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Precursors of Executive Function in Infants With Sickle Cell Anemia

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Abstract

Executive dysfunction occurs in sickle cell anemia, but there are few early data. Infants with sickle cell anemia (n = 14) and controls (n = 14) performed the "A-not-B" and Object Retrieval search tasks, measuring precursors of executive function at 9 and 12 months. Significant group differences were not found. However, for the A-not-B task, 7 of 11 sickle cell anemia infants scored in the lower 2 performance categories at 9 months, but only 1 at 12 months ($P = .024$); controls obtained scores at 12 months that were statistically comparable to the scores they had already obtained at 9 months. On the Object Retrieval task, 9- and 12-month controls showed comparable scores, whereas infants with sickle cell anemia continued to improve ($P = .027$); at 9 months, those with lower hemoglobin oxygen saturation passed fewer trials ($R_s = 0.670$, $P = .024$) and took longer to obtain the toy ($R_s = –0.664$, $P = .013$). Subtle delays in acquiring developmental skills may underlie abnormal executive function in childhood.

Keywords

anemia, sickle cell, cognition, neuropsychology, executive, dysfunction, function

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Exposure to the risk factors for cerebral infarction is likely from infancy in children with sickle cell anemia.[1] The main hemoglobin changes from fetal to sickle during the first year of life and the key characteristic of red blood cells containing sickle hemoglobin is that they tend to deform on exposure to hypoxia. Using pulse oximetry, it is possible to measure hemoglobin oxygen saturation noninvasively. There is evidence for a higher risk of acute central nervous system events, including stroke,[2] in patients with sickle cell anemia and low hemoglobin oxygen saturation. The available evidence suggests that chronic hemoglobin oxygen desaturation, cerebrovascular disease, and infarction are often established and brain development sometimes compromised very early in childhood,[1,3,4] before the onset of clinical stroke or school difficulties.

To our knowledge, 3 centers have thus far examined cognitive functioning in infants with sickle cell anemia using the Denver Developmental Screening Test,[5] the Bayley Scales,[6] and the Bayley Neurodevelopmental Screener,[7] but only the latter study was case controlled. Although the results of standardized developmental scales provide important information, the scores are averaged across domains of function such as language, visuoperception, and memory, similar to IQ in older children. This means that relative strengths and weaknesses in particular cognitive domains, such as executive function (eg, working memory, inhibition, attention), which has been widely investigated in older children with sickle cell anemia,[8-10] may be masked. A more recent study administered the Delayed Response test, a measure of early working memory development, to toddlers (12-18 months) and young children (32-40 months) and reported an increase in accuracy and a decrease in number of perseverative errors between these 2 age groups.[11] Importantly, accuracy was decreased in HbSS/HbSβ^o children who are at higher risk of neurologic impairment compared to the HbSC/Hbβ^+ children, and this was irrespective of age group. This study provides an important indication that early, albeit subtle, sickle cell anemia neuropathology might contribute to altered or deficient emergence of executive function. Nevertheless, the wide age range within the groups, particularly within the younger group, may have concealed significant differences between the higher and lower risk groups in the pace of early executive function development, particularly as skills

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such as working memory show considerable rate of progression during infancy.[12-15]

Two search tasks, namely, detour-reaching or Object Retrieval, and A-not-B, have been investigated in normally developing infants.[12-20] These tasks have been described as measures of inhibition, attention, and working memory in infants,[12,13] processes that are associated with executive function at maturity. Monkey brain-lesion studies[14,15,21,22] and human infant brain-activation studies[23,24] suggest that the frontal lobes contribute to performance on these tasks. In addition, children with phenylketonuria provide an important model for infants with sickle cell anemia, as this disorder, which alters dopaminergic transmission in the frontal lobes, has been shown to detrimentally affect search skill in infants and executive function in later childhood.[25]

The possibility that deficits in precursors of executive function begin to emerge in infancy in children with sickle cell anemia, approximately one-third of whom will develop overt or covert frontal lobe infarction by midchildhood,[26] is an important direction for research, and one that we believe is best tested in longitudinal studies with demographic controls. To our knowledge, the A-not-B and Object Retrieval tasks have not been used to test the development of the precursors of executive function in infants (<1 year) with sickle cell anemia. Specifically, we predicted a delay in the acquisition of those skills assessed by the Object Retrieval and A-not-B tasks, namely, working memory, inhibition, and attention. Such evidence would provide further support for the view that the precursors of cognitive deficit in sickle cell anemia appear early in life, before the onset of clinical stroke.[7,11] We also hypothesized that poorer performance on these measures would be associated with physiological indices of sickle cell anemia severity: hemoglobin,[4,7,27] hemoglobin oxygen saturation,[2,7] and mean cerebral blood flow velocity measured by transcranial Doppler.[4,7,28]

Methods

Participants

Infants with sickle cell anemia (n = 14) were diagnosed with hemoglobin SS either by prenatal screening or by cord-blood screening at birth. None had any neurologic events, and they did not have neuroimaging. In the first year of life, 5 had dactylitis, of whom 2 had splenomegaly and 1 wheezed, whereas another 2 also wheezed. Control infants (n = 14) were born at the same London hospital that sickle cell anemia infants attended for clinic appointments. Criteria for inclusion of controls were parents of African or Afro-Caribbean descent, a negative test for sickle cell anemia, and absence of significant medical history. This cohort is described in greater detail in an earlier report that documents general neurodevelopment of this group from 3 months to 1 year.[7] The present report describes the results of the A-not-B and Object Retrieval tests that were administered at 9 and 12 months in order to explore the feasibility and practicality of administering these measures longitudinally to infants with sickle cell anemia. Not all infants completed both assessments at both ages, and further details about sample size are provided below. We lost data points due to nonattendance, equipment failure, examiner error (A-not-B in 1 case), and/or the infant's disinterest in the game.

Search Tasks

For both the A-not-B and Object Retrieval search tasks, all trials were video-taped and graded off-line.

A-not-B task. An A-not-B table was constructed to the specifications of A. Diamond.[13] The infant was seated on the parent's lap, opposite the examiner. For the purpose of the present study of only a small number of infants, performance was graded according to level of success based on a simple criterion: (1) Infants who obtained a toy when partially hidden by a cloth (not in either well and administered first) were categorized as *partial*; (2) Infants who obtained a completely hidden toy (not in either well and administered second) were categorized as *complete*; (3) Infants who went on to successfully retrieve a toy from well A (when both wells were simultaneously covered with separate cloths) but who were unable to switch to well B within the first 5 well trials were categorized as *A-not-B*; (4) Infants who were able to subsequently inhibit the desire to reach to the previously rewarded well (A) and switch to well B after 2 correct trials at A were categorized as *AB*. Consistent with Diamond's published protocol,[13] 9-month infants had an initial 3-second delay for well trials, and 12-month infants had a 5-second delay. During the delay, the infants' attention was directed away from the wells by calling their name and counting out loud. We expected our 9-month infants to obtain a complete or A-not-B category score, and at 12 months a distribution more skewed toward AB performance. At 9 months, an A-not-B category score was obtained from 14 infants with sickle cell anemia and 12 controls. This was reduced to 11 and 10, respectively, at 12 months. Longitudinal analysis included 11 infants with sickle cell anemia and 9 controls, that is, the infants in each group who completed both assessments.

Object retrieval task.[12] A desired toy was hidden under a clear Perspex box that, when on the table, effectively had only 1 side open. The infant was required to retrieve the toy without delay, that is, inhibit the desire to reach straight "through" the closed box top and detour around the box to the open side. Scores were averaged across side of box opening: (1) easy condition (toy partially out of box; 5 trials); (2) moderate condition (toy just inside box; 5 trials); (c) hard condition (toy deep inside box; 9 trials). The percentage of trials in which the toy was successfully retrieved in each condition was recorded for each infant. The time taken to retrieve the toy in the hard condition was recorded: the time the infant first looked at the box to the moment he or she made contact with the toy (purposeful grasp). At 9 months, Object Retrieval task data were obtained from 14 infants with sickle cell anemia, of whom 2 infants did not complete enough trials to be included in the "hard–toy deep inside" condition (percentage correct and mean time measures); complete data were obtained from 10 control infants. At 12 months, 9 sickle cell anemia infants and 10 control infants completed the Object Retrieval task. For longitudinal analysis, complete Object Retrieval task data were obtained from a subgroup of 8 sickle cell anemia infants and 9 control infants at both 9- and 12-month assessments.

Results

Group Differences

In this preliminary study of only a small number of infants, significant group differences were not found in either of the tasks (Figures 1A, B and 2A, B): all group comparisons had $P > .2$. Of

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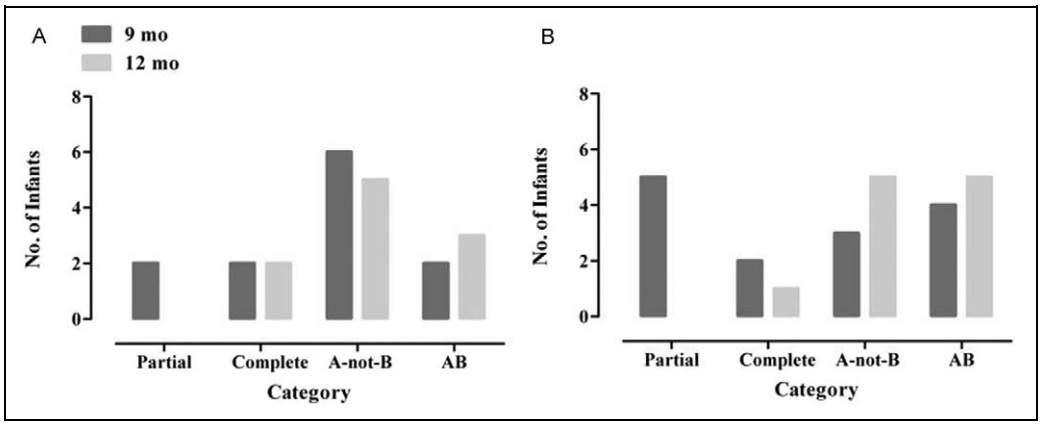

Figure 1. The number of (A) controls and (B) infants with sickle cell anemia scoring within each category in the A-not-B task at 9 and 12 months.

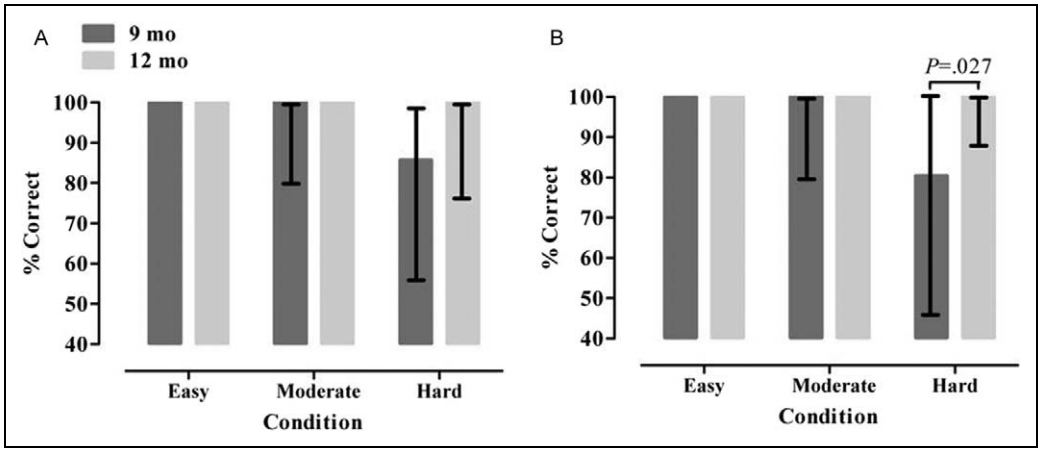

Figure 2. The percentage of correct trials on the Object Retrieval task in (A) controls and (B) infants with sickle cell anemia at 9 and 12 months. The vertical lines denote the range when 100% success rate was not obtained by all infants.

note, however, the number of sickle cell anemia infants (5 of 14; compared to 2 of 12 controls) who did not uncover a completely hidden toy ("partial") at 9 months on the A-not-B task was unexpectedly large considering that we expected most infants to be at the A-not-B or higher level by this age.[13] However, a similar number of sickle cell anemia infants (4 of 14) actually performed at the highest level (AB), indicating variable performance. The majority of control and sickle cell anemia infants were able to do all easy and moderately hard trials on the Object Retrieval task by 9 months, consistent with normative performance on this task.[13]

Longitudinal Analysis

Notwithstanding the absence of significant group differences, it is of interest that some infants with sickle cell anemia showed subtle evidence of developmental delay, and this provides some support for our hypothesis as well as highlighting the need for conducting further studies with larger numbers of infants. Specifically, statistical analyses suggest that sickle cell anemia infants continued to improve on these tasks between 9 and 12 months, whereas at 9 months the performance of control infants was already statistically comparable to their 12-month level of performance.

A-not-B at 9 and 12 months in sickle cell anemia and control infants. The distribution of category scores remained unchanged in control infants between 9 and 12 months (MH test: $P > .05$), suggesting that their performance at 9 months was already comparable to that at 12 months. By contrast, infants with sickle cell anemia continued to show development between 9 and 12 months (MH test: $P = .024$).

Object retrieval at 9 and 12 months in sickle cell anemia and control infants. Although control infants showed no statistical improvement between 9 and 12 months (Wilcoxon: condition: easy, $P = 1$; moderate, $P = .317$; hard, $P = .136$), again suggesting that their performance at 9 months was already comparable to that at 12 months, greater performance accuracy at 12 compared to 9 months was revealed for hard trials in infants with sickle cell anemia (easy, $P = 1$; moderate, $P = .157$; hard, $P = .027$). Moreover, although the control group showed a significant decrease between 9 and 12 months in the mean time taken to obtain the toy in the hard condition (9 months:

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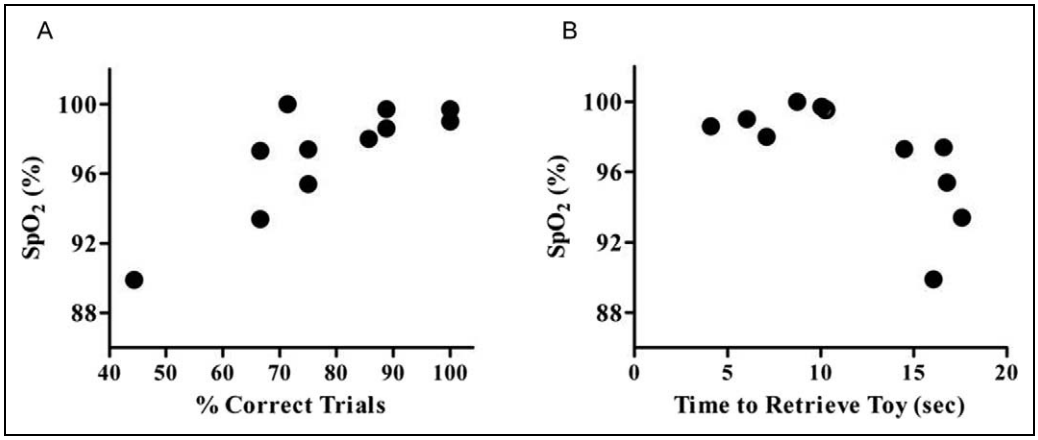

Figure 3. Correlation between daytime hemoglobin oxygen saturation and (A) percentage of correct trials in hard condition and (B) time taken to obtain toy in Object Retrieval task at 9 months in infants with sickle cell anemia.

median = 9.1 seconds, range = 4.0-13.3; 12 months: median = 4.4 seconds, range = 2.1-7.9, $P = .038$), a decrease of similar magnitude was not observed in infants with sickle cell anemia (9 months: median = 9.4 seconds; range = 4.9-16.8; 12 months: median = 6.3 seconds, range = 3.1-18.6, $P = .161$).

Association between A-not-B and Object Retrieval measures and indices of disease severity in infants with sickle cell anemia. (1) A hemoglobin value was obtained from all sickle cell anemia infants during the first year of life: n = 14; median, 9.5 g/dL; range, 5.7 to 11.0. In half of the infants (7 of 14), the hemoglobin value was obtained within 1 month of the 9-month assessment. There were no correlations between 9-month hemoglobin and 9-month Object Retrieval or A-not-B measures. (2) Hemoglobin oxygen saturation was measured by pulse oximetry in the majority of infants with sickle cell anemia on the same day as the A-not-B and OR tests were administered (9 and 12 months). There were no correlations between the 9- or 12-month hemoglobin oxygen saturation and A-not-B measures. There was, however, a significant association between hemoglobin oxygen saturation and both accuracy (percentage correct) and speed of toy retrieval in the hard trials of the Object Retrieval task. Greater accuracy was achieved by those infants with higher hemoglobin oxygen saturation (n = 11, $R_s = 0.670$, 2-tailed, $P = .024$; Figure 3A), and those infants with sickle cell anemia who had the lowest hemoglobin oxygen saturation values took longest to obtain the toy ($R_s = -0.664$, $P = .013$; Figure 3B). At 12 months, these correlations were in the same direction ($R_s = 0.412$, $R_s = -0.595$, respectively), but fell short of statistical significance, perhaps partly due to the fact that hemoglobin oxygen saturation data were available for a smaller number of infants (n = 8). (3) Cerebral blood flow velocity assessed by transcranial Doppler sonography was recorded as the maximum value across sides for the middle cerebral artery and for the basilar artery.[7] There were no significant correlations between mean cerebral blood flow velocity and either A-not-B or Object Retrieval indices at 9 or 12 months.

Discussion

These preliminary results show a ceiling effect for both search tasks in control and sickle cell anemia infants, but with some evidence for a lag in performance at harder levels for those with sickle cell anemia. At first hand, it can be considered that the A-not-B and Object Retrieval tasks are less sensitive to subtle brain abnormality in infants with sickle cell anemia than predicted. However, this was a preliminary study of only a small number of infants, and the variability of scores in the sickle cell anemia group in particular suggests that significant group differences may be detected with adequate sample sizes. Such research is particularly important as it is widely assumed that early development in these children is relatively normal. Moreover, research with typically developing children has identified cognitive competence in toddlers as an important predictor of executive function behavior (self-regulation, impulsivity) in later childhood,[29] and recent evidence obtained from preschoolers suggests that this trajectory may indeed be altered from the age of 1 year in children with sickle cell anemia.[11] Taken together, the evidence from our infants, and that already published in toddlers[11] with sickle cell anemia, suggests a need for longitudinal study of cognitive development from early infancy into childhood, using demographic controls and recruiting large numbers of infants through multicenter cooperation.

Early ''deficit'' in a proportion of infants in our study may be transient, evident in the comparable performance between sickle cell anemia and control infants at 12 months. Physiological adaptations to the challenge of anemia and hypoxemia, such as increase in cardiac output and cerebral blood flow,[30,31] may explain any cognitive ''catch-up'' in infants with sickle cell anemia. On the other hand, the ceiling effect, in part resulting from our simplistic scoring criterion particularly on the A-not-B test, suggests that infants should be studied from an earlier age. Evaluating further the length of delay infants can tolerate before making the A not B error could be a useful future approach. This aspect of the task has been linked to prefrontal cortical development, and the length of delay

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that typically developing infants can tolerate increases systematically by about 2 seconds per month over the second half of the first year.[12] Other age-appropriate tests should also be introduced from 12 months to track any abnormal development into the second year of life. Importantly, using a battery of tests including the delayed response task (similar to the A-not-B), developmental delay has been documented in toddlers and preschool children with sickle cell disease.[11] Our longitudinal data are limited but provide useful complementary evidence that such delay in executive function development may begin even earlier, from the first year of life.

It is of interest that there may be reduced processing speed in infants with sickle cell anemia (Object Retrieval task). Delayed response time in complex tasks has recently been found in children living at high altitude where oxygen supply is reduced so that hemoglobin oxygen saturation is approximately 92%,[32] and in preschoolers with overnight intermittent hemoglobin oxygen desaturation,[33] and is potentially reversible.[34,35] However, although surgery for adenotonsillar hypertrophy may improve oxygen delivery to the brain and cognition in children with sleep-disordered breathing[35] its benefit in children with sickle cell anemia is less apparent.[36] Despite some existing evidence for delayed processing speed in children with sickle cell anemia,[37-39] in general there are few data exploring the possibility of a link between hemoglobin oxygen saturation and processing speed in this condition. The association between hemoglobin oxygen saturation and time to retrieve the toy on the Object Retrieval task in our infants with sickle cell anemia is therefore novel and of potential interest, being consistent with evidence obtained from other groups of children exposed to chronic and/or intermittent hypoxia.

The primary aim of this study was to pilot the use of the A-not-B and Object Retrieval tests in an opportunistic sample of infants with sickle cell anemia compared with controls in order to explore feasibility and potential usefulness. As such, it is important to outline those limitations of our study that may be addressed in order to establish the utility of these measures in infants with sickle cell anemia. First, it was not possible for the neuropsychologist to remain blinded to sickle cell anemia status, mainly because of the fact that some parents were anxious for further information about sickle cell anemia in addition to that given by their hematologist. Nevertheless, the testing was standardized and informal comments by an independent observer who remained blinded to sickle cell anemia status confirmed that the administration was consistent. Second, the predominantly male sickle cell anemia group (11 males) and female Control group (9 females) did not permit examination of any within-group gender differences. Third, multicenter studies of infants may be necessary to allow sample sizes of adequate power (as have previously been conducted for older children, eg, Cooperative Study of Sickle Cell Disease) but would require a high level of cooperation, particularly with respect to consistency in administration and consensus in grading performance.

Despite the lack of significant group differences, we believe that the predicted subtle developmental delay observed in a proportion of the infants with sickle cell anemia on both tasks provides a basis for conducting larger studies, adequately powered for group comparisons at ages from 6 months onward. This line of research may permit an understanding of neurodevelopment in children with sickle cell anemia, an increasingly prevalent condition, to the extent that some of its features, such as low hemoglobin oxygen saturation, may potentially be modified before the onset of irreversible brain damage.

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Author Contributions

AMH devised the study, collected the data and wrote the first draft of the manuscript. PTT recruited the infants in the study. PTT, FJK, and MdH edited the manuscript. FJK and MdH suggested analyses for the data.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Permission was obtained from the Great Ormond Street Hospital Research Ethics Committee and The Royal London Hospital Ethics Committee.

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