Transcranial Doppler Ultrasonography and Executive Dysfunction in Children with Sickle Cell Disease

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Objective To identify behavioral manifestations of executive dysfunction that are associated with cerebrovasculopathy, as measured by transcranial Doppler (TCD) ultrasonography, in children with sickle cell disease (HbSS).

Methods Participants were 62 children and adolescents with HbSS disease who had no documented history of cerebrovascular accident. Children were classified according to the National Institutes of Health Stroke Prevention Trial in Sickle Cell Anemia (STOP) criteria (i.e., normal, conditional, and abnormal). Results Although children with abnormal TCD values were rated by their parents as exhibiting greater executive dysfunction in the areas of inhibitory control, problem-solving flexibility, and modulation of emotional responses compared with children in the conditional group, these differences were not clinically significant. In contrast, teachers rated children in the abnormal TCD group as having clinically significant executive dysfunction as manifested in their ability to solve problems in working memory, plan and organize, and self-monitor. Conclusions Our findings lend preliminary support for the utility of teacher-completed screening instruments designed to assess everyday behaviors associated with executive dysfunction in children with HbSS disease, especially among those children at greatest risk for neurological impairment as identified by TCD ultrasonography.

Key words transcranial Doppler ultrasonography; sickle cell disease; behavior; pediatric.

Sickle cell disease (SCD) is a group of genetic disorders characterized by the production of abnormal hemoglobin. Sickle cell anemia (HbSS), which constitutes the homozygous expression of the sickle β-globin gene, is characterized by lower hemoglobin levels and a higher frequency and severity of symptomatology compared with the other sickle cell disorders. Perhaps some of the most devastating outcomes in pediatric SCD are neurological complications. To this end, cerebrovascular accident (CVA) is a leading cause of morbidity and mortality, occurring at an estimated incidence of 4% to 8% among children with HbSS disease (Ohene-Frempong et al., 1998; Powers, Wilson, Imbus, Pegelow, & Allen, 1978). In fact, children with SCD also may evidence neurological pathology prior to the presentation of clinically apparent signs and symptoms. As many as 11% to 17% of children with HbSS disease evidence “silent cerebral infarcts,” lesions of infarction/ischemia identified on brain magnetic resonance imaging (MRI) in otherwise asymptomatic children (Hindmarsh, Brozovic, Brook, & Davies, 1987; Moser et al., 1996; Pavlakis et al., 1988). Silent cerebral infarct is likely accounted for by chronic hypoxia in the microvasculature ensuing from progressive cerebrovascular disease in the major cerebral arteries (Kugler et al., 1993; Moser et al., 1996; Wang et al., 1998).

Related to these findings, an increasing number of researchers have suggested that behavioral and emotional problems are associated with neurological impairments (Tramontana & Hooper, 1997), but behavioral...
correlates of SCD have been difficult to specify. Not surprisingly, an increased incidence of somatic complaints (e.g., frequency of painful sickle cell crises) among children with SCD have been reported (Kell, Kliewer, Erickson, & Ohene-Frempong, 1998; Morgan & Jackson, 1986). However, among the investigations that have examined the association between behavioral functioning and neurological status, findings have been equivocal. Several studies have failed to report differences on broad-band measures of behavior between children with SCD and CVA and children with SCD and no history of CVA (Armstrong et al., 1996; Cohen, Branch, McKie, & Adams, 1994; Hariman, Griffith, Hurtig, & Keehn, 1991; Thompson et al., 1999). In contrast, in a recent investigation, Brown and colleagues (2000) reported significant differences on measures of externalizing behavior problems for children with SCD and CVA, compared with children with no central nervous system (CNS) pathology. However, group means were not in the clinically significant range. Thus, the association between behavioral ratings and neurological status in children with SCD remains inconclusive.

Although behavioral correlates of pediatric SCD are not clear, an increasing number of researchers support the hypothesis that impaired attention and executive dysfunction occur in children with SCD but no history of stroke (Fowler et al., 1988; Noll et al., 2001), children with SCD and silent infarct (Brown et al., 2000; DeBaun et al., 1997; Schatz, Brown, Pascual, Hsu, & DeBaun, 2001), and children with SCD and overt CVA (Brown et al., 2000; Craft, Brown, Pascual, Hsu, & DeBaun, 1993; Schatz et al., 1999; White, Salorio, Schatz, & DeBaun, 2000). Deficits in the processing of subtle prosodic information also have been reported for children with SCD and a history of CVA (Boni, Brown, Davis, Hsu, & Hopkins, 2001). Interestingly, these neurocognitive impairments also are characteristic of several developmental disorders, including attention-deficit/hyperactivity disorder, Asperger’s syndrome, and nonverbal learning disability. Because behavior problems coexist with neurological impairments (Tramontana & Hooper, 1997), children with SCD who experience progressive cerebrovascular disease may be at marked risk for the development of child behavior problems associated with inattention and executive dysfunction, rather than typical externalizing and internalizing behavior problems that are readily endorsed by teachers and parents on traditional rating scales.

The advent of transcranial Doppler (TCD) ultrasonography made possible the further characterization of the progressive nature of cerebrovascular disease in pediatric SCD. Likened to a stethoscope that allows the clinician to “listen” to the blood flow changes within the major intracranial vessels (McCarty, Thomas-Lukes, & Gomez, 1997), TCD ultrasonography is a valid procedure for the detection of cerebrovascular stenosis on the basis of elevated blood flow velocity in the narrowed artery. Children with SCD typically demonstrate a 40% to 50% higher mean velocity of blood flow than do children without anemia (Adams et al., 1988). A number of investigations reported that when cerebral blood flow exceeded 170 cm/sec in this population of children, the probability of subsequent stroke could be reliably predicted (Adams, Nichols, Figueroa, McKie, & Lott, 1992; Adams et al., 1997; Kogutt, Goldway, Gupta, Kaneko, & Humbert, 1994; Seibert et al., 1993; Siegel, Luker, Glauser, & DeBaun, 1995; Verhach et al., 1995). Elevated blood flow velocities in the major cerebral arteries may be associated with hypoperfusion in the distal vasculature and concomitant chronic hypoxia. In a recent investigation of the neuropsychological correlates of TCD data among children with HbSS disease, elevated TCD values were associated with impaired performance on laboratory-based psychometric measures of executive function and sustained attention/concentration (Kral et al., 2003). Following from this finding, children with elevated TCD readings may evidence executive dysfunction in everyday behaviors.

Our study sought to extend the findings of the National Institutes of Health Stroke Prevention Trial in Sickle Cell Anemia (STOP) (Adams et al., 1997, 1998) by investigating the usefulness of TCD diagnostic groupings for identifying executive dysfunction as well as behavioral problems in children with HbSS disease. This study represents the first known investigation to examine the association between TCD-measured cerebral blood flow velocity and various behavioral problems (e.g., executive dysfunction manifested in everyday behaviors) in children with HbSS, as rated by both parents and teachers. We examined the usefulness of TCD diagnostic groupings for the identification of problems associated with executive dysfunction, internalizing and externalizing symptoms, and deficits in adaptive behavior. We hypothesized that relative to children who displayed TCD ultrasonography values in the normal range (<170 cm/sec), children with values in the conditional (170–200 cm/sec) and abnormal (>200 cm/sec) ranges would exhibit a greater frequency of behavioral problems associated with inattention and executive dysfunction, as reported by both parents and teachers. Finally, based
on research that addresses the appropriateness of specific assessments for the detection of neurological impairment in children with SCD (Kral, Brown, & Hynd, 2001), we hypothesized that parent and teacher ratings of everyday behaviors affected by executive dysfunction would be significantly associated with cerebrovasculopathy, as measured by TCD ultrasonography, compared with broad-band teacher and parent ratings of internalizing and externalizing child behavior problems.

Methods

Participants

Participants were 62 children and adolescents with HbSS disease receiving treatment at two major university-affiliated teaching hospitals in the southeastern United States. These hospitals serve primarily individuals of lower socioeconomic status (SES). Most of our sample, then, was composed of fairly low SES individuals, which is characteristic of other investigations of children and adolescents with SCD (Boni et al., 2001; Brown et al., 2000; levers, Brown, Lambert, Hsu, & Eckman, 1998).

Approximately 600 children with SCD were followed at each center during the 18-month data collection period (between 2000 and 2002). Children and adolescents who met study criteria were referred to the investigators by pediatric hematologists. Included were patients between the ages of 6.0 years and 16.11 years, with a confirmed diagnosis of HbSS, who also were participants in the multicenter STOP investigation. Patients were excluded from the study if they had a history of birth complications, traumatic brain injury, known CVA, or major chronic illness other than SCD. Five prospective participants declined study enrollment because of transportation difficulties (n = 2) and concerns about school absence (n = 3).

Following approval from the institutional review boards of both participating institutions, informed consent was obtained from the participants' caregivers, and assent was obtained from children 12 years and older. Demographic information was obtained through a questionnaire, and medical information was obtained from computerized databases at both institutions. For each participating child, laboratory data (e.g., hematocrit, which is the percentage of whole blood comprising red blood cells) closest in time to the collection of the behavioral data were recorded from the hospital laboratory computerized database. Caregivers also provided written consent to obtain information from the teachers of participating children. Educational history, including grade retention and special education placement, was obtained through a questionnaire administered to both parents and teachers. The participation rate of parents and teachers was 100%. When parents and teachers reported discrepant information about participants' educational history, teacher report of grade retention and special education placement was coded, as teachers had ready access to accurate information in the participants' educational records.

Transcranial Doppler Methods

TCD studies of blood flow velocity in the basal cerebral arteries were performed by a trained technician, as detailed by Adams and colleagues (1997) in the STOP study. Velocities in the proximal middle cerebral arteries (pMCA), distal internal carotid arteries (dICA), and bifurcation of the internal carotid arteries (bifICA) were recorded. The highest time-averaged mean velocity (Vmean) among these recordings was used in the statistical analyses. Following the guidelines of the STOP study, participants were assigned to the normal TCD group if the highest Vmean was less than 170 cm/sec (n = 25), to the conditional group if the highest Vmean was between 170 and 200 cm/sec (n = 17), and to the abnormal group if the highest Vmean exceeded 200 cm/sec (n = 20). TCD studies for participants in the normal and conditional categories were obtained within a 6-month period prior to data collection. It should be noted that TCD ratings classified as abnormal are relatively rare. For example, an average of one child per year at one of our institutions, which serves over 600 pediatric patients with SCD, was classified as having an abnormal TCD reading. Due to this relative infrequency, those participants with abnormal TCD readings within a 5-year period prior to data collection were enrolled from both institutions. As part of the STOP protocol, only patients in the abnormal group were receiving chronic blood transfusions for primary stroke prevention. In contrast, children with conditional TCD readings evidenced normal TCD data within the 5-year period prior to study enrollment; they qualified for participation in the study on the basis of the TCD designation at the time of study enrollment. Finally, participants in the normal group demonstrated normal TCD readings within a 5-year period prior to study enrollment, as verified by a review of their medical records.

Intellectual Functioning

General intellectual functioning was assessed for each child in order to investigate potential differences for
cognitive functioning across TCD diagnostic groups, as intellectual functioning has demonstrated a significant correlation with behavioral functioning among children with SCD (Thompson et al., 1999). Measures of intelligence were obtained using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999a). The WASI consists of subtests from traditional Wechsler scales that have the highest loadings (e.g., >.70) on g, or general intellectual functioning (Sattler, 2001; Wechsler, 1999b). The WASI allows for assessment of full-scale intelligence quotient (FSIQ) functioning; this age-referenced standard score was used in the statistical analyses.

Academic Classification and Retention
Participant caregivers provided information on each child's academic history at study enrollment, including whether the child had ever been retained, received special education services, or both. Grade retention was defined as a child repeating a grade in school due to either lack of educational progress or excessive school absenteeism secondary to SCD complications. Special education placement was defined as receipt of special education services either in the regular education classroom (e.g., 504 plan) or in an alternative classroom placement (e.g., resource classroom or self-contained classroom).

Behavioral Functioning
Behavioral functioning was assessed across multiple sources (home and school) and from multiple informants (parents and teachers). Specifically, a broad-band behavior rating scale was completed by each participating child's parent and teacher. In addition, each participating child's parent and teacher completed a narrow-band behavior rating scale designed to assess executive functions.

Each participant's parent and teacher were asked to complete the Behavior Assessment System for Children (BASC) (Reynolds & Kamphaus, 1992), a broad-band behavior rating scale that is normed for chronological age and designed to assess an array of maladaptive and adaptive child and adolescent behaviors. The parent rating scales (BASC-PRS) and teacher rating scales (BASC-TRS) each are composed of items that assess internalizing (e.g., depression, anxiety, social withdrawal), externalizing (hyperactivity, aggression, conduct problems), and adaptive behaviors (social skills, leadership skills, study skills). Data support the reliability, internal consistency, and construct validity of this instrument. The BASC-PRS yields age-referenced T-scores for 12 clinical scales, which combine to form four composite scores: externalizing problems, internalizing problems, behavioral symptoms index (a global composite of internalizing and externalizing behavioral problems), and adaptive skills. The BASC-TRS yields similar information, with the addition of two clinical scales, which combine to produce an additional composite, school problems. T-scores from the parent and teacher behavior rating scales were used in the statistical analyses.

Each participant's parent and teacher also were asked to complete the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, & Kenworthy, 2000), a narrow-band rating scale designed to assess everyday behaviors associated with executive dysfunction in the home and school environments. The BRIEF comprises 86 items designed to assess various aspects of executive function, including ability to inhibit emotional and behavioral responses, cognitive flexibility, working memory, planning and organization skills, and initiative. Data support the reliability, internal consistency, and construct validity of this instrument. The BRIEF yields age-referenced T-scores for eight clinical scales, which combine to form three composite scores: the behavioral regulation index, the metacognition index, and the global executive composite. T-scores from the parent and teacher questionnaires were used in the statistical analyses.

Data Analyses
Due to insufficient statistical power, multivariate analyses were not feasible. Thus, a series of separate one-way analyses of covariance (ANCOVAs), using the general linear model, was performed for the BRIEF clinical scales and for the BASC internalizing, externalizing, and adaptive behavior composite scores for both parent and teacher data. Group assignment based on TCD findings served as the independent variable (normal <170 cm/sec; conditional = 170–200 cm/sec; and abnormal >200 cm/sec). Hematocrit served as a covariate to control for the effects of transfusion in the abnormal TCD group. TCD data were treated categorically in these analyses to further explore the clinical utility of the TCD diagnostic groups; analyses were conducted to determine whether a variety of behaviors (e.g., executive dysfunction) differed across the three categories of TCD diagnostic groupings, controlling for the differential effect of hematocrit. Given the exploratory nature of these analyses, the a priori α level was set at .05. Finally,
Fisher’s least-significant-difference (LSD) planned contrasts were performed for any dependent measure for which there was a significant univariate effect.

**Results**

Of the total participants (N = 62), 43.5% were male (n = 27) and 56.5% were female (n = 35). The mean age was 121.4 months (SD = 31.4, range = 73.0 to 192.0 months). The mean FSIQ standard score was 89.27 (SD = 17.80, SD = 41.18). Most TCD values were found in the pMCA (57.3%; n = 35), but 16.4% were obtained in the dICA (n = 10), and 26.2% were found in the bifICA (n = 16). Just over half of the values for the highest time-averaged Vmean were obtained on the left side (55.7%; n = 34), compared with 44.3% of the values obtained on the right side (n = 27). We performed a series of separate one-way analyses of variance (ANOVA), using the general linear model, on each of the dependent measures (BASC and BRIEF composite scores) using artery (pMCA, dICA, bifICA) as the independent variable. No significant main effects were obtained for any of the dependent measures.

A large percentage of caregivers in our sample were mothers (87.1%; n = 54). Other caregivers were biological fathers (6.5%; n = 4), grandmothers (4.8%; n = 3), and an aunt (1.6%; n = 1). Although most caregivers had graduated from high school (69.4%; n = 43), approximately one sixth had not completed high school and had not been granted an equivalent diploma (17.7%; n = 11). Eight (12.9%) caregivers did not report educational attainment. The mean years of education were 12.48 (SD = 1.79, range = 8–16). For those caregivers who reported family income (n = 55), most had annual incomes of less than $19,000 (59.7%; n = 37). The remainder of the sample had incomes ranging from $20,000 to $30,000 (14.5%; n = 9), $31,000 to $40,000 (17.7%; n = 5), and above $40,000 (6.5%; n = 4).

Table I presents the participant age, gender, general intellectual functioning, academic classification and retention, caregiver’s education, family income, and illness severity data (i.e., highest time-averaged Vmean TCD reading and hematocrit) for each of the three TCD diagnostic groups. Differences were found for special education placement. Significantly more children in the abnormal group were receiving special education services, compared with the normal and conditional groups (x^2 = 9.49, p < .01). Although the comparison did not reach statistical significance, a greater frequency of grade retentions was found for the groups with elevated TCD values. As expected, a significant group difference was found for the highest time-averaged TCD Vmean, F(2, 56) = 161.32, p < .001. Post-hoc analyses revealed that the highest time-averaged Vmean was higher in the conditional group than the normal group (p < .001), and higher in the abnormal group than the conditional group (p < .001). No differences were found for the other demographic variables.

As presented in Table II, the results of one-way ANCOVAs on the parent BRIEF behavioral regulation scales revealed a statistically significant effect for the inhibition scale, F(2, 54) = 3.32, p < .05. Post-hoc analyses revealed that the abnormal group obtained significantly higher scores than the conditional group (p < .05). A statistically significant effect also was revealed for the emotional control scale, F(2, 54) = 7.33, p < .01. Post-hoc analyses revealed that the conditional group obtained significantly lower scores than both the normal (p < .05) and abnormal (p < .01) groups. A trend toward statistical significance was revealed for the shift scale, yielding a small effect size, F(2, 54) = 3.12, p = .053, partial η^2 = .10. Post-hoc analyses revealed that the abnormal group obtained significantly higher scores than the conditional group (p < .05).

The one-way ANCOVAs on the metacognitive scales of the parent BRIEF did not yield statistically significant effects.

The results of one-way ANCOVAs on the teacher BRIEF metacognitive scales revealed a statistically significant effect for the monitor scale, F(2, 55) = 4.42, p < .05. Post-hoc analyses revealed that the abnormal group obtained higher scores (i.e., greater dysfunction) than both the normal (p < .05) and conditional (p < .05) groups. Also, trends toward significance, albeit with small effect sizes, were revealed for the working memory scale, F(2, 55) = 3.08, p = .054, partial η^2 = .10, and the plan/organize scale, F(2, 55) = 3.02, p = .057, partial η^2 = .10. Post-hoc analyses revealed that the abnormal group obtained higher scores on both scales, compared with both the normal (p < .05) and conditional (p < .05) groups.

The one-way ANCOVAs on the behavioral regulation scales of the teacher BRIEF were not statistically significant. One-way ANCOVAs performed on the
Table I. Demographic Characteristics and Illness Severity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normal n = 25</th>
<th>Conditional n = 17</th>
<th>Abnormal n = 20</th>
<th>Entire Sample N = 62</th>
<th>$F_{1,2}^2$</th>
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<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>n</td>
<td>%</td>
<td>M</td>
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<tr>
<td>Age, mos</td>
<td>126.84</td>
<td>28.08</td>
<td>108.29</td>
<td>35.07</td>
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<tr>
<td>Females</td>
<td>10</td>
<td>40</td>
<td>13</td>
<td>77</td>
<td>12</td>
</tr>
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<td>WASI FSIQ</td>
<td>91.22</td>
<td>10.42</td>
<td>89.12</td>
<td>7.52</td>
<td>87.15</td>
</tr>
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<td>20</td>
<td>1</td>
<td>6</td>
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<td>Caregiver education</td>
<td>12.36</td>
<td>1.81</td>
<td>12.73</td>
<td>2.15</td>
<td>12.41</td>
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<tr>
<td>Family income</td>
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<tr>
<td>&lt; $19,000</td>
<td>15</td>
<td>60</td>
<td>12</td>
<td>71</td>
<td>10</td>
</tr>
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<td>$20,000–$30,000</td>
<td>4</td>
<td>16</td>
<td>1</td>
<td>6</td>
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</tr>
<tr>
<td>$31,000–$40,000</td>
<td>–</td>
<td>2</td>
<td>2</td>
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<td>3</td>
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<td>8</td>
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<td>1</td>
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<tr>
<td>Illness severity</td>
<td></td>
<td></td>
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<tr>
<td>TCD (cm/sec)</td>
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<td>16.75</td>
<td>182.53</td>
<td>9.77</td>
<td>221.78</td>
</tr>
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</table>

WASI FSIQ = Wechsler Abbreviated Scale of Intelligence full-scale intelligence quotient; TCD = transcranial Doppler (ultrasonography).

* Post-hoc analysis = 1 < 2 < 3. ** Post-hoc analysis = 1 < 2 < 3.
*** p < .001.
BASC-PRS and the BASC-TRS composite scores did not yield any statistically significant main effects. In fact, mean scores for each of the BASC-PRS and BASC-TRS clinical scales were well within the average range.

**Discussion**

Our investigation examined the relationship between cerebral blood flow velocity, measured by TCD ultrasonography, and a variety of behavioral problems (e.g., everyday behaviors associated with executive dysfunction) in a sample of children with sickle cell anemia (HbSS) with no documented history of CVA. This study is unique because it is the first known investigation examining behavioral correlates of TCD ultrasonography data. Our investigation offers the additional advantage of examining a variety of behaviors reported by both parents and teachers on both broad-band and narrow-band rating scales.

Parents in our study reported greater difficulty with behavioral regulation (i.e., executive dysfunction) for children in the abnormal group compared with peers.
with SCD in the conditional TCD group on the narrow-band rating of executive function. Children with abnormal TCD values were rated by their parents as exhibiting greater executive dysfunction in the areas of inhibitory control and modulation of emotional responses than children in the conditional group. Parents also reported a trend toward greater problem-solving inflexibility for children in the abnormal TCD group compared with those in the conditional group. Given the rather small effect size, these data should be interpreted with caution. In contrast, teachers rated children in the abnormal TCD group as evidencing greater difficulty with metacognitive skills relative to children in the other two TCD groups. Specifically, children in the abnormal group were rated by their teachers as having greater executive dysfunction in their ability to self-monitor. Teachers also reported a trend toward greater difficulty for children in the abnormal group to solve problems in working memory and plan/organize, relative to children in the other two groups. Although these data are provocative, the results warrant additional replication given the small effect sizes obtained.

An examination of the subscales for the parent BRIEF revealed consistently lower mean scores for the conditional group compared with either the normal or abnormal group. This unexpected finding may be explained by statistical artifact. For example, the small sample size and the large variance within the various subscales may account for this finding, especially given the small effect size yielded by the statistical result that was not significant. An alternative explanation may be that parents are less reliable and accurate raters of everyday behaviors associated with executive dysfunction, given that the lowest mean scores were reported for children with borderline cerebrovasculopathy (i.e., children with conditional TCD studies).

It should be noted that for those parent ratings that yielded statistically significant group differences, the mean scores were not clinically significant (i.e., group means for the three TCD groups were below a T-score of 60). In contrast, group differences for teacher ratings of executive dysfunction yielded clinically relevant findings (i.e., each of the mean T-scores for the abnormal group were above a T-score of 60 or the 90th percentile). The differences between the parent and the teacher report may relate to the different perspectives of the informants. For example, the structure imposed by the classroom setting permits teachers to observe metacognitive skills, whereas the generally unstructured home environment permits parents to observe self-regulation of behavior and affect. Thus, our finding of differences between raters is likely a function of the behaviors most frequently observed in the raters’ respective environments. One possibility is that the classroom context allows for more salient identification of executive dysfunction. Hence, teacher ratings may be more robust in terms of identifying everyday behaviors associated with executive dysfunction. Taken together, our data provide preliminary evidence for the viability of teacher ratings, relative to parent ratings, as screeners of executive dysfunction in children with SCD.

Of particular interest is our finding that children with normal, conditional, and abnormal TCD values were rated similarly by both parents and teachers on broad-band measures of externalizing (e.g., aggression) and internalizing (e.g., anxiety) behavioral problems and adaptive behavior skills. None of the STOP-designated TCD groups yielded mean parent or teacher ratings that were in the clinical range on the broad-band behavior rating scales.

Our results lend preliminary support for the growing body of evidence suggestive of deficits in executive function among children with HbSS disease with various stages of CNS pathology (Brown et al., 2000; DeBaun et al., 1998; Schatz et al., 1999). Consistent with our previous findings that yielded significant effects for laboratory-based neuropsychological measures of executive functions (Kral et al., 2003), the present data employing narrow-band, easily administered rating scales support our previous findings of executive dysfunction, particularly among children with more severe cerebrovasculopathy. Although neither teacher nor parent ratings on the broad-band scales (i.e., BASC) yielded significant effects, our results suggest that ratings of everyday behaviors associated with executive dysfunction appear more sensitive to cerebrovasculopathy than do broad-band measures of child behavior problems. These data also are consistent with the neuropsychological literature, which suggests that measures of specific functions (e.g., attention, executive functions) often are more reliable in identifying CNS pathology than are neurocognitive measures of general functioning (e.g., tests of intelligence, academic achievement; Kral et al., 2003; Schatz, Finke, Kellett, & Kramer, 2002). In fact, although the purpose of this particular investigation was to describe behavioral functioning among the three identified TCD groups, it also should be noted that no statistically significant differences were found among the groups on the measure of general intellectual functioning (WASI FSIQ).
Because our data suggest that children with the most severe cerebrovasculopathy (as measured by TCD ultrasonography) evidenced the greatest executive dysfunction, we posit that the frontal systems are vulnerable to progressive pathology in the major cerebral arteries in pediatric SCD. In fact, this observation is corroborated by Brown and colleagues (2000), who found that the majority of children with deficits in attention and executive function also evidenced impairment in the region of the frontal lobes, as documented by MRI. The data also are consistent with those of Pavlakis and associates (1988), who found that CVAs most frequently occurred in the frontal lobes. It remains unclear as to why this region of the brain seems most vulnerable to insult. For children, cerebrovasculopathy associated with HbSS disease may interfere with the dynamic nature of development in the frontal cortex over time. Clearly, future research efforts will need to investigate the mechanism by which the frontal systems are affected by the progressive nature of cerebrovascular disease in pediatric SCD.

The contribution of our investigation must be interpreted within the limitations of the study design. The small sample size may have mitigated statistical power and for this reason could have diminished significant effects that otherwise may have been detected with a larger sample. Additional research will need to include multisite, collaborative clinical samples to ensure larger cohorts of children with SCD. Both longitudinal designs and experimental studies are needed to explore other effects when evaluating such complex behaviors as inattention and executive dysfunction. For example, whether impairments in executive function represent the cumulative effects of progressive cerebrovasculopathy (e.g., chronic hypoxia) remains to be addressed in future longitudinal investigations with serial neuropsychological assessment. In addition, random assignment to treatment groups was not possible in this investigation, given participants' enrollment in the National Institutes of Health STOP trial (Adams et al., 1997, 1998). That is, the STOP protocol necessitated treatment for participants in the abnormal TCD group only. Therefore, the abnormal group in this study was necessarily confounded by the transfusion therapy they received. It would be ideal if future experimental designs by random assignment to treatment groups could control for the possible rehabilitative effects of transfusion therapy. This would assist in determining the influence of transfusion treatment on behavioral functioning for children with SCD. Finally, unlike their counterparts who were in either the normal or conditional group, children with the most severe classification of cerebrovascular disease also were the most likely to have been in their respective TCD group for the longest duration. Thus, group differences in executive functioning may in part be attributable to duration of time spent with elevated blood flow velocities, rather than simple categorization based on absolute blood flow velocity. Future research efforts will need to control for these confounds, although it is well recognized that standard of care for these patients would preclude many parsimonious experimental designs.

Notwithstanding these limitations, the results of this investigation corroborate our earlier findings to suggest that the assessment of executive function may identify children who have CNS pathology, as designated on both TCD (Kral et al., 2003) and MRI (Brown et al., 2000). Most important, the data underscore the usefulness of easily administered rating scales designed to assess everyday behaviors associated with executive dysfunction for the purpose of screening children with HbSS disease who are at risk for neurological impairment.

Although our data provide preliminary support for the utility of TCD ultrasonography—in particular, the use of teacher-completed behavioral ratings—for the purpose of screening those children at greatest risk for neurological impairment, additional validity studies are warranted given the generally provocative findings provided here. Clearly, additional study is needed prior to endorsing these rating scales for the purpose of clinical screening. Such investigation will need to corroborate TCD findings and behavior ratings with neuroimaging techniques, including MRI and magnetic resonance angiography (MRA), to determine whether those functions identified as impaired are associated with CNS structural abnormalities. Finally, additional study is needed regarding the validation of teacher ratings of behavior and children's neuropsychological functioning on laboratory-based measures of executive function.

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