Developmental Function in Toddlers With Sickle Cell Anemia

**WHAT'S KNOWN ON THIS SUBJECT:** Children with sickle cell anemia are at risk of central nervous system damage, including stroke. Even children without evidence of abnormality on neuroimaging are at risk of significant declines in neurocognitive function, starting at early ages.

**WHAT THIS STUDY ADDS:** This study adds the observation that poorer neurocognitive and behavioral function is associated with older age in infants and toddlers with sickle cell anemia, much earlier than previously expected.

**abstract**

**BACKGROUND:** Neurocognitive impairment occurs in children and adults with sickle cell anemia, but little is known about neurodevelopment in very young children. We examined the neurodevelopmental status of infants participating in the Pediatric Hydroxyurea Phase III Clinical Trial (Baby Hug) to determine relationships with age, cerebral blood flow velocity, and hemoglobin concentration.

**METHODS:** Standardized measures of infant neurodevelopment were administered to 193 infants with hemoglobin SS or hemoglobin S-β0 thalassemia between 7 and 18 months of age at the time of their baseline evaluation. Associations between neurodevelopmental scores and age, family income, parent education, hemoglobin concentration, and transcranial Doppler velocity were examined.

**RESULTS:** Mean functioning on the baseline neurodevelopment scales was in the average range. There were no mental development scores <70 (impaired); 22 children had scores in the clinically significant range, 11 with impaired psychomotor scores and 11 with problematic behavior rating scores. Significantly poorer performance was observed with older age at baseline. Behavior rating scores were an average of 2.82 percentile points lower per month of age, with similar patterns observed with parent report using adaptive behavior scales. Parent-reported functional abilities and hemoglobin were negatively associated with higher transcranial Doppler velocities.

**CONCLUSIONS:** Whereas overall functioning was in the normal range, behavioral and adaptive function was poorer with older age, even in this very young group of children. Explanatory mechanisms for this association between poorer developmental function and older age need to be identified. *Pediatrics* 2013;131:e406–e414

**AUTHORS:** F. Daniel Armstrong, PhD,a T. David Elkin, PhD,a R. Clark Brown, MD, PhD,b Penny Glass, PhD,d Sohail Rana, MD,e James F. Casella, MD,a Ram V. Kalpatthi, MD,e Steven Pavlakis, MD,a Zhibao Mi, MD, PhD,b and Winfred C. Wang, MDf for the Baby Hug Investigators

aDepartment of Pediatrics, University of Miami Miller School of Medicine and Holtz Children’s Hospital at University of Miami/Jackson Memorial Medical Center, Miami, Florida; bDepartment of Psychiatry and Human Behavior, University of Mississippi School of Medicine, Jackson, Mississippi; cDepartment of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; dDepartment of Pediatrics, Children’s National Medical Center, Washington, District of Columbia; eDepartment of Pediatrics, Howard University College of Medicine, Washington, District of Columbia; and fDepartment of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

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**ABBREVIATIONS**

BSID—Bayley Scales of Infant Development, second edition

BRS—Behavior Rating Scale

CNS—central nervous system

HbSS—hemoglobin SS

MDI—Mental Developmental Index

MRA—magnetic resonance angiography

PDI—Psychomotor Development Index

SCT—silent cerebral infarct

TCD—transcranial Doppler ultrasonography

VABS—Vineland Adaptive Behavior Scales

**KEY WORDS**

sickle cell disease, cognitive development, transcranial Doppler, Bayley Scales, toddlers

The trial has been registered at www.clinicaltrials.gov (identifier NCT00006400).

Dr Mi’s current affiliation is VA Cooperative Studies Program, Perry Point, Maryland.

Drs Armstrong, Elkin, Brown, Glass, Rana, Casella, Kalpatthi, Pavlakis, Mi, and Wang made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of the data; contributed to drafting and revising the article for critical intellectual content; and approved the final version of the article submitted for publication review.

There were many others who contributed to this study but who did not meet the criteria for authorship. These individuals are included in the Acknowledgements.

(Continued on last page)
The central nervous system (CNS) is a major target for ischemic damage in individuals with sickle cell disease. Between 22% and 40% of children with sickle cell anemia (SCA; hemoglobin SS [HbSS] and hemoglobin S-β thalassemia) will experience a clinically evident stroke or a more subtle infarct seen on neuroimaging (silent cerebral infarct [SCI]), before age 15 years. Neurocognitive impairment, particularly in the functional domains of executive function (processing speed, memory, attention and concentration, visual processing, and visual-motor integration), is associated with both silent and overt stroke. Neurocognitive impairment can occur in the absence of overt or silent stroke; however, the exact timing, magnitude, and frequency of these deficits are not known. Because the most rapid growth of brain occurs during the prenatal period and first 2 years after birth, damage to the brain can occur during infancy and the toddler years but not be detected functionally until much later. In addition, elevated stroke risk associated with higher cerebral vascular flow rates detected by transcranial Doppler ultrasonography (TCD) is also associated with poorer neurocognitive function.

Changes in the CNS white and gray matter and cerebral blood vessels do not fully account for the range of neurocognitive impairment in children with SCA. The Cooperative Study of Sickle Cell Disease, a multicenter natural history study of children followed from birth through adolescence, reported that neurocognitive function was ~1 SD lower over the period between 6 and 16 years of age in a subgroup of children with SCA who had no evidence of abnormality on brain MRI. This suggested that other mechanisms besides stroke may contribute to a broader range of risk for neurocognitive impairment for children with SCA than previously considered. One potential mechanism may be chronic anemia, which was found to be associated with below-average nonverbal function in 33% of neurologically intact adults with SCA.

Investigations of early neurodevelopmental function in infants and toddlers with SCA have yielded mixed results. No significant impairment was found in infants screened by using the Denver Developmental Screening Test, although there was a trend for older children to have more questionable and abnormal performance. Another prospective study in infants with SCA evaluated by using the Bayley Scales of Infant Development at ages 6, 12, 24, and 36 months of age reported a significant decline in function on cognitive (Mental Developmental Index [MDI]) but not psychomotor (Psychomotor Development Index [PDI]) function. The decline was most evident between 12 and 24 months of age. In a recent report from the BABY HUG trial in 23 children aged 10 to 18 months (mean = 13.7 months) who completed baseline MRI/ magnetic resonance angiography (MRA) of the brain, 3 had evidence of silent infarcts that were associated with increased TCD flow velocity (time-averaged mean maximum [TAMM]) and low hemoglobin F concentrations, but not with older age or impaired developmental function. These same children represent a subset of this report. Although few in number, these studies suggest that CNS and neurodevelopmental risks are present for very young children with SCA.

In 2003, in a randomized, double-blind, multicenter, placebo-controlled clinical trial of hydroxyurea (Baby Hug), screening of infants with SCA between the ages of 7 and 18 months of age at time of enrollment was initiated. The primary endpoints of the 2-year trial were preservation of spleen and renal function, with neurodevelopmental safety and secondary efficacy endpoint. As part of eligibility determination before randomization on the trial, neurodevelopmental screening, TCD velocity measurement, and neurologic examination were performed. Early in the trial, MRI/MRA neuroimaging was required, but this was discontinued because of safety concerns related to sedation. This report describes baseline neurodevelopmental status of the children screened for participation in BABY HUG and its relationship to increasing age at the time of screening, TCD TAMM velocity, and anemia.

METHODS

The BABY HUG protocol was approved by the local Institutional Review Boards of 14 participating clinical centers. Infants with HbSS or HbS-β thalassemia between 7 and 18 months of age were identified for possible participation in the Baby Hug trial, and informed consent was obtained from their parents or guardians. The trial is registered with clinicaltrials.gov (identifier NCT00006400), although this report includes only baseline data obtained before randomization.

Screening to determine study eligibility included, but was not limited to, collection of blood and urine samples, demographic data, physical and neurologic examinations, TCD ultrasonography of the major vessels of the brain, and assessment of neurodevelopmental function. The Bayley Scales of Infant Development, second edition (BSID-II), was administered by a psychologist, trained psychometrician, or psychology fellow under the supervision of the local center psychologist. Parents were interviewed about their children’s adaptive behavior with the use of the Survey Edition of the Vineland Adaptive Behavior Scales (VABS), a standardized, age-normed measure of adaptive function. Examinations were primarily administered in English. Infants were...
included if a translator in their non-English, native language was available to assist the examiner in providing prompts and determining accuracy of verbal responses in the infant’s native language. Age corrections for prematurity were made through 12 months of age.

Neurodevelopmental Measures

**BSID-II**

The BSID-II is an examiner-administered measure of infant development in the areas of mental abilities (MDI), motor abilities (PDI), and behavioral adaptation (Behavior Rating Scale [BRS]). Basal and ceiling performance for the MDI and PDI were obtained, and standardized scores, with a mean of 100 and SD of 15, were determined on the basis of a child’s performance relative to population norms for the age of the child at the time of testing. The BRS (expressed as a percentile, with scores below the 10th percentile considered clinically significant) represents a summary of the examiner’s observations of the child during administration of the MDI and PDI. The total behavior raw score is converted to percentile rank according to population norms, on the basis of the child’s age (6–12 months or 13–42 months). The BSID-II represented the “gold standard” of assessment of infant neurodevelopment at the time the BABY HUG screenings took place.

**VABS**

The VABS is a parent interview measure that obtains a parent report of their child’s adaptive behavior from age 1 month through adolescence. Parents are asked to indicate whether their child always (2), sometimes (1), or never (0) demonstrates age-normed adaptive behaviors. Scores standardized for age with a mean of 100 and SD of 15 were obtained for the functional areas of Daily Living, Communication, Social, and Motor Function.

Data Management and Analyses

The BSID-II and VABS were scored at the local centers, then sent to the coordinating center by using electronic data capture in which the raw data were entered into a scoring program. Discrepancies between local scoring and central scoring were reviewed and resolved for accuracy.

Scatterplots were used to show the bivariate relationships of the continuous variables. Spearman’s correlation coefficients and the corresponding $P$ values were used to measure the strength and statistical significance of the correlations. A generalized linear mixed model with robust variance estimates was used to test these associations of neuropsychological functions with demographic characteristics and clinical factors. The clinical and demographic factors were considered as independent variables to determine associations in the model with the outcomes. First, single explanatory variables were used for single-level or single-factor analyses, and then multiple explanatory variables were used as multiple factors to control for confounding effects. The analysis was performed by using SAS version 9.13 (SAS Institute Inc, Cary, NC).

**RESULTS**

**Subject Characteristics**

There were 208 infants who received consent for screening, including 90 males and 118 females, with ages ranging from 7 to 18 months (mean age = 12.7 ± 2.7 months). Most of the infants had HbSS ($n = 201$) and were African American ($n = 200$). Almost 40% of the 198 families who provided income information had annual income of <$20,000; however, functional impact varied by state and urban versus rural location. Most of the primary caregivers had earned a high school degree or the equivalent or postsecondary education beyond high school (84.5%) (Table 1).

Of the 208 potential participants, 1 was excluded because of an MDI <70 and 14 were excluded for other reasons related to study inclusion and exclusion criteria. BSID-II evaluations were completed for 193 infants who were randomly assigned in the subsequent clinical trial. Scores were in the average range (standard score between 85 and 115) for the BSID-II MDI and PDI, VABS Communication, Daily Living, Socialization, and Motor Skills scales, and (>10th percentile) for the BSID-II BRS. None of the participants had an MDI in the impaired (<70) range, but 11 had PDI scores in the impaired (<70) range, and 11 others had BRS scores lower than the 10th percentile (clinically significant). There was no overlap between the 11 with impaired PDI scores and the 11 with BRS scores <10th percentile (Table 2).

**TABLE 1** Demographic characteristics

<table>
<thead>
<tr>
<th>Variables and Definitions</th>
<th>$n$</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell genotype</td>
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<td></td>
</tr>
<tr>
<td>HbSS</td>
<td>201</td>
<td>96.6</td>
</tr>
<tr>
<td>HbSβ° thal</td>
<td>7</td>
<td>3.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90</td>
<td>43.3</td>
</tr>
<tr>
<td>Female</td>
<td>118</td>
<td>56.7</td>
</tr>
<tr>
<td>Primary caregiver’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not complete high</td>
<td>32</td>
<td>15.5</td>
</tr>
<tr>
<td>school</td>
<td>127</td>
<td>61.3</td>
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<tr>
<td>High school or</td>
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<td></td>
</tr>
<tr>
<td>associate’s degree</td>
<td>30</td>
<td>14.5</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>18</td>
<td>8.7</td>
</tr>
<tr>
<td>Postgraduate degree</td>
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<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20,000</td>
<td>79</td>
<td>39.9</td>
</tr>
<tr>
<td>$20,000–$39,999</td>
<td>49</td>
<td>24.8</td>
</tr>
<tr>
<td>$40,000–$79,999</td>
<td>48</td>
<td>24.2</td>
</tr>
<tr>
<td>$80,000–$149,999</td>
<td>16</td>
<td>8.1</td>
</tr>
<tr>
<td>≥$150,000</td>
<td>6</td>
<td>3.0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 mo</td>
<td>37</td>
<td>17.8</td>
</tr>
<tr>
<td>10–12 mo</td>
<td>79</td>
<td>38.0</td>
</tr>
<tr>
<td>13–16 mo</td>
<td>60</td>
<td>28.9</td>
</tr>
<tr>
<td>&gt;16 mo</td>
<td>32</td>
<td>15.3</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
</tr>
<tr>
<td>African American</td>
<td>200</td>
<td>96.2</td>
</tr>
<tr>
<td>Non-African American</td>
<td>8</td>
<td>3.8</td>
</tr>
</tbody>
</table>

HbSβ° thal, hemoglobin S β° thalassemia.
For the 185 infants who completed TCD exams, TAMM, hemoglobin, and reticulocyte counts have been previously reported, with moderate correlation between TAMM velocities and age and hemoglobin concentration. The mean time between complete blood count and completion of the neurodevelopmental tests and parent report measures was 17 days (median = 10 days).

**Bivariate Correlations**

Among the BSID-II and VABS scores, only the behavior and the motor PDI scores were uncorrelated with other baseline clinical and demographic variables. The remaining BSID-II and VABS scores were significantly correlated with ≥1 of the independent variables. Significant negative correlations were found between the BSID-II BRS percentile with age ($r = -.24$) and reticulocyte count/100 ($r = -.15$), such that the mean BRS was 2.82 lower for each month of incremental age between 7 and 18 months of age at study entry (Fig 1). The associations between MDI and age ($r = -.14$) and PDI and age ($r = .003$) were nonsignificant. Similarly, significant moderate negative relationships were found between age and the Communication Domain ($r = -.33$), Daily Living Domain ($r = -.40$), and Socialization Domain ($r = -.19$) of the VABS. A significant positive correlation was found for age and the Motor Skills Domain ($r = .24$) (Fig 2).

TAMM velocity was not significantly associated with any of the scales of the BSID-II (MDI: $r = -.07$; PDI: $r = -.04$) but was significantly inversely correlated with the Communications Domain ($r = -.24$), Daily Living Skills ($r = -.15$), and Socialization Domain ($r = -.18$) of the VABS. In each case, lower adaptive function scores were associated with higher TCD TAMM velocity, even for TAMM velocities in the normal range (Fig 3).

<table>
<thead>
<tr>
<th>TABLE 2 Neur...</th>
<th>Classification, n (%)</th>
<th>Classification, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables Mean ± SD</td>
<td>&lt;70, ≤10th Percentile</td>
<td>70–84, 10th–29th Percentile</td>
</tr>
<tr>
<td>BSID-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental MDI</td>
<td>96.6 ± 9.8</td>
<td>0</td>
</tr>
<tr>
<td>Motor PDI</td>
<td>96.9 ± 13.7</td>
<td>11 (5.7)</td>
</tr>
<tr>
<td>Behavior, BRS percentile</td>
<td>63.7 ± 30.9</td>
<td>11 (5.7)</td>
</tr>
<tr>
<td>VABS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>102.8 ± 10.3</td>
<td>0</td>
</tr>
<tr>
<td>Daily Living Skills</td>
<td>107.9 ± 11.1</td>
<td>0</td>
</tr>
<tr>
<td>Socialization</td>
<td>106.4 ± 9.6</td>
<td>0</td>
</tr>
<tr>
<td>Motor Skills</td>
<td>101.1 ± 8.8</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on standard scores: mean = 100, SD=15; average or better, ≥85; impaired <70.

* Based on percentile scores: average, ≥30th percentile; clinically significant, <10th percentile.

**FIGURE 1**
Scatterplot of BSID-II BRS percentile with age and reticulocyte count/100.

**FIGURE 2**
Scatterplot of BSID-II BRS percentile with age and reticulocyte count/100.

$\text{BSID-II}
\begin{align*}
\text{Mental MDI} & \; 96.6 \pm 9.8 \\
\text{Motor PDI} & \; 96.9 \pm 13.7 \\
\text{Behavior, BRS percentile} & \; 63.7 \pm 30.9 \\
\end{align*}
\begin{align*}
\text{VABS} & \\
\text{Communication} & \; 102.8 \pm 10.3 \\
\text{Daily Living Skills} & \; 107.9 \pm 11.1 \\
\text{Socialization} & \; 106.4 \pm 9.6 \\
\text{Motor Skills} & \; 101.1 \pm 8.8 \\
\end{align*}$
Categorical Analysis of Variance

Children were grouped into 4 age categories (≤10 months, 10–12 months, 13–16 months, and >16 months), and scores on the MDI, PDI, and BRS were compared by using analysis of variance. Age-group differences were significant for each of the measures (MDI, \( P < .0001 \); PDI, \( P = .0291 \); BRS, \( P = .0102 \)). Scores for the MDI and PDI for the 13- to 16-month olds were higher than for the 2 younger groups but were lower for the >16-month group. BRS scores were consecutively lower for each age group with increasing age (Table 3).

Hierarchical Multiple Regression Analysis

Hierarchical multiple regression analyses using family income and maternal education, with stepwise entry of hemoglobin, reticulocyte count, TCD TMM, and age, were used to determine the independent and combined contributions for the MDI, PDI, and BRS. Resulting models found significant effects for primary caregiver education for MDI (\( P = .011 \)), family income for MDI (\( P = .0003 \)) and PDI (\( P = .0332 \)), and age for the BRS (\( P = .0006 \)) (Table 4).

Multivariate Analyses

Multivariate analysis was performed by using a generalized linear mixed model. Each normalized score from 7 BSID-II and VABS subscale scores served as a dependent variable for the analysis. Family income, primary caregiver’s educational level, and infant age, hemoglobin concentration, TMM velocity, and reticulocyte count were the independent variables. For each BSID-II and VABS score, infant age and family income showed negative associations (−.72 and −2.11, respectively) with the dependent variable (Table 5).
DISCUSSION

Overall, we found that infants with SCA between 7 and 18 months of age were functioning in the average range when compared with population norms. Similarly, as we have previously reported for this same group of study participants, cerebral blood flow velocities were mostly within the normal range. None of the infants had mental abilities (MDI) in the impaired range (this was an exclusion criterion for participation), but 22 had either psychomotor development or behavior rating scores considered clinically significant (11 with PDI scores in the impaired range and 11 with BRS scores in the clinically significant range). Most lived in homes with family incomes above the federal poverty level and had parents who had completed high school or had post–high school education.

Given these positive indicators, it was concerning to see that the BRS on the BSID-II and the Communication, Daily Living, and Socialization Domains on the VABS were negatively associated with age. Of note, the BRS rating was, on average, 2.82 percentile points lower with each month of older age between 7 and 18 months of age at time of screening. Hemoglobin concentration was not associated with either BSID-II or VABS scales, but TAMM velocities were associated with lower VABS Communication and Socialization scores.

In the hierarchical multivariate regression analysis, where the indexes of

TABLE 3 BSID Scores by Categorical Age Group

<table>
<thead>
<tr>
<th>Age Category</th>
<th>MDI</th>
<th>PDI</th>
<th>BRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 mo (n = 32)</td>
<td>99 (8.3)</td>
<td>95 (12.6)</td>
<td>77 (25.2)</td>
</tr>
<tr>
<td>10–12 mo (n = 75)</td>
<td>95 (8.9)</td>
<td>96 (13.1)</td>
<td>68 (30.1)</td>
</tr>
<tr>
<td>13–16 mo (n = 55)</td>
<td>100 (9.9)</td>
<td>101 (14.2)</td>
<td>60 (31.4)</td>
</tr>
<tr>
<td>≥16 mo (n = 31)</td>
<td>91 (10.1)</td>
<td>94 (13.5)</td>
<td>52 (32.9)</td>
</tr>
</tbody>
</table>

Data are presented as means (SD).

*P < .0001.
*P = .0291.
*P = .0102.
TABLE 4 Hierarchical Multivariate Regression for MDI, PDI, and BRS Using Demographic and Hematologic Independent Variables

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>P</th>
<th>Effect</th>
<th>Estimate</th>
<th>P</th>
<th>Effect</th>
<th>Estimate</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>110.75</td>
<td>&lt;0.0001</td>
<td>89.58</td>
<td>&lt;0.0001</td>
<td>100.06</td>
<td>0.0013</td>
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<tr>
<td>Primary caregiver education</td>
<td>2.53</td>
<td>0.0204</td>
<td>1.90</td>
<td>0.2332</td>
<td>1.52</td>
<td>0.6614</td>
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<tr>
<td>Family income</td>
<td>-2.79</td>
<td>0.0004</td>
<td>-2.52</td>
<td>0.0291</td>
<td>-1.52</td>
<td>0.3455</td>
<td></td>
</tr>
<tr>
<td>Age (mo)</td>
<td>-0.59</td>
<td>0.1602</td>
<td>0.28</td>
<td>0.1602</td>
<td>-2.60</td>
<td>0.0046</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>-0.71</td>
<td>0.2738</td>
<td>0.65</td>
<td>0.4599</td>
<td>0.07</td>
<td>0.8709</td>
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<tr>
<td>TCD TAMM (cm/s)</td>
<td>0.0035</td>
<td>0.9520</td>
<td>-0.001</td>
<td>0.9864</td>
<td>0.018</td>
<td>0.8781</td>
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</tr>
<tr>
<td>Reticulocyte count/100</td>
<td>-0.01</td>
<td>0.1709</td>
<td>-0.003</td>
<td>0.7570</td>
<td>-0.02</td>
<td>0.3253</td>
<td></td>
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</table>

TABLE 5 Mixed Model (With BSID-II and VABS Scores as Dependent Variables)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>109.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (mo)</td>
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<td>0.0057</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.0877</td>
<td>0.9054</td>
</tr>
<tr>
<td>TCD TAMM (cm/s)</td>
<td>-0.0158</td>
<td>0.6255</td>
</tr>
<tr>
<td>Family income</td>
<td>-2.1094</td>
<td>0.0023</td>
</tr>
<tr>
<td>Primary caregiver education</td>
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<td>0.1227</td>
</tr>
<tr>
<td>Reticulocyte count/100</td>
<td>-0.4025</td>
<td>0.5392</td>
</tr>
</tbody>
</table>

The BSID-II and VABS scores were considered as outcome variables, primary caregiver education was associated with MDI, family income was associated with MDI and PDI, and age was associated with BRS percentile. This association between MDI and primary caregiver education was expected because the MDI is heavily influenced by language development. When all variables of the BSID-II and VABS were entered in a mixed-model analysis, the contribution of primary caregiver education was no longer significant, but the associations between age and family income with the poorer function on the aggregate dependent variables remained robust. Other investigators have reported a decline in function, particularly between age 12 and 24 months, in children with sickle cell disease, and our cross-sectional findings support this observation. Because the median age of stroke occurrence has been reported to be as young as age 3 years, and 13% of a subset of the BABY HUG population who underwent MRI/MRA studies had silent infarcts, both lower neurodevelopmental function and higher TCD flow velocity with older age early in life are of particular clinical concern.

These results have several implications. Continued investigation into the mechanism for poorer neurocognitive function with older age in children with SCA is needed, because a number of potential and modifiable mechanisms may contribute to these outcomes. Neuroimaging was not performed for most of the participants in this study, but SCI risk was seen in the subset who did undergo MRI/MRA, which is consistent with other studies in children in this age group. As previously reported by the BABY HUG trial with a subset of this sample, whereas most of the children had TCD velocities in the normal range (defined by the normal range of the STOP trial), there was a trend toward greater flow velocity with older age. The association between higher reticulocyte count and poorer behavioral function suggests that additional hematologic or clinical factors may affect this outcome. Anemia may be associated with low-level chronic hypoxia, a mechanism that may contribute to significant neurocognitive impairment over time, or with perfusion insufficiency. A recent report on neurologically intact adults with SCA between 20 and 40 years of age found that 33% had nonverbal performance below the average range, and that this was significantly associated with older age and lower hemoglobin concentrations. Thus, the patterns seen in the BABY HUG infants may signal the onset of progressive, long-term difficulties that extend well into adulthood. Neurocognitive impairment in sickle cell disease has clearly been linked to infarction, but new investigations should focus on other mechanisms such as anemia and associated hemolysis and compromised nitric oxide availability.

These results point to the need for early identification and the development of interventional approaches. It is possible that hydroxyurea may be associated with improved neurocognitive development. Although the BABY HUG trial found no overall differences between infants treated with hydroxyurea and a placebo group, detailed analyses of the neurodevelopmental outcomes of the BABY HUG trial were not been completed at the time of this report, so this question is not yet answered. These data may also support reconsideration of the criteria currently considered for hematopoietic stem cell transplantation in children with SCA, although there is no published evidence indicating that hematopoietic stem cell transplantation at an early age would prevent neurologic decline.

At this time, a significant adverse event (eg, stroke, acute chest syndrome) is usually required for consideration of transplantation. Another option currently under investigation is chronic transfusion, which may improve neurodevelopment in children with SCI. The report of the BABY HUG clinical trial will provide important information about the course of neurodevelopment.
for children receiving treatment; this report provides information about early neurodevelopmental function before treatment and at a very early time in life. These results may lead to improved screening for risk. Consequently, because signs of risk for poorer neurodevelopmental function appear very early in life, interventions including hydroxyurea, transfusion therapy, and HCST should be evaluated for use shortly after the diagnosis of sickle hemoglobinopathy at a very early age.

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