Neurocognitive Functioning and Magnetic Resonance Imaging in Children With Sickle Cell Disease

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Objective: To examine neurocognitive functioning in children classified with overt cerebral vascular accidents (CVAs), silent infarcts, or without central nervous system (CNS) pathology on magnetic resonance imaging.

Methods: Participants were 63 children and adolescents with sickle cell disease (SCD).

Results: Children with overt CVAs and silent infarcts differed from their peers without CNS pathology on measures of attention and executive functioning.

Conclusions: We consider these deficits the result of the high frequency of frontal lobe deficits incurred by children with SCD. Recommendations include the use of tests designed to measure attention and executive functioning as a way of screening children with SCD for possible CNS pathology. We also suggest that future research examine the mechanism underlying frontal lobe involvement for individuals with SCD.

Key words: sickle cell disease; neurocognitive; cerebral vascular accident; attention.
tion and executive functioning screening measures were the most useful in identifying children with cerebral infarcts.

Research further indicates that children with SCD but without any overt signs or symptoms of a cerebral vascular accident may still be at significant risk for cognitive impairment. For example, Fowler and colleagues (1988) and Swift and associates (1989) reported that, compared to healthy and comparison sibling controls, children with SCD without overt symptoms of a CVA still scored lower on tests of intellectual functioning and academic achievement. Wasserman, Wilmas, Fairclough, Mulhern, and Wang (1991) compared sibling controls to 43 children with SCD ages 8 to 16 years with no overt neurological dysfunction. They found that the children with SCD still scored lower on measures of intelligence, although no differences appeared in academic achievement. In addition, children 12 years of age or younger showed language-based deficits on the Luria-Nebraska Neuropsychological Battery (Golden, 1987). Brown and associates (Brown, Buchanan, et al., 1993) used a battery of neurocognitive measures to compare children and adolescents with SCD but without CVAs or overt neurological dysfunction to nondiseased siblings. Children with SCD performed more poorly than siblings on measures of sustained attention. These findings are consistent with those of Rodgers, Clark, and Kessler (1984), who found evidence of altered metabolism in the frontal lobe area on positron emission tomography (PET). These studies indicate the likelihood of deficits in attention and executive functioning in patients with SCD, including those with overt CVAs (DeBaun et al., 1998; Rodgers et al., 1984; Schatz et al., 1999) and those with no documented evidence of infarcts (Brown, Buchanan, et al., 1993; Goonan, Brown, Buchanan, & Eckman, 1994).

The possibility that a significant percentage of children with SCD (11% to 20%) with no evidence of overt neurological disease on physical examination may have cerebral infarction detectable only by magnetic resonance imaging (MRI) has also been investigated (Kinney et al., 1999; Pavlakis et al., 1988). The most current definitive investigation of silent cerebral infarction with neuropsychological data has been a subset of the Cooperative Study of Sickle Cell Disease (CCSCD) (Armstrong et al., 1996). Participants in this large, multisite, collaborative clinical research program included 194 children with SCD, 135 of whom had the HbSS type.

The incidence of central nervous system (CNS) abnormalities identified on MRI was 17%, with over 10% of the sample categorized as having a silent infarct. When children with HbSS were considered alone, over one-fifth of the sample had abnormal findings on MRI, over 15% of which were consistent with a silent infarct. Because most of the patients with silent infarcts had HbSS type SCD, neurocognitive functioning was examined for these participants. Children with a clinical history of a CVA were compared to those with MRI evidence of a silent infarct or no MRI abnormality. Measures included tests of intelligence, academic achievement, motor speed, and parent ratings of behavioral adjustment. Children with a clinical stroke as revealed on MRI showed the highest frequency of neurocognitive deficits, including impairments in intellectual functioning, language abilities, visual-motor and visual-spatial processing, academic achievement, and sequential memory. Children with silent infarcts did not show problems as severe or pervasive as those who demonstrated overt CVAs, although they did perform more poorly than those with no MRI abnormality on visual-motor speed, arithmetic, and vocabulary.

We wanted to extend the research of Armstrong and associates (1996) by examining the neurocognitive functioning of children with SCD and clinical stroke and children with SCD and silent infarcts, with both conditions documented on MRI scans. We extended Armstrong’s original investigation by using additional indices of neurocognitive functioning, including measures of attention and executive functioning and specific neuropsychological measures of language. Also included were parent reports of behavioral adjustment and adaptive competence. Our study was unique because it included a battery of measures associated with attention, concentration, and executive functioning and specifically related these measures to MRI findings. In addition, consistent with the Armstrong design, children and adolescents in the two MRI categories (i.e., overt CVA, silent infarct) were compared to those participants with no documented MRI abnormality. We hypothesized that, relative to their counterparts with no documented MRI abnormality, children with overt clinical strokes and those with silent infarcts would perform less well on global measures of intellectual functioning and academic achievement and on tasks of attention and executive functioning, language, and visual-motor and visual-spatial processing.
Method

Participants

Participants were 63 children and adolescents with SCD receiving their treatment at a comprehensive National Institutes of Health sickle cell center. This center is located at a major university-affiliated teaching hospital that serves primarily individuals of lower socioeconomic status (SES). Thus, our sample is composed primarily of a fairly low SES group, and this is characteristic of other investigations of children and adolescents with sickle cell syndromes (Hurtig, Koepke, & Park, 1989; levers, Brown, Lambert, Hsu, & Eckman, 1998). Approximately 500 children with sickle cell syndromes were followed at this center at the time that the data were collected, from 1993 to 1998. Participants had been referred to us by pediatric hematologists to investigate their cognitive, academic, and emotional functioning (Brown, Armstrong, & Eckman, 1993; Brown, Doepke, & Kaslow, 1993; Devine, Brown, Lambert, Donegan, & Eckman, 1999; levers et al., 1998). The children were specifically referred to the investigators because of possible learning problems and adjustment difficulties.

This investigation was approved by the Institutional Review Board. Informed consent was obtained from the participants’ caregivers. For those children and adolescents capable of understanding the nature of the study, assent was obtained. Demographic information was obtained through questionnaires, and medical information was obtained by chart reviews as well as an examination of the computer database employed for the NIH sickle cell center. Caregivers were paid $30 for participation in the study. MRI examinations of the brain were conducted for clinical purposes within 3 months of the neurocognitive assessment. The length of the neurocognitive evaluation was approximately 3 hours.

Measures

Neurocognitive Battery. Based on literature on neuropsychological functioning in children with SCD (Bonner et al., 1999; Brown, Armstrong, & Eckman, 1993; Brown, Doepke, & Kaslow, 1993; White & DeBaun, 1998), a neurocognitive battery was constructed to assess six domains of functioning: general intellectual functioning, academic achievement, attention and executive functioning, language, visual-spatial and motor processing, and behavioral ratings of internalizing and externalizing behavioral adjustment and adaptive behavior. The measures comprising the battery are described below.

The Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler, 1991) allows for the assessment of verbal (VIQ), performance (PIQ), and full-scale intellectual functioning (FSIQ).

The Woodcock-Johnson Psychoeducational Test Battery: Tests of Achievement-Revised (WJ-R) (Woodcock & Johnson, 1990) was used to assess academic achievement in broad mathematics (calculation and applied problems subtests) and broad reading (letter-word identification and passage comprehension subtests). Broad Reading and Broad Mathematics scores were used in the analyses.

Participants were administered the Cancellation A’s Task (Diller et al., 1974) that assesses capacity for sustained attention on a repetitive response task. Performance is scored for errors of omission and commission and time to complete. In addition, children with SCD were administered the Trail Making Test (Reitan & Wolfson, 1985) that assesses speed for attention, sequencing, mental flexibility, and visual search. Scoring is expressed in terms of the time in seconds required for Part A and Part B of the test. Finally, the Freedom-from-Distractibility factor of the WISC-III was included in this domain because it is associated with sequential processing, attention, and automatic functioning.

The Boston Naming Test (Kaplan & Goodglass, 1983) assessed expressive language ability, measured by the ability to name pictured objects. A total naming score was employed for analyses. Additionally, the Rapid Automatized Naming (RAN) (Denckla & Rudel, 1974) was administered. Rapid naming tasks can differentiate between individuals with a reading disability, those with other learning disabilities, and those without reading problems (Blachman, 1997; Denckla & Rudel, 1974). The total number of errors was used for statistical analyses.

The Purdue Pegboard (Tiffin, 1987) requires children to place small round pegs into holes in a standard board within a 30-second interval and assesses motor speed and coordination. The raw score is derived from the total number of pegs that are correctly placed with each hand.

The Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1991) is a 113-item measure completed by caregivers that addresses a broad range of internalizing (e.g., depression, anxiety) and externalizing (e.g., acting-out behaviors) behaviors.
in children and adolescents. Caregivers rated the severity of each of the symptoms that they observed in their child. In addition, we administered the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984), a widely used, semistructured parental interview that assesses adaptive behavior across several domains of functioning, including communication, daily living, socialization, and motor skills. The Adaptive Behavior composite score was used in our analysis.

**Magnetic Resonance Imaging Studies.** MRI studies of the brain without contrast were performed in accordance with standard practices. Children who were younger and those who needed assistance were sedated in accordance with the guidelines outlined by the American Academy of Pediatrics (Committee on Drugs, 1992). Our procedures were similar to those of the CCSCD investigation (Armstrong et al., 1996) and other studies (DeBaun et al., 1998; Schatz et al., 1999). Each child’s MRI was reviewed independently by both a pediatric neuroradiologist and a pediatric radiologist. Any disagreements between the two radiologists were resolved by consensus. MRI readings were classified without CNS pathology as normal (no CNS pathology), cerebral infarction, atrophy, and cerebral infarction and atrophy. Children with infarction were classified as having had either clinically apparent CVAs or silent infarction. If the records showed no history of a CVA and the neurologic examination was unremarkable, the children with MRI scans suggestive of infarction were classified as having a silent infarct (n = 11). Children with a documented history of a CVA that was recorded in the medical record and who also had an MRI indicating an infarct were classified as having a clinical history of a CVA (n = 22). If there was no pathology shown in the medical record or the MRI, the child was classified as normal or without CNS pathology (n = 30).

**Data Analyses.** A series of separate one-way multivariate analyses of variance (MANOVA) was performed for each domain of measures (i.e., measures of intellectual functioning, academic achievement, attention and executive functioning, language, visual-spatial and motor processing, behavioral ratings of adjustment), and the classification of CNS pathology shown on physical examination and MRI reading (i.e., clinical stroke or CVA, “silent” stroke, and scan without evidence of CNS pathology) served as the independent variable. Thus, six MANOVAs were performed; significant multivariate tests were followed by analyses of variance (ANOVA), and post hoc analyses were performed on any dependent measure for which there was a significant ANOVA.

**Results**

Of the participants, 60.3% were male (n = 38) and 39.7% were female (n = 25), and the mean age was 9.75 years (SD = 2.87, range = 6.33 to 17.00 years). Grades in school ranged from kindergarten to tenth with a mean of third grade (M = 3.56, SD = 2.75). Children were primarily in regular classrooms (63.5%; n = 40), although 34.9% (n = 22) were receiving special education resource services (i.e., part-time resource help in certain subjects). One child was in a self-contained special education classroom (1.3%). The children and adolescents had the following types of SCD: HbSS (n = 48; 76.2%), HbSC (the heterozygous condition for hemoglobin S and hemoglobin C) (n = 15; 23.8%). Children and adolescents in the two SCD groups (i.e., HbSS, HbSC) were compared on hemoglobin, symptoms ever, and symptoms in the past year. The results of t tests revealed that participants with HbSS disease (M_hemoglobin = 8.22, SD = 1.14) had lower hemoglobin than did their peers with HbSC disease (M_hemoglobin = 11.07, SD = 1.19) (t = 12.9, p < .001). In addition, the results of t tests revealed that participants with HbSS disease (M_symptoms_ever = 3.79, SD = 2.24) had a greater number of symptoms ever than did their peers with HbSC disease (M_symptoms_ever = 1.90, SD = 1.48) (t = 5.59, p < .001). Finally, the results of t tests indicated that children and adolescents with HbSS disease (M_symptoms_past_year = 2.43, SD = 1.89) had a greater number of symptoms in the past year than did their counterparts with HbSC disease (M_symptoms_past_year = 1.05, SD = 1.34) (t = 4.78, p < .001). Thus, participants with HbSS disease clearly had greater disease severity than did their peers with HbSC disease.

Most caregivers in our sample were mothers (87.3%, n = 55). Other caregivers were fathers (7.9%, n = 5), grandmothers (1.6%, n = 1), and aunts (3.2%, n = 2). The marital status of caregivers was 23.8% (n = 15) currently married, 39.7% (n = 25) single, 34.9% (n = 22) separated or divorced, and 1.6% (n = 1) widowed. Although most caregivers had graduated from high school (n = 49; 77.8%), approximately one fourth had not completed high school and had not been granted an equivalent diploma through testing (n = 14; 22.2%). The mean
avascular necrosis, osteomyelitis, dactylitis, pria-
pism, and delayed puberty. Symptoms were re-
corded if they had occurred within the past year
(number of symptoms within the past year) or if
they had been present prior to this period of time
(symptoms ever). No differences were found for any
of the demographic variables. As expected, how-
ever, significant differences were found for symp-
toms ever, $F(2, 60) = 5.77, p < .005$, and the mean
hemoglobin within the past three clinic visits,$F(2,
60) = 4.24, p < .02$. All post hoc comparisons for
this study were performed using Tukey’s HSD proce-
dure. The results of post hoc tests performed on the
means revealed that for symptoms ever, the group
classified without CNS pathology differed from the
group with overt strokes. In addition, the group
classified without CNS pathology differed from the

years of education was 12.56 ($SD = 1.61$, range = 9
to 16 years). Most of the families had annual in-
comes of less than $10,000 ($n = 35; 55.6\%$). The
remainder of the sample had incomes ranging
$10,000–$19,999 ($n = 13, 20.6\%$), $20,000–$30,000
($n = 12; 19.1\%$), $31,000–$40,000 ($n = 2; 3.2\%$),
and above $40,000 ($n = 1, 1.6\%$).

Table I presents the subject age and gender, care-
givers’ marital status, education, income, and sever-
ity of disease (i.e., number of symptoms within the
past year, number of symptoms ever, mean hemo-
globin of the past three visits) for each of three des-
nignated MRI groups. Symptoms included seizures,
headaches, auditory and ocular complications,
splenic sequestration, microspleenia, splenomegaly,
hepatomegaly, cardiomegaly, acute chest syndrome,
lung abnormalities, renal complications, gallstones,
group classified with silent infarcts ($p < .01$). An examination of the means showed that the group with overt CVAs evidenced a greater frequency of symptoms ever than did either the group classified without CNS pathology or the silent infarct group. An examination of the mean hemoglobin scores revealed that the group classified without CNS pathology had significantly higher mean hemoglobin ($p < .03$) than the group with overt CVAs. Thus, as expected because of the greater severity of their disease, the children with overt CVAs had a higher frequency of symptoms ever and lower hemoglobin scores than children classified without CNS pathology. The children with silent infarcts had a higher frequency of symptoms ever than the group classified without CNS pathology.

The results of a one-way MANOVA on the attention-executive functioning factor yielded a statistically significant main effect, $F(12, 64) = 2.13$, $p < .03$. Separate ANOVAs were performed on each of the dependent measures and a statistically significant effect was revealed for the Trail Making B time score, $F(2, 60) = 6.62$, $p < .003$. To determine the source of statistical significance between the three groups, post hoc analyses were performed on the Trail Making B time score. The results of these Tukey HSD post hoc tests indicated that the group designated without CNS pathology completed the test more rapidly than the group classified with silent infarcts ($p < .007$). The children with silent infarcts took more time to complete the task than those with overt CVAs ($p < .03$). See Table II for these means.

The results of the ANOVA performed for the Cancellation A’s Omission error score revealed a significant main effect, $F(2, 60) = 3.72$, $p < .03$. Post hoc analyses revealed that the children classified without CNS pathology differed from the children with overt CVAs on the omission error score ($p < .01$), and there was a difference that approached statistical significance for the children with overt CVAs to differ from the participants classified with silent infarcts ($p < .06$). An examination of the means indicates that the children classified without CNS pathology had fewer omission errors than the group with overt CVAs. Finally, a difference that approached statistical significance was revealed for the ANOVA performed on the Cancellation A’s Commission Error score, $F(2, 60) = 2.48$, $p < .09$. No other statistically significant ANOVAs for measures of the attention-executive function domain were revealed. None of the remaining MANOVAs was statistically significant.

Finally, the children who were diagnosed with either overt CVAs or silent infarcts were classified according to the area of the brain where they had sustained damage. Areas included the frontal lobe ($n = 31$), the temporal lobe ($n = 17$), the parietal lobe ($n = 25$), the occipital lobe ($n = 11$), the thalamus ($n = 4$), putamen ($n = 10$), globus pallidus ($n = 9$), caudate nucleus ($n = 14$), and internal capsule ($n = 10$). For the entire sample, the highest frequency of damage was in the frontal lobe. In fact, 93.9% ($n = 31$) of the CVA and silent group had sustained some type of frontal lobe injury. A series of chi-square analyses was performed to determine whether there were differences among the three MRI groups (without CNS pathology, silent infarcts, and overt CVAs). The results of the frequencies between the three groups revealed differences between all of the areas, with the exception of the thalamus. The highest frequency of impairments was found for children in the overt CVA group followed by the silent infarct group. The frequencies and chi-square analyses of the various areas of impairment are presented in Table III. Finally, to determine whether the children who evidenced frontal lobe impairment as documented by MRI performed more poorly than the children who did not evidence frontal lobe impairments on the measures of attention and concentration that previously had been found to be significant, a series of $t$ tests was performed on the Trail Making B time score, the Cancellation A’s Omission error score, and the Cancellation A’s Commission score. The results of these analyses revealed that the children with documented frontal lobe impairment performed more poorly on both the Cancellation A’s Omission, ($t[48] = -2.41$, $p < .02$; $M_{\text{Frontal Lobe Impairment}} = 5.84$, $SD = 7.93$, $M_{\text{Nonfrontal Lobe Impairment}} = 1.72$, $SD = 3.23$) and the Commission error scores ($t[48] = -2.12$, $p < .04$; $M_{\text{Frontal Lobe Impairment}} = 5.28$, $SD = 6.95$, $M_{\text{Nonfrontal Lobe Impairment}} = 2.08$, $SD = 2.98$). No significant between group difference was found for the Trail Making B time score.

**Discussion**

Our study examined the neurocognitive functioning of children with SCD who had either CVAs or silent strokes. In addition, these two cohorts of chil-
children were compared to children with SCD with no evidence of CNS pathology as revealed on MRI. We incorporated specific assessments of neurocognitive functioning, including measures of attention and executive functioning, language, and adaptive competence. We also measured more global indices of cognitive functioning such as general intelligence and academic achievement. Children with documented clinical strokes performed more poorly than their peers on tasks requiring sustained attention and effort or on tasks that were associated with frontal lobe involvement. In the area of attention, children who showed silent strokes on the MRI also showed similar impairments as their peers who sustained overt strokes. Finally, MRI scans revealed a high frequency of frontal lobe deficits in children who sustained CVAs.

These data extend the findings of Armstrong and associates (1996), who found evidence of general deficits in intellectual functioning and academic performance in children with SCD who had CVAs and silent infarcts. Our investigation suggests...
that children with SCD and either clinical strokes or silent infarcts show attention problems, as assessed by traditional neuropsychological measures. In fact, our findings are in accord with those of several investigators (Brown, Buchanan, et al., 1993; Cohen et al., 1997; DeBaun et al., 1998; Schatz et al., 1999), who have provided strong evidence that cognitive measures of attention and concentration are the most useful indices to identify children with possible cerebral infarcts. This is helpful in identifying children who should be serious candidates for further radiologic evaluation. In support of this notion, DeBaun et al. (1998) concluded that screening measures of attention and executive functioning are valuable in the identification of children and adolescents with SCD in whom CNS involvement is suspected.

Of interest is the finding that the highest frequency of functional impairments on the MRI revealed overt infarcts in the frontal lobe. These data are consistent with those of Rodgers et al. (1984), who found evidence of altered metabolism in the frontal lobe area of adult patients with SCD as indicated on PET scans. Our findings are coupled with other findings of impairments in the area of attention and concentration, neurocognitive processes that traditionally have been associated with frontal lobe functioning (Boliek & Obrzut, 1997; Shue & Douglas, 1992). The data in our investigation and other studies (Brown, Buchanan, et al., 1993; Cohen et al., 1997; DeBaun et al., 1998; Schatz et al., 1999) underscore the importance of the assessment and identification of problems associated with attention, concentration, and executive functioning in children with SCD who are suspected of having CNS involvement. As Schatz et al. (1999) observed, in case studies of individuals with frontal lobe injuries, global tests of intellectual and academic functioning do not adequately identify frontal lobe deficits. Although such assessments are important, they may in fact underestimate the extent of cognitive impairments for children with documented frontal lobe involvement. Given that alternatives to neuropsychological assessments require sedation for younger children, are quite costly, and are inconvenient for families, the identification of neurological impairments through cognitive screening appears to be a practical means of selecting children who are candidates for more extensive medical evaluation.

In contrast to the CSSSCD findings (Armstrong et al., 1996) and other studies (for review see, Brown, Armstrong, & Eckman, 1993; Brown, Doepke, & Kaslow, 1993), our investigation did not provide any evidence for statistically significant global deficits in mental abilities, academic achievement, or visual-motor functioning, although the children in the CVA group performed more poorly than the children in the other groups. The absence of evidence is surprising, and we offer three possible explanations. First, the relatively low power offered by this type of clinical study could have muted effects that may have been significant in a larger sample. Second, significant variability across most of the measures in each of the domain areas and error variance may have diminished the possibility of significant effects that also may have occurred with a larger sample. Third, the more compelling explanation is related to the fact that all of the patients were specifically referred to this study because of longstanding histories of academic difficulties, delays in cognitive development, and evidence of a clinical stroke; nearly 40% of the sample was receiving special education services, including those children designated without CNS pathology. In fact, one third of the group designated with no MRI pathology was receiving special education services. Thus, the relatively low scores for the group designated without CNS pathology may have produced “floor” effects that diminished the possibility of significance, especially on global measures of functioning such as intelligence and academic achievement. For example, the mean FSIQ for the CVA and silent stroke group in our study was similar to the means reported by Armstrong et al. (1996), but the mean FSIQ for the children without CNS pathology in our

<table>
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<th>Table III. Frequencies of Damage as Revealed on MRI</th>
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<td>Group membership</td>
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There were no areas of damage in any of the 30 members of the normal group; 93.9% (n = 31/33) of all CVA and Silent groups had frontal lobe involvement.
controls will bring the problems of these children into sharper focus. Finally, the children designated without CNS pathology on the MRI exams included children who also had HbSc disease who were not represented in the other groups (i.e., CVA group and silent infarct group). Because no differences were found on any of the neurocognitive measures between the children having HbSS and HbSC disease within the group designated without CNS pathology (i.e., normal group), the presence of children with HbSC and HbSS disease in this group is not likely confounded.

Despite these limitations, our results underscore the importance of using tests that measure attention and concentration in the assessment of children with SCD, particularly for children who have sustained overt strokes or silent infarcts. Future research will need to identify the mechanisms underlying frontal lobe deficits for children who have sustained infarcts. Recently, Schatz et al. (1999) provided important preliminary data that both the specific region of the brain is affected and the total volume of cerebral injury influence cognitive functioning. Examining both the location and volume of cerebral infarction is a good direction for further investigation. Finally, the data in our study and the findings of other investigations (Brown, Buchanan, et al., 1993; Schatz et al., 1999) provide some preliminary foundation for the management and rehabilitation of these children, particularly in the educational environment. Given the pervasiveness of attention problems in children with SCD, psychological and medical interventions designed to enhance attention and concentration represent a promising area for future research. Hopefully, such interventions will enhance the quality of life for these children as they struggle with the associated cognitive morbidities presented by this lifelong disease.

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