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Neurocognitive Screening with the Brigance Preschool Screen-II in Three Year-Old Children with Sickle Cell Disease

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Abstract

Background—Neurocognitive deficits have been described in school age children with sickle cell disease (SCD), even in the absence of stroke or silent infarcts. However, the age of onset and factors contributing to this problem have not been well studied. We hypothesized that in children with SCD the failure rate with Brigance screening would be higher than in the normal population.

Methods—We reviewed retrospectively the Brigance Preschool Screen-II test results in three year-old children with SCD. Findings were correlated with hemoglobinopathy genotype, hemoglobin level, transcranial Doppler ultrasound (TCD) velocities, and treatment with hydroxyurea, as well as with psychosocial factors.

Results—Eighty-eight children with SCD followed by the St. Jude Sickle Cell Center (mean age 3.5 years) had neurocognitive screening during their regular clinic visits. Forty-four (50%) children had scores below the normal cut-off value for their age (twice the national failure rate of 25%). Failures were associated with less parental education ($p=0.005$ for maternal and $p=0.03$ for paternal education levels) and with speech deficits ($p=0.01$), but were not associated with sickle cell genotype or hemoglobin concentration.

Conclusion—These preliminary data suggest that psychosocial factors may have more profound effects on early childhood development than disease-related factors in this group of young sickle cell patients. A larger prospective study with appropriate controls is warranted to validate these findings, which have implications for the etiology and prevention of neurocognitive decline in children with SCD.

Keywords

sickle cell disease; preschool children; neurocognitive screening

Introduction

Central nervous system complications are among the most devastating manifestations of sickle cell disease (SCD) and include stroke, silent infarcts and neurocognitive deficits.

Strokes occur in 5-10% and silent infarcts in 17-23% of children with sickle cell anemia[1-5]. Both stroke and silent infarcts have been associated with significant neurocognitive deficits[6-12]. However, children with SCD who do not have any evidence of overt stroke or silent infarct also show consistently lower scores on general IQ measures, with the most common decrements found in attention and executive functioning[7,9,12,13]. The majority of studies involving neurocognitive testing of children with SCD have been performed in school-aged subjects[14-18]. However, there is increasing evidence that compromise of neurodevelopment begins before five years of age in children with SCD[19-24].

Our objective was to evaluate neurodevelopment in pre-school age children with SCD using a standard screening test and examine the relationship between scores and medical and socioeconomic variables. We performed a retrospective chart review of three year-old children with SCD who were evaluated with the Brigance Preschool Screen-II during their clinic visits at St. Jude Children's Research Hospital[25]. Our hypothesis was that the failure rate with Brigance screening in these young children with SCD would be higher than in the normal population. This report summarizes our findings.

Methods

Neurodevelopmental screening

The Brigance Screen was designed to be used by teachers, paraprofessionals, special educators, psychologists, physicians, occupational and physical therapists, and speech-language pathologists. We utilized The Brigance Preschool Screen-II in part for logistic considerations. The test can be administered and scored within 15-20 minutes, so it can easily be incorporated into a clinic visit. At the completion of testing, the results can be shared with the family immediately.

Children with SCD who were followed at St. Jude Children's Research Hospital regularly met with a teacher based in the SCD clinic at the time of a routine outpatient clinic visit, beginning at approximately 2.5 years of age. At this initial meeting, the teacher provided information on the Brigance screening test that would be performed after the child turned three years-old. At the first visit after the child turned three, the teacher administered the Brigance Preschool Screen-II.

All subjects were at their baseline status and were not experiencing a pain crisis or other acute illness at the time of testing. The evaluation was performed in a clinic room with the family in attendance. One parent or guardian usually filled out the Brigance Screening Background Information Form while the child was being examined. The parent was instructed not to give any verbal or non-verbal clues during testing. After completion of the screening test, the teacher collected the Background Information Form from the parent and left the room for about ten minutes to score the assessment. The teacher then returned to the clinic room to discuss the results with the parent/guardian. After explaining the significance of scores on the Data Sheet, the teacher made recommendations as indicated. In general, those children who scored below the cut-off for their age were referred to early intervention

programs such as Head Start as well as to the Department of Behavioral Medicine for more detailed neurocognitive testing.

Brigance Screening Tests

The screening tests created by Albert H. Brigance were designed to assess development in children from birth through the end of the first grade (7 years, 6 months) [25]. They sample children's skills in a broad range of areas including fine and gross motor, articulation, expressive and receptive language, general knowledge, personal-social skills, and pre-academic skills, thereby making it possible to identify a child's strengths and weaknesses and to determine what additional evaluations are needed (e.g., psychoeducational, speech-language, occupational/physical therapy, etc.). They are widely used in educational settings to identify children who would benefit from diagnostic testing or special services.

The Brigance Screens were normed on a geographically diverse sample of 1,366 children representative of the population of the United States in terms of ethnicity, gender, parental level of education, and psychosocial risk status. Fourteen percent of the children were African-American and 21% of the parents had not graduated from high school.

The test is scored by assigning a point value to each skill assessed. The motor domain for three year-old children includes copying a vertical/horizontal line, circle, and plus sign; stacking 6-10 blocks, standing on one foot, and walking forward heel-and-toe. For the communication domain, subjects are expected to point to objects according to use, point to body parts, name pictures, repeat 4-8 syllable sentences, and use prepositions and irregular plurals. The academic/preacademic domain entails giving first, middle and last names and age, as well as pointing to colors when named. As items are administered, correct responses are circled on the appropriate Data Sheet. Scoring is accomplished by adding the number of correct responses per subtest and entering these figures on the Data Sheet. Total points are then compared with cut-offs (median score for the age group minus standard error) established for various age groups to detect probable delays as well as academic talent/giftedness.

Data collection

This was a retrospective review of data from children with SCD who completed neurocognitive screening with the Brigance Preschool Screen II during a routine clinical visit. This study was approved by the St. Jude Children's Research Hospital Institutional Review Board and was determined to be exempt from the requirement for informed consent.

Data regarding medical history, hemoglobinopathy genotype, hemoglobin level (obtained on the day of Brigance testing), transcranial Doppler ultrasound (TCD) velocities (from an exam performed within six months of testing), and treatment with hydroxyurea or chronic transfusion, were obtained from patients' medical records. The Brigance screening tests results and responses to the Brigance Screening Background Information Form were obtained from the teachers' records.

Statistical analysis

The associations between each pair of categorical variables were explored using Fisher's Exact test (2×2) or the Fisher-Freeman-Halton test (2×C). For singly ordered (2×C) tables, the Kruskal-Wallis (KW) test was used. A difference in group medians was tested using the Wilcoxon-Mann-Whitney (WMW) test (two categories). P-values were reported descriptively. For statistical analysis, HbSS and HbSβ^othalassemia patients were grouped together as they were considered to be at higher risk for neurocognitive compromise. The second group consisted of patients with HbSC, HbSβ⁺thalassemia and HbS/Hope.

Results

Patient characteristics

Eighty-eight children with SCD between the ages of 3.0 to <4.0 years underwent assessment using the Brigance Preschool Screen-II between January 2006 and August 2008. The Brigance screening was offered to all age-eligible children with SCD. None of the families declined testing, so this cohort included all three year-old children with SCD followed in our clinic who kept their appointment and were at baseline state of health. Forty-three (49%) of these children were females. Forty-four children (50%) had HbSS, 23 (26%) HbSC, 14 (16%) HbSβ⁺thalassemia, six (7 %) HbSβ^othalassemia, and one (1%) HbS/Hope. Ten children had been receiving hydroxyurea for at least six months at the time of testing. Mean hemoglobin level for the entire cohort was 9.7±1.6 gm/dL (range: 6.2-12.6 gm/dL) and 14% of the patients had a hemoglobin level below 8 gm/dL. The mean TCD velocity was 151±27 cm/sec for the 44 patients who had a TCD exam within six months of Brigance testing. Thirty-five patients (80%) had a normal TCD velocity, seven (16%) had a conditional exam and two (5%) had an abnormal exam.

The mean ages of the mothers and fathers were 28.4 ± 6.6 years and 31.0 ± 7.9 years, respectively. Although most of the parents were high school graduates, 18% of mothers and 15% of fathers had not completed high school. The majority of parents (58%) were not living together. Forty-percent of the families had an annual income of less than \$15,000. Sixty-four percent of the children were enrolled in pre-Kindergarten at the time of the exam.

Brigance Preschool Screen-II Test Results

Forty-four of the 88 patients (50%) had a Brigance screening score below the cut-off for their age. Hemoglobin genotype was unrelated to the scores on the Brigance test (Table I). There were no associations between the scores and age (or > 3.5 years old), gender, Hb concentration, treatment with hydroxyurea, TCD velocities, enrollment in Pre-Kindergarten, whether or not the parents were living together, and parental income level. However, the results were significantly associated with parents' education level and inversely correlated with the detection of a speech problem by the examiner. The most significant association was with the maternal education level (p = 0.005).

Discussion

There have been few studies examining neurocognitive development in preschool age children with SCD (Table II). The Cooperative Study of Sickle Cell Disease administered the Denver Developmental Screening Test to 344 children younger than six years of age and showed that questionable and abnormal scores were more common in children with SCD 3-5 years of age than in younger children (12.6% versus 3.8%, $p=0.002$) [19]. This suggested that development is relatively normal before three years of age, but may decline shortly thereafter. Chua-Lim et al. studied 4-6 year-old children with HbSS and found that they scored significantly lower than controls in several parameters such as verbal output, visual input, fine motor and motor sequential output as well as short term memory[26]. In a study of kindergarten children by Steen et al., those with SCD scored significantly lower than controls in auditory discrimination and exhibited a trend toward a lower score in language skills[21]. Thompson et al. studied 89 African-American children with SCD using the Bayley Scales of Infant Development II (BSID-II) at 6, 12, 24 and 36 months of age[20]. Mental Developmental Index (MDI) declined significantly between the 12- and 24-month assessment points. In a study by Schatz et al. involving children from one to 3.5 years of age, Denver II results were abnormal for 30%[24]. Our study showed that 50% of 3-year-old children with SCD had scores below the cut-off value for their age (twice the national failure rate of 25%). In summary, the above studies show a consistent pattern of neurocognitive compromise in children with SCD that starts before they enter elementary school. However, definitive data regarding time of onset of this deficit are lacking. Several of the above studies also have shown that cognitive ability tends to decrease with increasing age, which has been presumed to be a reflection of cumulative deleterious effects of SCD on the brain[6,19,20].

The pathophysiology of neurocognitive compromise in children with SCD is unclear and may be multifactorial. Disease specific factors such as anemia, chronic hypoxemia, nutritional effects on the brain due to a higher basal metabolic rate and cerebral infarcts may be responsible for most of the effects of sickle cell disease on cognitive development[12,27,28]. Unlike a recent report in adults with SCD, we did not find an association between the Brigance test scores and hemoglobin level[29]. This may have been related to the relatively high mean hemoglobin level for this cohort of children. In a pediatric study in which the severity of anemia in SCD was shown to correlate with IQ, children whose hematocrits were $\geq 20\%$ had significantly lower verbal and performance scores[12]. In our study, only 14% of patients had a hemoglobin level less than 8 gm/dL, perhaps precluding a similar finding.

Recent data also have shown an association between neurocognitive testing results and TCD findings. In a study by Kral et al. involving 60 children with HbSS, subjects with abnormal TCD velocities performed worse than those with conditional TCD values on measures of verbal intelligence and executive function[30]. Children with conditional TCD velocities performed worse than those with normal TCDs on measures of sustained attention/concentration and executive function. In general, higher flow velocity was associated with poorer neurodevelopmental function. Hogan et al. examined 28 infants (14 SCD and 14 controls) with the Bayley Infant Neurodevelopmental Screener (BINS) at age 3, 9 and 12

months[22]. At nine months, the BINS raw scores correlated negatively with TCD velocity and positively with hemoglobin level. We did not find an association between the Brigance screening scores and TCD values. This may have been related to our relatively small sample size, as well as their young age.

A crucial unanswered question is the influence of psychosocial factors on the neurocognitive performance of children with SCD. Family environment and parental characteristics have been found to be independent predictors of cognitive development in young children with SCD[31]. In the study by Tarazi et al., socioeconomic status was significantly correlated with most domain scores and, based on regression analyses, accounted for 18 - 47% of the variance in functioning in children with SCD aged three years to five years, 11 months[23]. Psychosocial factors, such as number of children living in the home and parental stress levels, were negatively associated with Motor/Visuomotor skills, and the number of weekly hours in school/day care was positively associated with language-related skills. To our knowledge, our study is the first in subjects with SCD that showed a correlation between neurocognitive development and maternal education level. Several studies not involving SCD have shown that maternal education level is a strong predictor of early language development[32,33,34]. For example, one study involving four year-old children enrolled in Head Start showed that maternal education was a significant predictor of the child's performance of Peabody Picture Vocabulary Test-III[33]. The authors concluded that even in a sample of mothers with relatively low education levels (mean years in school 11.75 ± 1.76), children of mothers with higher education levels had higher vocabulary and letter-word identification abilities than children of mothers with lower education levels. It is generally hypothesized that parents' lower education level is likely associated with a lessened ability to read to young children at home. Another possibility is that mothers with higher education levels work full-time and their children go to daycare where they are in an enriched environment. However, in our analysis, we did not see any difference between children who are enrolled in daycare when compared with those who are not. Income level and presence of both parents at home did not have a statistically significant effect either. Improving neurocognitive outcomes in these young children may require interventions such as promoting the completion of high school and improving financial support for higher education for mothers and/or providing more resources that benefit the child.

The limitations of our study include cross-sectional design. We have not performed serial testing in these children, so we do not know the implications of these results or the efficacy of interventions such as enrollment in Head Start programs. We plan to collect kindergarten data in the future and look for associations with the Brigance Preschool Screen-II results. In one report, poor performance on the Brigance Screen at 4-5 years of age predicted academic dysfunction more than six years later[36].

The Brigance test is only a screening tool so results should be considered preliminary. Relatively few of our patients have had formal neuropsychological testing, so we were unable to make more detailed neurocognitive analyses. However, the ease of administration of the Brigance test and the ability to share results with parents immediately make this screen very suitable for application in the clinical setting as well as in clinical research studies that investigate ways to improve neurocognitive outcomes.

Conclusions

In this retrospective study, we found a remarkably high proportion of three year-old children with SCD whose scores were below the normal cut-off for their age when they were evaluated with the Brigance Preschool Screen-II. The most significant factor affecting this outcome was maternal education level. This result needs to be confirmed in a prospective study, with the addition of controls from similar racial and socioeconomic backgrounds, in order to define appropriate treatment and/or prevention strategies.

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Table I

Associations between the Brigance Preschool Screen-II pass-fail results and medical/psychosocial variables.

Variable (No. of patients)	Pass (%)	Fail (%)	p-value
Age (years) 3.0 to 3.5 (44) >3.5 to 4.0 (44)	56.8 43.2	43.2 56.8	0.29
Gender Female (43) Male (45)	53.5 46.7	46.5 53.3	0.67
Hb genotype HbSS/HbS β^o thal (50) HbSC/HbS β^o thal/HbSHope (38)	48.0 52.6	52.0 47.4	0.83
Hb level 8 gm/dL (12) >8 gm/dL (76)	50.0 50.0	50.0 50.0	1.00
TCD result Normal (35) Low conditional (2) High conditional (5) Abnormal (2)	48.6 100.0 40.0 50.0	51.4 0.0 60.0 50.0	0.96
Treatment with hydroxyurea Yes (10) No (78)	50.0 50.0	50.0 50.0	1.00
Mother's education level Did not complete high school (14) High school/GED (40) Some college (11) College degree (14)	28.6 47.5 63.6 78.6	71.4 52.5 36.4 21.4	0.0051
Father's education level Did not complete high school (10) High school/GED (41) Some college (7) College degree (9)	40.0 43.9 57.1 88.9	60.0 56.1 42.9 11.1	0.03
Parents living together Yes (49) No (35)	45.7 55.1	54.3 44.9	0.51
Income level (\$/year) <15,000 (16) 15-35,000 (16) >35,000 (8)	50.0 62.5 87.5	50.0 37.5 12.5	0.12
Enrollment in pre-K Yes (55) No (31)	54.6 45.2	45.5 54.8	0.50
Speech problems Yes (30) No (58)	30.0 60.3	70.0 39.7	0.013

TABLE II

Previous studies of neurocognitive development in pre-school/kindergarten age children with SCD.

Year	Author	Exam	Age	# of Patients/ Controls	Results
1993	Chua-Lim	PEER/McCarthy	4-6 yr	10/10	↓ scores on PEER
1993	Wang	DDST	0-5 yr	344/0	↑ Q/A scores in 3-5 yr olds
2002	Thompson	Bayley	0.5-3 yr	89/0	↓ in MDI; 12→24 mo.
2002	Steen	Developing Skills Checklist	Kinder garden	34/68	↓ in auditory discrimination
2005	Hogan	Bayley	3-12 mo	14/14	↑ risk of ND delay; 3→9 mo.
2007	Tarazi	Wechsler, others	3-6 yr	26/0	FSIQ = 89
2008	Schatz	Denver II	1-3.5 yr	50/0	Suspect outcome in 30%

PEER, Pediatric Examination of Educational Readiness; DDST, Denver Developmental Screening Test; Q/A, questionable/abnormal; MDI, mental developmental index; ND, neurodevelopmental; FSIQ, full scale intelligence quotient.