our adult population with SCD. Twelve patients without intracranial stenoses, however, also had velocities >123.5 cm/s. For these patients, the meaning of the higher TCD velocities is uncertain. In children with SCD, abnormal TCD velocities can be detected before intracranial stenoses are detectable by MRA.\(^21\) In the STOP study, all children had TAMM velocities >200 cm/s, and only 25% of them had abnormal MRA.\(^9\) Prophylactic blood transfusion was protective against stroke irrespective of the presence of intracranial stenoses.\(^6,21\) If the pathophysiology of the cerebrovascular disease is similar in adults and children with SCD, our patients with TAMM velocities >123.5 cm/s might be at risk for stroke even in the absence of structural neuroimaging abnormalities.

The prevalence of MRI abnormalities in our adult patients with SCD was higher than that described in children.\(^10,12\) It is likely that the burden of silent cerebrovascular disease in patients with SCD increases with age.\(^10,12,15\) In children with SCD, the presence of silent lesions on brain MRI correlates with an increased risk of overt stroke.\(^22\) In a previous report, neurologically asymptomatic adults with SCD were found to have a frequency of silent infarcts similar to that described for children and higher in the subset of older patients. In this report, the authors did not study the association between brain lesions and large artery abnormalities, because neither MRA nor TCD was performed.\(^23\) We showed that abnormalities in brain MRI were more frequent in patients with stenoses and intracranial arterial tortuosity, suggesting that large vessel disease is implicated in the pathophysiology of the silent lesions.

Our study has a number of limitations. First, our objective was to describe the brain imaging abnormalities in adult patients with SCD and to correlate them with TCD findings. For this reason, we used a cross-sectional study design. This type of design, however, does not allow us to assess the role of intracranial stenoses or TCD velocities on the risk of stroke in adults with SCD; therefore, we cannot recommend altering clinical practice (eg, prophylactic blood transfusion in adults) based on our results. Second, we did not have a control group to compare with. Nevertheless, we think that a healthy and age-matched control group would have added little to our results. In a previous publication, we compared the TCD characteristics of age-matched healthy adults with our adult patients with SCD and found that healthy control subjects have lower TAMM velocities when compared with adults.
with SCD.\textsuperscript{7,8} Additionally, the frequency of brain MRI abnormalities in a healthy and young population is negligible.\textsuperscript{24} Third, the number of patients evaluated in our study is lower when compared with TCD studies evaluating children with SCD. Nevertheless, it is important to emphasize that the first neuroimaging studies of children with SCD had a sample size similar to ours and that we used a convenience sample that included all patients being followed in our hospital.\textsuperscript{6,19} Additionally, we believe that our sample size was adequate from the descriptive point of view because of the high frequency of neuroimaging abnormalities found in our patients. Although we had a similar frequency of intracranial stenoses when compared with the pediatric population with SCD, the absolute number of patients with intracranial stenoses was small (8 total intracranial stenoses, 5 stenoses of the MCA/internal carotid artery). Nevertheless, we found that patients with intracranial stenoses had much higher velocities than those without stenoses (effect size >30%) and variability was small, which makes the statistics robust despite the small number of patients. The calculated power for detecting differences in TAMM velocities between the 2 groups was 90% at an α level of 0.05. Finally, the false-positive rate of TCD (24%) together with a low false-negative rate for the detection of intracranial stenoses was adequate for a screening test. It is important to emphasize, however, that the receiver operator characteristic model and the cutoff value of TAMM velocities were applicable to our patient population and would need to be externally validated to be clinically useful.

In conclusion, the frequency of brain imaging abnormalities detected by MRI in adults with SCD was higher than that described for children. TCD velocities associated with intracranial stenoses in adults were lower than those described for the pediatric population with SCD. The meaning of these findings in terms of overt stroke risk can only be determined by prospective studies done in adult patients with SCD. The use of TCD and MRI together may prove to be a powerful tool in defining adult patients with SCD at high risk for cerebrovascular events.

Disclosures

None.

References


Brain Magnetic Resonance Imaging Abnormalities in Adult Patients With Sickle Cell Disease. Correlation With Transcranial Doppler Findings
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