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Developmental screening in pediatric sickle cell disease: Disease-related risk and screening outcomes in four year-olds

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Abstract

Objective—Studies of early child development in sickle cell disease (SCD) have found modest associations between disease-related risks and developmental status in infants and toddlers, but such associations are evident by early elementary school. We screened four-year-old children with SCD using two screening strategies to assess if biomedical risk factors for neurologic disease are related to developmental screening outcomes at this intermediate age.

Methods—Seventy-seven four-year-old children with SCD (M = 4.5 years, SD = 0.3 years) completed developmental screenings at routine hematology visits using child testing (Fluharty Preschool Speech and Language Screenings Test, 2nd edition) and parent-report (Ages and Stages Questionnaire, 2nd edition) procedures. Genotype and other biomedical variables were coded from medical records.

Results—Children with higher-risk SCD genotypes (n = 52) showed lower performance than children with lower-risk genotypes (n = 25) on a measure related to neurologic disease risk in older children (syntactic processing); genotype risk was also related to rates of positive screenings on parent-reported developmental milestones (52% positive screenings in high-risk genotypes *versus* 12% in low-risk genotypes). Screening outcomes were also related to transcranial Doppler ultrasound findings assessing cerebral blood flow.

Conclusions—Developmental screening at age four years may be a useful target age for identifying preschoolers with sickle cell-related neurodevelopmental concerns. Parent-report of developmental milestones and behavioral testing each may have a role in screening for children in need of follow-up services to address potential neurodevelopmental effects from SCD.

Keywords

sickle cell disease; child development; preschool children; neurodevelopmental disorders

Children with sickle cell disease (SCD) are at an elevated risk for neurocognitive deficits that impact quality of life, particularly in terms of school functioning.[1–3] The risks for

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neurocognitive deficits vary substantially by SCD genotype. For example, SCD-related morbidities such as silent cerebral infarction and sleep disordered breathing occur at significantly higher rates in children with higher-risk genotypes.[4–5] These and other sources of neurocognitive deficits occur in toddlers and preschool age children.[4–5] Early detection of neurocognitive deficits may be important for preventative interventions, yet the methods for how and when to begin assessing for these disease-related impacts are not known. The present study compares the use of two different approaches to developmental screening to detect disease-related developmental concerns in preschool age children.

Prior research provides limited information on what methods can best identify SCD-related neurocognitive concerns in early childhood. Studies of infants through three year-olds using the Bayley Scales of Infant Development to assess cognitive and motor development have indicated increasing age is associated with an increased risk for cognitive/developmental delays relative to general age norms.[6–7] However, the cognitive/developmental delays observed on the Bayley Scales have not been shown to be associated with known neurologic risk factors in SCD, such as genotype,[7–8] anemia severity,[6,8] or cerebral blood flow velocity from transcranial Doppler ultrasound (TCD).[6] Although one report has found associations between the Bayley behavior problems scale and anemia severity.[6] Other specific SCD morbidities have often not been included in the study analyses, which may be important given a report that delays on either Bayley mental or motor scores were related to severe pain episodes in young children with SCD.[8] Similar results to the Bayley scales have been reported with the Denver-II and Brigance screening tools, indicating no association between the neurologic risk factors examined (i.e., genotype, anemia severity, cerebral blood flow velocity) and developmental status with these measures in the first three years of life.[9–10]

Armstrong and colleagues examined scores from the Vineland Adaptive Behavior Scales in infants and toddlers and found bivariate associations with higher cerebral blood flow velocity from TCD correlating with lower parent-reported developmental scores on all scales except the Motor domain.[6] These associations were not statistically significant in multivariate models controlling for age, socioeconomic status, and anemia severity variables. Other studies with small samples have reported associations between cognitive or developmental measures and SCD-related biomedical risks in infants and toddlers (i.e., anemia severity, cerebral blood flow velocity); however, it is unclear why these associations are not more evident in studies using similar methods with larger samples.[6,9–14]

There is much less data available on the association of biomedical risks in SCD with cognitive/developmental functioning in older preschool age children. The only larger-scale study of children in this age range used the Denver-II screening tool and did not demonstrate an association between Denver-II results and SCD genotype in older preschoolers (36 – 60 months).[9] However, the validity of the Denver-II screening algorithm has been questioned.[15] Two studies examining preschool readiness scales in four-to-five year-olds found that children with SCD were at higher risk for positive screenings than non-SCD comparison children, but the specificity of these findings to neurologic risks was not determined.[16–17] Tarazi and colleagues examined short-term memory, visual-motor, language, and visual-spatial skills in a small sample of 3-, 4-, and 5-year-old children with a variety of SCD genotypes.[18] These data indicated a socioeconomic status measure was the best predictor of

cognitive functioning with no association between cognitive domains and SCD genotype, anemia severity, or frequency of medical symptoms.

One potential limitation of all of these studies is the use of a relatively broad measurement approach assessing many areas of cognition or development, which fails to focus on specific abilities more likely to be impacted by disease-related processes in SCD. For example, measures of processing speed, working memory, and other aspects of executive function may be more sensitive and specific to cerebrovascular impacts from SCD.[19] However, norm-referenced measures of these abilities for preschoolers are not widely available.

The goal of the current study was to evaluate if SCD-related neurodevelopmental risks could be identified in four-year-old children using a targeted, direct assessment approach versus a general, parent-reported approach to screening. Four years of age was chosen because it is intermediate between most studies showing modest-to-no association between developmental outcomes and neurologic risk factors in infants and toddlers and those showing more robust associations in elementary school age children.[19–20] For the targeted screening approach, we evaluated two constructs, a primary construct (syntactic processing) and a comparison construct (articulation). Syntactic processing has been shown to be related to SCD genotype risk (higher *versus* lower risk genotypes) and cerebrovascular risk (blood flow velocity in the middle cerebral artery) in kindergarten and first grade children with SCD.[20–21] We have speculated that syntactic processing demonstrates these associations with neurologic risk factors because it is highly dependent on working memory.[21] Articulation was assessed as a comparison construct (not expected to be related to SCD neurologic risks) that we find to be a common area of concern that parents express about their young children. For the general, parent-based approach, a developmental screening tool recommended for broad pediatric developmental screening was selected.[22]

We hypothesized that syntactic processing scores would be lower in children with higher-risk SCD genotypes than those with lower-risk genotypes. We also predicted that the targeted screening approach would show better sensitivity to genotype-risk than the broader, parent-report screening tool. Finally, we explored additional potential risk factors by examining screening outcomes in relation to other indicators of neurologic risk in SCD (i.e., blood flow velocity based on TCD results and history of a sleep apnea diagnosis).

Methods

Participants

The dataset for study analyses included 77 four-year-old children who completed developmental screenings as part of their routine care at a pediatric hematology specialty clinic in the Southeastern United States between January 2010 and December 2016 (see Table 1). Screenings were presented to parents as part of routine care for all children as recommended by The American Academy of Pediatrics and completed at the clinic either before or after the medical appointment. Medical chart reviews were initially conducted for 100 four-year-old children with SCD who participated in the developmental screening program; however, twenty-three cases had only one screening instrument. Twenty-one of these cases included only parent report due to time constraints or lack of cooperation by the

child with behavioral testing. In two cases, there was a lack of time and parents were primarily interested in child testing related to language development, so the Fluharty-2 was administered. Children who completed only one of the two screening procedures did not differ statistically from those completing both screening procedures in terms of age, gender, insurance status, rate of high- versus low-risk SCD genotypes, hospitalizations in the past year, or hemoglobin level from the routine blood draw the day of the screening. One-hundred thirty-two children with SCD fitting the age range for four-year-old screenings (ages 48–59 months) were seen for routine health maintenance visits during the study time frame. Most parents who refused the screening cited lack of time as the primary reason, though specific reasons for refusing the screening were not collected systematically.

Measures

Fluharty Preschool Speech and Language Screening Test, 2nd edition (Fluharty-2)—The Articulation, Repeating Sentences, and Describing Actions subtests of the Fluharty-2 were administered in that order to children following standardized procedures as described in the test manual.[23] The Articulation subtest assesses articulation and phonology. The Repeating Sentences and Describing Actions subtests were selected because they assess syntactic abilities; these two scores were combined to create a composite standardized score for this construct per the test manual. For four-year-olds the Articulation subtest and all composite scores show internal consistency reliability coefficients of alpha > . 80 for the general normative sample; subgroup analyses based on ethnicity or disability status showed similar reliability. The Fluharty-2 has scoring rules to accommodate African American Vernacular English (AAVE), including scoring related to phonology, verb tense, negation, and other grammatical characteristics such that responses consistent with the language rules for AAVE can also be given full credit. The developers have also evaluated differential item functioning, which showed minimal-to-no bias based on gender or ethnicity for validity coefficients.

Ages and Stages Questionnaire, 2nd edition (ASQ-2)—The ASQ-2 is a parent-reported developmental screening questionnaire for children ages 4 to 60 months based on parent report designed to identify children who may have developmental delays.[24] Parents rate whether the child demonstrates specific developmental milestones (“yes”, “sometimes”, “no”) in the domains of Communication, Gross Motor, Fine Motor, Problem Solving, and Personal-Social. Norm-referenced cut-off scores are used to identify positive screenings at the domain-level based on the total score for each domain. There are different forms based on chronological age of the child. The test publishers have reported excellent reliability (r > . 90) based on test-retest and inter-rater reliability. Convergent validity with developmental assessments has also been demonstrated with an overall agreement of 83%.

Medical Chart Review—Details of the patient’s demographic characteristics, routine blood lab data, history of disease complications, and developmental screening results were obtained through medical chart review using a medical chart coding sheet to provide a structured form for the review of electronic and paper medical charts. Inter-rater reliability using a second coder has indicated kappa values of .87 to 1.0 for the variables coded with a median kappa of .97. Information on age at screening, gender, race/ethnicity, and insurance

status were collected for demographic descriptors. Race/ethnicity codes from the medical records were based on U.S. census categories. Hemoglobin, white blood cell counts, and platelet counts were recorded from the routine blood lab data collected for the health maintenance visit. History of hospitalizations over the past year and prior treatment with therapeutic levels of hydroxyurea or chronic blood transfusion therapy was recorded. We also recorded whether children had a history of asthma or a history of either acute chest syndrome or hospitalization for pneumonia. Acute chest syndrome and pneumonia were combined as a single category due to the difficulties in differential diagnosis.

TCD exams were completed by all patients with higher-risk genotypes within the previous 12 months of the screening to assess for stroke risk. Outcomes of TCD exams were based on the STOP protocol method.[25] Abnormal exams are based on confirming an abnormal TCD screening with a second TCD exam. Occasionally, magnetic resonance angiography (MRA) was collected before the second TCD exam and chronic transfusion therapy to prevent stroke was started based on MRA results showing vessel occlusion. Two children with abnormal TCD exams had concurrently completed the developmental screening and were not yet on chronic transfusion therapy. One child with an abnormal TCD exam was not on transfusion therapy due to objections based on religious beliefs and was started on hydroxyurea therapy. As in a prior study, we recorded the higher velocity measure from either the left or right middle cerebral artery for the TCD exam closest to the date of the developmental screening as a continuous measure of cerebral blood flow velocity (M = 103 days; range 0 – 358 days).[19]

All children receive screenings for sleep apnea as part of routine hematologic health maintenance visits and children with positive screening results were referred for overnight polysomnography at a dedicated sleep lab (n = 11). The outcome of the overnight polysomnography exam was recorded to identify history of known sleep apnea based on standardized methods.[26] Nine children had received structural brain MR exams to assess for cerebral infarction as part of their clinical care (seven with normal exams and two with silent cerebral infarction). Finally, information on the results of the developmental screenings were obtained, including raw and norm-based scores from the developmental screening instruments.

Procedures

Appropriate institutional board approval was obtained prior to medical chart review. After patients participated in a developmental screening, the first author reviewed the patients' electronic and paper charts to record study data as the primary coder.

Measures were collected as part of developmental screenings offered to parents for children at ages 24–35 months or 48–59 months. Screenings were performed in the context of the child's routine hematological health maintenance appointments. If the child was not feeling well that day (e.g., fever, pain), screenings were re-scheduled for the next appointment. Psychologists or doctoral-level psychology students with training in child and family assessment completed the screenings. Depending on parent preferences, screenings were conducted either before or after the child's physical examination by the hematologist. Children and their parents were accompanied by the psychology staff to the psychology

office located within the hematology clinic. Rapport building activities were done with the child (e.g., drawing with crayons) while the purpose and procedures were explained to the parent in more detail. A brief, semi-structured interview was also conducted with the parent to become more familiar with the child and their family. The ASQ-2 questionnaire was given to parents to complete while the psychology staff person administered the Fluharty-2 to the child. Parents were encouraged to complete items that they were confident they could rate and told to leave blank items they were unsure of how to rate. Following administration of the Fluharty-2, the psychology staff person would review the ASQ-2 with the parent to determine if there were any difficulties completing items. If parents were unsure of how to complete items, materials were provided to test the item with the child (e.g., given a pair of safety scissors and asked to cut paper). The screening measures were then scored and feedback about the results was provided to the parent. For the Fluharty-2, we consider scores more than 1.5 standard deviations below age norms as positive screening results.

If developmental concerns were present based on parent report or child testing, two follow-up procedures were used. First, parents were given tips sheets for developmentally appropriate activities to promote development in the area of concern and the types of activities were reviewed with the parent. Second, sources of appropriate developmental services were reviewed with the parent and information about these services and/or a direct referral was provided depending on parent preferences.

Data Analyses

The syntactic processing composite score from the Fluharty-2 was compared for lower-risk *versus* higher-risk SCD genotypes via an independent samples t-test to test our first hypothesis. For comparison purposes, we used a parallel independent samples t-test to evaluate the Articulation score from the Fluharty-2. We also compared outcomes on the ASQ-2 by genotype risk group using a chi-square test; the presence of any positive screening in any domain was used to indicate a positive screening result per standard interpretation of the ASQ-2. For descriptive tests of ASQ-2 outcomes for specific domains of the measure we used the Fisher Exact test due to <5 expected cases in some cells.

To evaluate our second hypothesis, we computed effect-size measurements (Cohen's *d*) for the above analyses with the expectation that the largest effect size would be for syntactic processing. For our exploratory analyses, we examined Pearson correlations, point biserial correlations, or phi coefficients (depending on the scaling of the variables) to assess for any relationships with TCD outcomes or history of sleep apnea among the children with high-risk genotypes. The low-risk genotype group was excluded from these analyses due to the absence of any variability in the neurologic risk measures within the group. Finally, to assess the specificity of any findings for neurologic risk factors, we used similar Pearson correlation, point biserial correlations, or phi coefficients to examine for associations between screening outcomes and demographic variables or other clinical history variables. Scatterplots were examined for all correlations involving continuous measures to rule-out the influence of outliers. The alpha level for each analysis was set at $p < .05$.

Results

For our first hypothesis, children with higher-risk genotypes showed lower scores for syntactic processing than children with lower-risk genotypes (see Table 2). Articulation scores did not differ statistically between these groups. Rates of positive screening tests with the ASQ-2 were statistically different between the genotype groups: There were higher rates of positive screens among children with higher-risk genotypes. Most of the difference in ASQ-2 outcomes was due to ratings in the Fine Motor domain, which was the only domain to differ in outcomes by genotype group. Contrary to our expectations, the ASQ-2 screening results showed the largest effect size for difference between genotype groups ($d = .83$), followed by the syntactic processing score ($d = .56$).

Given the unexpected effect size difference for the syntactic processing score in relation to the ASQ-2, we conducted *post hoc* analyses of the syntactic processing score using our cut-off score for a positive screening (> 1.5 standard deviations below age norms), rather than a continuous score, to assess how the cut-off score used in our screening program would have impacted outcomes. This approach showed better differentiation between low-risk and high-risk genotypes ($d = .74$; see Table 2), but the effect size was still not larger than for the ASQ-2. Screening outcomes for the ASQ-2 and Fluharty-2 syntactic processing measure showed only moderate convergence, $X^2(1, N = 77) = 25.93$, $p < .001$. Forty-one out of forty-seven children (87%) with negative screenings on the ASQ-2 had negative screenings on the Fluharty-2 syntactic processing measure and seventeen of thirty children (57%) with positive screenings on the ASQ-2 had positive screenings on the Fluharty-2 syntactic processing measure. There was similar overall convergence between positive outcomes for the Fine Motor domain and Fluharty-2 syntactic processing, $X^2(1, N = 77) = 16.32$, $p < .001$. Forty-seven out of fifty-eight children (81%) with negative screenings in the Fine Motor domain had negative screenings on the Fluharty-2 syntactic processing measure and thirteen of nineteen children (68%) with positive screenings in the Fine Motor domain had positive screenings on the Fluharty-2 syntactic processing measure.

Associations with neurologic risk, demographic, and other clinical variables are shown in Table 3. For the Fluharty-2 syntactic processing measure, there was a correlation between older child age and higher scores. In addition, a history of abnormal TCD exams or higher cerebral blood flow velocities in the MCA were associated with lower scores on the Fluharty-2 syntactic processing measure. Syntactic processing scores were higher among children with normal or conditional TCD exams ($n = 47$; M = 89.8, SD = 12.9) than children with abnormal TCD exams ($n = 5$; M = 76.0, SD = 10.6), $t(50) = 2.31$, $p = .025$. Follow-up analyses examining TCD velocities for only children with normal or conditional TCD results showed no association with syntactic processing scores ($r = -.04$, $p = .77$), suggesting the association occurred when stroke risk was elevated.

For syntactic processing scores *post hoc* follow-up analyses were run to assess whether co-varying age would impact the association with TCD variables. A simultaneous linear regression analysis was run with Fluharty-2 syntactic processing scores as the dependent variable and the independent variables were age and cerebral blood flow velocity in the MCA. The overall model was statistically significant, $F(2,49) = 5.88$, $p = .005$, $R^2 = .194$.

Both age, $t = 2.66$, $p = .01$, and cerebral blood flow velocity in the MCA, $t = -2.26$, $p = .03$, were uniquely associated with syntactic processing scores. A similar pattern was present using the normal/abnormal dichotomy for TCD outcomes as the dependent variable, $F(2,49) = 6.50$, $p = .003$, $R^2 = .210$, with age, $t = 2.65$, $p = .01$, and TCD outcome, $t = -2.49$, $p = .02$, uniquely associated with syntactic processing scores.

For the ASQ-2, a positive overall screening outcome or positive Fine Motor domain outcome were associated with a history of an abnormal TCD exam. Positive screenings for the Fine Motor domain were also associated with higher cerebral blood flow velocity in the MCA. Positive overall screening outcomes on the ASQ-2 were at a lower rate among children with normal or conditional TCD exams ($n = 22/47$; 47%) than children with abnormal TCD exams ($n = 5/5$; 100%), Fisher Exact $p = .003$. Positive Fine Motor domain outcomes were at a lower rate among children with normal or conditional TCD exams ($n = 13/47$; 28%) than children with abnormal TCD exams ($n = 5/5$; 100%), Fisher Exact $p = .03$. Children with negative Fine Motor domain outcomes had lower cerebral blood flow velocity in the MCA ($n = 47$; M = 145.0 cm/s, SD = 12.9) than those with positive Fine Motor domain outcomes, ($n = 5$; M = 167.9 cm/s, SD = 51.5), $t(50) = 2.24$, $p = .030$. Follow-up analyses examining TCD velocities for only children with normal or conditional TCD results showed no association with ASQ outcomes ($r = -.07$, $p = .64$ for overall screening; $r = -.06$, $p = .71$ for Fine Motor domain), suggesting the association occurred when stroke risk was elevated. Finally, although the overall rate of MR exams and known silent cerebral infarction was too low to consider statistical analyses, we noted that one child with known silent cerebral infarcts had positive screenings on all three measures (Fluharty-2 Syntax, Fluharty-2 Articulation, ASQ-2) and the second child only had a positive screening on the ASQ-2 (due to the Problem Solving domain).

Discussion

The present study examined two different screening strategies in four-year-old children to evaluate if assessing a key construct related to disease risks in older children (i.e., syntactic processing) would show the strongest association with genotype-risk as compared to a general developmental screening tool. Both screening approaches demonstrated that higher-risk genotypes showed more concerning screening outcomes. Counter to our hypothesis, the parent-reported, general developmental screening tool differentiated between the two genotype risk groups at least as well as our focused screening approach as reflected in the effect size measures examined. It is notable that our cut-off score (> 1.5 SD below age norms) used for syntactic processing scores in the screening program showed a stronger effect size than the continuous scores in relation to genotype risk groups. This indicates there is a subgroup among the children with higher-risk genotypes with lower scores driving the group difference in syntactic processing.

We also examined other variables that might explain differences in developmental status within the higher-risk genotype group. The results primarily indicated that performance on developmental screening measures was related to higher cerebral blood flow velocity, as measured by TCD, but not to other demographic or disease-related measures (e.g., insurance status, hospitalization rate, ACD history). The association between cerebral blood flow

velocity and syntactic processing replicates a previous study in kindergarten and first graders.[21] The magnitude of associations with cerebral blood flow observed in the present study is similar to those reported by Armstrong and colleagues for several Vineland Adaptive Behavior domains, which like the ASQ-2, are based on parent report. Although the multivariate models presented by Armstrong and colleagues did not include TCD velocities as significant predictors of Vineland scores, this may have been because they co-varied reticulocyte count in the statistical models, which has significant collinearity with TCD velocities.[27]

There are currently limited guidelines for the role of psychological and developmental testing in the routine health care of children with SCD. Hematology management guidelines indicate the importance of monitoring the child's development at least every 6 – 12 months as part of medical evaluations and also suggest clinicians consider formal neurocognitive testing for school-age children with school attendance and/or performance concerns.[28] Additional guidelines as to what types of developmental monitoring procedures are feasible and sensitive to developmental concerns in SCD would be helpful. The data from the current study, in conjunction with previous studies, suggest that formal developmental screening and/or assessment tools may be useful to integrate into routine hematological care given the high rate of developmental concerns identified. It is unclear how consistently developmental screenings occur for children with SCD as part of their primary pediatric care. In our experience parents usually report no memory of prior developmental screenings, which is consistent with national data on screening practices.[29] Formal screening procedures at four years of age, as focused on in this study, would align with the American Academy of Pediatrics recommendation for screening for school readiness at four years of age for all children.[22] In the U.S. the 2010 Patient Protection and Affordable Care Act only reimburses for developmental screenings as preventive services for children under three years of age, which could pose a barrier to providing screenings at four years of age in many clinic settings. Integrating screenings into hematological care may be important for identifying children with elevated risk for poor neurocognitive outcomes due to SCD and could also be used to address the broader recommendations for assessing school readiness at this age.

The question of what procedures are most useful for identifying children with SCD-related developmental concerns is unclear. We found statistically significant, but only moderate, convergence across the two screening approaches; this suggests each method provides unique information. It appeared that ASQ-2 results were largely driven by outcomes for the Fine Motor domain and that this domain showed a stronger association with TCD measures of neurologic risk than the overall ASQ-2 results. It is possible that our targeted screening strategy was overly narrow and that there are other critical areas of development that need to be included within a targeted screening strategy to improve the detection of sickle cell-related neurodevelopmental risk. It is also notable that the rate of positive screenings for children with high-risk genotypes was 42% for the Fluharty-2 syntactic processing measure and 52% for the ASQ-2, indicating that either approach in isolation may generate a significant rate of positive screenings among higher-risk genotypes. The current study was not designed to evaluate the rate of false positive or false negative screenings compared to a full developmental assessment, which is a limitation. However, the overall rate of positive

screenings is similar to the 46% rate of at-risk scores for three-year old children with SCD using the Mental Development Index of the Bayley Scales of Infant Development.[9]

Contrary to our expectations, the ASQ-2 may be at least as sensitive to disease-related risk factors as the Fluharty-2 based on our effect size measures. This is encouraging due to the ease of administration of the ASQ-2 compared to direct child behavioral measures, which may make such screening procedures more feasible in clinic settings with less psychosocial staff time. It is also possible that at this age parent-based measures need to be included in screenings due to the challenges in getting reliable data from direct child assessment. Alternately, parents in our study knew the medical history of their child at the time of the screening, whereas the examiner typically did not. It is possible that knowledge of their child's neurologic risks may have influenced responses on the parent-report measure, increasing the observed associations.

It is notable that there was nearly twice the rate of positive screenings on the Fluharty-2 than on the Communication domain of the ASQ-2, suggesting that the Fluharty-2 may be detecting language processing problems missed by the ASQ-2's language-related items. Child testing at this age, however, may have practical limitations. In addition to the staff time and training required, we found a positive correlation between age at testing and the syntactic processing measure, which was the last of the child testing measures administered. It is possible that older children within this age range are better able to sustain effort in this testing than the younger children; thus, we may have had error variance in our outcomes due to age-related differences in test-taking ability. It is notable that our observed association with age is most likely due to methodological factors as most studies have shown a negative correlation between age and positive screenings/assessments for developmental concerns.

There are other limitations that should be considered in interpreting the findings. This study was conducted at a single clinic and it is unclear how well the findings of this study may generalize to other contexts. For example, the screenings were conducted by psychology staff with doctoral-level training and we had access to convenient space within the clinic to minimize family burden in completing the procedures. Biomedical variables were collected through retrospective medical chart review and, despite high inter-rater agreement for our method, this poses limitations on the available data. For example, the null findings between a history of sleep apnea and developmental screening should be interpreted with caution as sleep studies were not collected systematically across patients. The findings relating abnormal TCD outcomes to developmental screenings was also based on a small number of children with abnormal TCD exams, which was to be expected given the base rate of abnormal exams at this age.[25] One should be cautious in considering the generalizability of such a finding given the small sample size. Finally, many studies of young children with SCD have found significant associations with social-environmental variables and developmental status.[6–7,10,12] The present study was not designed to assess these factors, which likely would have accounted for additional variance in the screening outcomes. Our use of insurance status as a proxy measure for socioeconomic status provided only a dichotomous variable, which would likely lessen the magnitude of any observed associations with the proxy measure.

Developmental screening for children with SCD in the preschool period has promise as a method to identify children at highest risk for SCD-related neurocognitive deficits and associated quality of life impacts. There are a range of intervention procedures that could be helpful to produce better outcomes for these children through cognitive remediation, environmental supports, or biomedical intervention.[30–32] The data from the present study suggest that we may be able to identify children with SCD-related neurocognitive deficits in the preschool period using brief developmental screening measures to allow for intervention planning prior to elementary school. Future work will need to replicate these findings and provide further guidance as to what screening procedures produce the necessary sensitivity and specificity to make good use of intervention resources. There is also limited guidance on how to best intervene based on positive screening results, though investigations of parent-based intervention approaches are actively being pursued.[33–34]

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Table 1

Descriptive Information for Study Sample.

Variable	Higher-risk genotypes (n = 52)	Lower-risk genotypes (n = 25)	Test statistic
Demographics			
Age (years)	4.5 ± 0.3	4.5 ± 0.3	$t(75) = 0.00$
Gender (M:F)	35 : 17	13 : 12	$X^2(1, N = 77) = 1.68$
Ethnicity (% African-American)	100%	100%	$X^2(1, N = 77) = 0.00$
Insurance Status			$X^2(1, N = 77) = 2.52$
- Medicaid only	43 (84%)	21 (84%)	
- Medicaid + Private	5 (10%)	4 (15%)	
- Private only	4 (8%)	0 (0%)	
Routine blood labs			
Hemoglobin (gr/dL)	8.3 ± 1.0	10.9 ± 0.7	$t(75) = 11.86^{**}$
White blood cells (k/uL)	13.9 ± 4.7	9.7 ± 4.1	$t(75) = -3.90^{**}$
Platelets (k/uL)	458.2 ± 160.5	297.0 ± 137.8	$t(75) = -4.31^{**}$
Clinical History			
Hospitalizations in past year (n)	1.1 ± 1.2	0.5 ± 0.7	$t(75) = -2.33^{*}$
Current hydroxyurea treatment (n)	13 (25%)	0 (0%)	*Fisher Exact p = .003***
History of asthma	4 (8%)	7 (28%)	*Fisher Exact p = .033**
History of ACS/pneumonia	22 (42%)	8 (32%)	*Fisher Exact p = .459*
Sleep apnea diagnosis (n)	6 (12%)	0 (0%)	*Fisher Exact p = .169*
Abnormal TCD exam^ (n)	5 (10%)	0 (0%)	*Fisher Exact p = .168*
Current chronic transfusion therapy (n)	2 (4%)	0 (0%)	*Fisher Exact p = .556*

Notes:

* $p < .05$;

** $p < .01$.

Continuous variables are presented as M ± SD. ACS = acute chest syndrome

Table 2

Screening Outcomes Measures according to Higher- *versus* Lower-risk Genotype Groups.

Screening tool	Higher-risk genotypes (n = 52)	Lower-risk genotypes (n = 25)	Test statistic
Fluharty-2 Syntactic Processing			
Standard Score (M ± SD)	88.5 ± 13.2	95.4 ± 10.4	$t(75) = 2.32^{*}$
> 1.5 S.D. below norms	n = 22 (42%)	n = 2 (8%)	*Fisher Exact p = .003***
Fluharty-2 Articulation			
Standard Score (M ± SD)	94.7 ± 11.8	98.7 ± 9.0	$t(75) = 1.48$
> 1.5 S.D. below norms	n = 6 (12%)	n = 2 (8%)	*Fisher Exact p = .716*
ASQ-2			
Any positive domain	n = 27 (52%)	n = 3 (12%)	*Fisher Exact p = .001***
- *Communication*	n = 12 (23%)	n = 3 (12%)	*Fisher Exact p = .360*
- *Gross Motor*	n = 8 (15%)	n = 2 (8%)	*Fisher Exact p = .485*
- *Fine Motor*	n = 18 (35%)	n = 1 (4%)	*Fisher Exact p = .004***
- *Problems Solving*	n = 7 (13%)	n = 1 (4%)	*Fisher Exact p = .263*
- *Personal-social*	n = 2 (4%)	n = 0 (0%)	*Fisher Exact p = .556*

Notes:

$^{*}p < .05$;

$^{**}p < .01$.

Overall rates of positive screening results across genotypes were 39% (30/77) for the ASQ-2 and 31% (24/77) for the Fluharty-2 Syntactic Processing score.

Table 3

Correlation Measures between Screening Results and Demographic/clinical Variables for Children with Higher-risk Genotypes ($n = 52$).

Independent variables	Dependent variables			
	Fluharty-2 Syntactic Processing Score	Fluharty-2 Articulation Score	ASQ-2 Overall Screening Outcome	ASQ-2 Fine Motor Domain Outcome
Demographics				
Age	.33*	.03	−.02	−.12
Gender	−.05	−.06	.10	−.07
Insurance status	.01	−.07	−.07	.06
Clinical variables				
Hospitalizations in past year	−.05	.06	.08	.05
Hydroxyurea therapy	.24	.16	−.07	.14
History of asthma	.12	.21	−.16	−.15
History of pneuomonia/ACS	.00	.19	−.03	.16
Sleep apnea diagnosis	.06	−.19	.11	.17
History of abnormal TCD	−.31*	−.18	.31*	.46**
Highest velocity in MCA	−.28*	−.16	.19	.30*

Notes: Data reflect Pearson correlations for tests between continuous variables, point biserial correlations for tests between dichotomous and continuous variables, and Phi coefficients for tests between dichotomous variables.

* = $p < .05$;

** = $p < .01$;

For gender, male = 0 and female = 1. For insurance status, 0 = Medicaid only and 1 = Private insurance with or without Medicaid. Hospitalizations in past year represents the number of hospital admissions in the 12 months prior to the screening. ACS = acute chest syndrome; TCD = transcranial Doppler ultrasound; MCA = middle cerebral artery. For the remaining clinical variables 0 = absent and 1 = present. ASQ-2 screening outcomes were coded as 0 = negative screen, 1 = positive screen.