HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2020 April 06.

Published in final edited form as:

Pediatr Blood Cancer. 2016 November ; 63(11): 1990–1997. doi:10.1002/pbc.26126.

Cognitive functioning in children from Nigeria with sickle cell anemia

Olubusola B. Oluwole[1], **Robert B. Noll**[2], **Daniel G. Winger**[3], **Olu Akinyanju**[4], **Enrico M. Novelli**[5]

[1]School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

[2]Department of Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania

[3]Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh, Pennsylvania

[4]Sickle Cell Foundation Nigeria, Lagos, Nigeria

[5]Division of Hematology/Oncology, Department of Medicine, Vascular Medicine Institute, University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract

Background: Cognitive impairment is a major neurological complication of sickle cell anemia (SCA) in the United States, but there are limited studies of cognitive impairment in Nigeria, the country with the highest SCA burden. We hypothesized that children from Nigeria with SCA have worse cognitive functioning than comparison children and explored the association between lower cognitive functioning and key laboratory demographic and socioeconomic variables among children with SCA.

Procedure: We conducted a cross-sectional survey, supplemented by anthropomorphic and laboratory data, among a convenience sample of children from Nigeria with and without SCA. We administered the Wechsler Intelligence Scale for Children, Version IV. Our primary outcome measures included (1) estimated IQ (Est. IQ), (2) working memory (WM), and (3) processing speed (PS).

Results: The sample included 56 children with SCA (mean age 9.20 [SD 2.75], 46.43% girls) and 44 comparison children (mean age 9.41 [SD 2.49], 40.91% girls). Children with SCA performed worse on Est. IQ (84.58 vs. 96.10, $P = 0.006$) and PS (86.69 vs 96.91, $P = 0.009$) than comparison children. There was no significant difference in WM between both groups. Factors associated with lower Est. IQ and PS among children with SCA included age, maternal education, weight-for-age Z scores, and height-for age Z scores.

Conclusion: In this small sample of children from Nigeria, we found worse cognitive functioning in children with SCA than in comparison children, and that sociodemographic and anthropomorphic factors were correlated with cognitive functioning.

Correspondence: Enrico M. Novelli, Division of Hematology/Oncology, Department of Medicine, Vascular Medicine Institute, University of Pittsburgh, Pittsburgh, PA 200 Lothrop St, Pittsburgh, PA 15213. noveex@upmc.edu.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Keywords

cognitive functioning; IQ; Nigeria; nutrition; sickle cell anemia

1 | INTRODUCTION

Patients with sickle cell anemia (SCA) experience a high burden of neurological complications including overt and silent strokes.[1,2] It is estimated that approximately 31–35% of children with SCA will suffer from silent strokes.[2,3] Silent strokes have been demonstrated to increase the risk of overt stroke and are associated with cognitive deficits.[4–7] Studies evaluating cognitive functioning in SCA have demonstrated lower IQ compared to children without SCA,[8,9] and deficits in specific domains including processing speed (PS), memory, and attention.[10,11] Cognitive impairment can adversely affect quality of life and adaptive functioning.

While the adverse impact of both types of strokes on cognitive development in SCA has been reported in multiple studies,[4,11,12] cognitive impairment may also occur in the absence of stroke,[9,13] suggesting that other factors may contribute to its pathogenesis. Disease-related risk factors such as hypoxia and lower hemoglobin levels have been demonstrated to be independent predictors, but they do not completely predict cognitive functioning in SCA.[13–16] Nutritional status has been shown to be associated with cognitive functioning in children and adults in general,[17–19] but not particularly in children with SCA. Lastly, sociodemographic factors such as home environment (e.g., parental education) have been associated with cognitive performance in the general population in the United States and in other countries.[20,21] This has not been extensively investigated in patients with SCA, especially outside the United States. Sub-Saharan Africa accounts for the highest annual SCA burden in the world with 79% of all newborns with SCA in 2010,[22] yet little is known about the cognitive functioning in children from Africa with SCA. This knowledge gap inhibits the development of targeted interventions to prevent or mitigate cognitive deficits in children with SCA.

This study compared the cognitive functioning of children from Nigeria with SCA to comparison children from Nigeria without SCA and explored the association of cognitive functioning with key demographic and laboratory data. We hypothesized that children with SCA would have worse cognitive performance, specifically estimated IQ (Est. IQ), working memory (WM), and PS, than comparison children and lower cognitive functioning would be associated with older age, lower hemoglobin levels, and poor nutritional status.

2 | METHODS

2.1 | Standard protocol approval and patient consent

We conducted a cross-sectional study in Lagos, Nigeria, from June to August 2012. Review and approval of the protocol were obtained from the International Review Board at the University of Pittsburgh (PRO12050138) and the International Review Board from Lagos University Teaching Hospital (LUTH), which also covers the Sickle Cell Foundation Nigeria

(SCFN) associated clinic and Lagos State University Teaching Hospital (LASUTH). All parents and guardians provided written informed consent to the study and children provided assent.

2.2 | Participants

Using convenience sampling, we approached eligible children from the pediatric sickle cell clinic at LUTH as well as four weekly sickle cell clinics at SCFN. Eligibility criteria included (i) English-speaking; (ii) age 6–16 years based on the recommended age range of the Wechsler Intelligence Scale for Children, Version IV (WISC-IV)[23]; (iii) laboratory diagnosis of homozygous hemoglobin S SCA by chart review; (iv) presenting for a routine clinic visit for comprehensive follow-up; and (v) absence of acute medical problems (i.e., any sickle cell related complication such as vaso-occlusive crisis or other acute pediatric illnesses) as determined by the physician managing their SCA. Exclusion criteria included (i) history of overt stroke, (ii) head injury, or (iii) blood transfusion within the past 3 months. We approached 82 children and 56 (68.3%) agreed to participate.

We also used convenience sampling to enroll children without SCA as a comparison group. Comparison children presenting for a well-child visit were approached at the general pediatric clinic at LASUTH. Eligibility criteria included (i) English-speaking, (ii) age 6–16 years, (iii) absence of SCA or heterozygous hemoglobin AS (sickle cell trait or carrier status, HbAS) by chart review, and (iv) presenting for a routine clinic visit for follow-up. A physician screened the children to ensure they did not have an acute or chronic illness or any self-reported history of head injury. We approached 76 children and 44 (58.6%) agreed to participate, of whom 9 (20%) were siblings of patients with SCA already enrolled in the study.

2.3 | Demographics

Demographic and medical history data were obtained from parents and guardians using an ad hoc generated questionnaire. Parents/guardians reported their age, employment status, number in household, marital status, and education levels. We classified parental education levels into categorical variables of less than secondary school versus greater than or equal to Ordinary National Diploma (OND)/National Certificate in Education (NCE) (Table 1). OND and NCE are comparable to an associate degree in the United States.

2.4 | Anthropometric and laboratory values

Patients' height and weight, and calculated weight-for-age Z scores (WFAZ) and height-for-age Z scores (HFAZ) were measured. WFAZ and HFAZ are measures of wasting and stunting, respectively. We measured hemoglobin levels at the time of the cognitive assessment using a STAT-Site® (Stanbio Laboratory, Boerne, TX) portable hemoglobin analyzer and peripheral oxygen levels using a fingertip pulse oximeter (Santa Medical, Tustin, CA). Most of the parents of comparison children declined to have hemoglobin levels obtained from their children.

2.5 | Neurocognitive measures

The WISC-IV is a measure of a child's intellectual ability and has been used extensively in the United States and cross-culturally.[14,24] We were able to administer the test without difficulty since English is the primary teaching language in Nigeria.

2.5.1 | Intelligence—We derived an estimated IQ (Est. IQ) using four WISC-IV subtests: coding (CD), symbol search (SYS), letter numbering (LN), and digit span (DS). The reliability coefficient of these four subtests with full-scale IQ is 0.826.[25] These four subtests were chosen because of their lower susceptibility to cross-cultural factors.

2.5.2 | Working memory (*WM*)—An index of WM was derived from a combination of the WISC-IV subtests DS and LN. Previous work has shown that these WISC-IV subtests provide a reliable and valid measure of WM.[26]

2.5.3 | Processing speed (*PS*)—An index of PS was derived from a combination of the WISC-IV subtests CD and SYS. Previous work has shown that these WISC-IV subtests provide a reliable and valid measure of PS.[27]

2.6 | Statistical methods

Sociodemographic, anthropomorphic, laboratory data, and measures of cognition were summarized using measures of central tendency and dispersion. We compared sample means between children with SCA and comparison children using Fisher's exact test for categorical variables and independent sample *t*-test for continuous variables. A multivariable linear regression analysis was performed to adjust for father's education level when comparing sample means since this variable approached significance when comparing both groups. The relationships between sociodemographic, anthropomorphic, laboratory measures, and each of the cognitive outcomes (Est. IQ, WM, PS) were explored using Pearson correlation coefficients for continuous predictors and independent sample *t*-test for categorical predictors.

All statistical analyses were performed in IBM SPSS version 22 (IBM Corp., Armonk, NY). Statistical significance was set at $P < 0.05$ for two-sided P values. Effect sizes (Cohen's d) were calculated by dividing the difference of the two sample means by the pooled standard deviation of the two groups. Effect sizes with absolute value 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively.[28]

3 | RESULTS

3.1 | Demographics

We enrolled 56 children with SCA and 44 comparison children (Table 1). There were no significant differences in age, gender, parental marital status, number of people in the household, or maternal and paternal education level between children with SCA and comparison children.

3.2 | Anthropometric and laboratory values

There were statistically significant differences between children with SCA and comparison children for all anthropometric and laboratory variables. Children with SCA were shorter (Table 2) and exhibited poorer nutritional status (WFAZ) than the comparisons.

3.3 | Neurocognitive domains

Children with SCA had significantly lower Est. IQ than comparison children (Table 3). Additionally, children with SCA had significantly worse PS than the comparison children. Children with SCA also exhibited significantly worse performance than comparison children on three WISC-IV subtests: CD, DS, and SYS (Table 3). Further analysis adjusting for father's education level produced similar results (Table 3).

3.4 | Correlates of neurocognitive functioning in children with SCA and comparison children

Within the SCA group, several outcomes negatively correlated with age including Est. IQ, WM, and PS (Table 4). Additionally, lower HFAZ strongly correlated with lower Est. IQ and WMI and moderately correlated with PS. Lower maternal education level was significantly associated with lower Est. IQ (Table 5) and PS within the SCA group. There was no significant association between paternal education, BMI, hemoglobin, peripheral oxygen saturation level, and any of the cognitive outcomes. Within the comparison group, there was a mild negative correlation between age, PS, and Est. IQ that was nonsignificant (Table 4). There was a strong correlation between stunting and PS. There was no significant association between BMI, peripheral oxygen saturation level, parental education levels with any of the cognitive outcomes (Tables 4 and 6). Hemoglobin was excluded from the analysis in comparison children given the small sample size (n = 12).

4 | DISCUSSION

In this sample of children in Lagos, Nigeria, we found that children with SCA have lower Est. IQ and PS than comparison children. Lower Est. IQ, PS, and WMI correlated with increasing age and lower WFAZ and HFAZ. We found no association between any of our primary outcomes and hemoglobin levels in the group with SCA. Our findings are consistent with findings in the United States and Cameroon that children with SCA have lower IQ when compared to a comparison group without SCA.[9,14,29] The average IQ of children with SCA in our cohort was 84.58 (SD = 15.3), which is similar to what was reported in prior studies.[4,5,10]

We found a relationship between older age and lower Est. IQ in children with SCA. In comparison children, while the relationship had a similar direction, it did not reach statistical significance. There have been conflicting results regarding the relationship between age and cognitive functioning in children with SCA, as some studies have demonstrated poorer cognitive functioning with increasing age,[4,9,13] younger age, or no difference.[10,30,31] The negative relationship between age and cognitive functioning in our cohort may be suggestive of an early age of onset of cognitive impairment. Since silent strokes may occur very early in life,[2] it is possible that prior to participation in this study, some children in our cohort

suffered from silent strokes, which are known to adversely affect IQ. These results should, however, be interpreted with caution, as the small sample size of the comparison group may have prevented us from detecting a similar association between age and cognitive functioning in the children without SCA. A prospective controlled longitudinal study will be needed to further explore the impact of aging on cognitive functioning of children in Nigeria.

In patients without SCA, cognitive deficits have been linked to nutritional deficiencies in vitamin B12, folate, and general nutritional status.[32,33] These comorbidities are highly prevalent in sub-Saharan Africa.[34] Our findings show that lower WFAZ was associated with lower Est. IQ and poorer cognitive performance on both WM and PS. Multiple studies have also shown a strong correlation between growth measures and cognitive development in different populations[21,35,36] In a cohort of U.S. children with SCA aged 4–8, height for age was correlated with all measures of cognitive functioning while BMI was only associated with academic achievement.[36–38] However, when a retrospective analysis of growth velocity data was conducted on a subset of patients from this cohort, BMI-for-age velocity, not height-for-age velocity, was significantly associated with cognitive scores.[38] In our study, lower HFAZ was also associated with worse cognitive performance. Growth failure in height and weight is highly prevalent in children with SCA in the United States,[39,40] with stunting being also common in children with SCA in Africa.[41,42] There are multiple potential explanations for growth deficits in SCA. Growth hormone levels have been demonstrated to be lower in children with SCA compared to children without SCA suggesting a possible contribution of endocrine factors to brain development impacting cognitive functioning. Children with SCA have also been shown to have uncompensated, higher resting metabolic rates leading to energy deficits. Malnutrition may be secondary to the acute and chronic inflammatory milieu of SCA and a hypermetabolic state leading to unmet caloric demand, particularly in low-income countries. Both malnutrition and lower cognitive functioning may also be reflective of a poorer home environment. In summary, the association we report between WFAZ and HFAZ and lower cognitive functioning in SCA is worthy of further scrutiny in future prospective studies and aggressive nutritional support may be a key intervention in the prevention or improvement of cognitive functioning.

We found no association between anemia, the main explanatory variable specific to patients with SCA, and the primary cognitive outcomes in our study. Previous studies have yielded contradictory results on the association between severity of anemia and cognitive functioning in adults and children.[5,9,14,15,43,44] This discrepancy may have multiple explanations. Severity of anemia is a major risk factor for stroke in SCA and stroke is clearly linked to cognitive impairment. Different inclusion/exclusion criteria regarding a history of silent stroke are expected to impact the association between cognitive functioning and level of anemia across studies. While our study was not designed to thoroughly investigate all possible variables associated with cognitive impairment, it suggests that in our population, sociodemographic and nutritional factors may be more likely to impact cognitive impairment than the level of anemia.

Home environment, including household income and parental education, has been associated with better cognitive performance and academic achievement in the general U.S.

population[45] as well as in African populations.[46] This is possibly a result of shared genetic influence, better learning environments, or both.[47,48] A significant relationship between maternal education and cognitive functioning in patients with SCA in the United States has been reported,[43] similar to the link-age reported for typically developing children in the Unites States and in Nigeria.[49] We extend this observation to children with SCA in Nigeria by showing that higher maternal education level is significantly associated with better performance on the cognitive tests for children with SCA. This relationship was not found within our comparison group, however, this could be due to its smaller sample size.

There are several limitations to our study. First, our comparison group included both siblings without SCA of our SCA cases and typically developing unrelated children. It is, therefore, conceivable that there would be statistical dependence between patients with SCA and their siblings without SCA. This might affect the results of our independent sample statistical tests, and our sample size did not permit a more complex analysis that could take potential data dependencies into account. Second, while we took care in excluding children with a history of overt stroke, self-reporting from the parents may have been erroneous, particularly in a setting where MRI testing to diagnose stroke is not routinely available. Other risk factors that may affect our cognitive outcomes such as transcranial Doppler velocity, and anthropometric and laboratory values such as prevalence of obstructive sleep apnea and preterm birth were also not available. Thus, the interplay between these comorbidities is not known. Third, the clinical venues where we recruited children with SCA and our comparison group of children were convenience clinics, which can lead to sampling bias. Future work might opt for classroom comparison peers who are of similar age and gender. The use of this strategy in the United States typically results in samples that are more balanced in regards to demographic characteristics.[50] Fourth, while our measure of Est. IQ has extremely high correlation with actual full-scale IQ in typically developing children,[24] it may not be so robustly correlated with full-scale IQ in children with neurobiological insults.

Future work might examine the validity coefficients of shortened forms of IQ tests in children with SCA. Fifth, although we tried to control for language biases by using certain WISC-IV subtests, our analysis did not adjust for language proficiency as some of the WISC-IV subtests may have slight biases against bilingual children. Lastly, we had a small sample size, completed many comparisons, and some of our variables had a moderate to high proportion of missing values, thus increasing the likelihood of Type 1 and Type 2 errors and preventing us from drawing definitive conclusions about the association between cognitive outcomes and the variables of interest. We are, however, encouraged by the finding that even nonsignificant correlations were in the same direction of those that reached statistical significance (e.g., the correlations between HFAZ and WM and the association between maternal education and WM).

In summary, we have shown that children with SCA in an urban setting in Nigeria have significantly lower Est. IQ and PS than comparison children. We have found that nutritional status and maternal educational levels are important determinants of cognitive functioning in this population, with age being a contributing factor. Finally, we have shown that subtests of the WISC-IV can discriminate cognitive functioning between patients with SCA and comparison children in Nigeria and may be a valuable diagnostic tool in this setting.

ACKNOWLEDGMENTS

The project described herein was supported by the National Institutes of Health through grant number UL1-TR-000005 and the University of Pittsburgh Clinical Scientist Training Program. The authors would like to thank the medical staff of Lagos University Teaching Hospital and Lagos State University Teaching Hospital. The authors also appreciate the help of Li Wang, statistician at the Clinical and Translational Science Institute as well as the medical and clinic staff at the Sickle Cell Foundation Nigeria. Lastly, the authors would like to provide a special recognition to the children and families who participated in the study.

ABBREVIATIONS

CD	coding
DS	digit span
Est. IQ	estimated IQ
HFAZ	height-for-age *Z* score
LASUTH	Lagos State University Teaching Hospital
LN	letter numbering
LUTH	Lagos University Teaching Hospital
NCE	National Certificate in Education
OND	Ordinary National Diploma
PS	processing speed
SCA	sickle cell anemia
SCFN	Sickle Cell Foundation Nigeria
SYS	symbol search
WFAZ	weight-for-age *Z* score
WISC-IV	Wechsler's Intelligence Scale for Children, Version IV
WM	working memory

REFERENCES

1. Ohene-Frempong K Stroke in sickle cell disease: demographic, clinical, and therapeutic considerations. Semin Hematol. 1991;28:213–219. [PubMed: 1887247]
2. DeBaun MR, Sarnaik SA, Rodeghier MJ, et al. Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, sex, and relative high systolic blood pressure. Blood. 2012;119:3684–3690. [PubMed: 22096242]
3. Bernaudin F, Verlhac S, Arnaud C, et al. Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. Blood. 2011;117:1130–1140; quiz 1436. [PubMed: 21068435]
4. Wang W, Enos L, Gallagher D, et al. Neuropsychologic performance in school-aged children with sickle cell disease: a report from the Cooperative Study of Sickle Cell Disease. J Pediatr. 2001;139:391–397. [PubMed: 11562619]

5. Bernaudin F, Verlhac S, Freard F, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. J Child Neurol. 2000;15:333–343. [PubMed: 10830200]
6. DeBaun MR, Schatz J, Siegel MJ, et al. Cognitive screening examinations for silent cerebral infarcts in sickle cell disease. Neurology. 1998;50:1678–182. [PubMed: 9633710]
7. Miller ST, Macklin EA, Pegelow CH, et al. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. J Pediatr. 2001;139:385–390. [PubMed: 11562618]
8. Hijmans CT, Fijnvandraat K, Grootenhuis MA, et al. Neurocognitive deficits in children with sickle cell disease: a comprehensive profile. Pediatr Blood Cancer. 2011;56:783–788. [PubMed: 21370411]
9. Schatz J, Finke RL, Kellett JM, Kramer JH. Cognitive functioning in children with sickle cell disease: a meta-analysis. J Pediatr Psychol. 2002;27:739–748. [PubMed: 12403864]
10. Noll RB, Stith L, Gartstein MA, et al. Neuropsychological functioning of youths with sickle cell disease: comparison with non-chronically ill peers. J Pediatr Psychol. 2001;26:69–78. [PubMed: 11181883]
11. Brown RT, Davis PC, Lambert R, Hsu L, Hopkins K, Eckman J. Neurocognitive functioning and magnetic resonance imaging in children with sickle cell disease. J Pediatr Psychol. 2000;25:503–513. [PubMed: 11007807]
12. Armstrong FD, Thompson RJ Jr., Wang W, et al. Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. Neuropsychology Committee of the Cooperative Study of Sickle Cell Disease. Pediatrics 1996;97(6 Pt 1):864–870. [PubMed: 8657528]
13. Steen RG, Xiong X, Mulhern RK, Langston JW, Wang WC. Subtle brain abnormalities in children with sickle cell disease: relationship to blood hematocrit. Ann Neurol. 1999;45:279–286. [PubMed: 10072041]
14. Ruffieux N, Njamnshi AK, Wonkam A, et al. Association between biological markers of sickle cell disease and cognitive functioning amongst Cameroonian children. Child Neuropsychol. 2013;19:143–160. [PubMed: 22176123]
15. Hijmans CT, Grootenhuis MA, Oosterlaan J, Heijboer H, Peters M, Fijnvandraat K. Neurocognitive deficits in children with sickle cell disease are associated with the severity of anemia. Pediatr Blood Cancer. 2011;57:297–302. [PubMed: 21671366]
16. Iampietro M, Giovannetti T, Tarazi R. Hypoxia and inflammation in children with sickle cell disease: implications for hippocampal functioning and episodic memory. Neuropsychol Rev. 2014;24:252–265. [PubMed: 24744195]
17. Ghosh S, Chowdhury SD, Chandra AM, Ghosh T. Grades of undernutrition and socioeconomic status influence cognitive development in school children of Kolkata. Am J Phys Anthropol. 2015;156:274–285. [PubMed: 25348835]
18. Waber DP, Eaglesfield D, Fitzmaurice GM, Bryce C, Harrison RH, Galler JR. Cognitive impairment as a mediator in the developmental pathway from infant malnutrition to adolescent depressive symptoms in Barbadian youth. J Dev Behav Pediatr. 2011;32:225–232. [PubMed: 21285893]
19. Galler JR, Ramsey FC, Salt P, Archer E. Long-term effects of early kwashiorkor compared with marasmus. III. Fine motor skills. J Pediatr Gastroenterol Nutr 1987;6:855–859. [PubMed: 3119813]
20. Kaplan GA, Turrell G, Lynch JW, Everson SA, Helkala EL, Salonen JT. Childhood socioeconomic position and cognitive function in adulthood. Int J Epidemiol. 2001;30:256–263. [PubMed: 11369724]
21. Crookston BT, Forste R, McClellan C, Georgiadis A, Heaton TB. Factors associated with cognitive achievement in late childhood and adolescence: the Young Lives cohort study of children in Ethiopia, India, Peru, and Vietnam. BMC Pediatr. 2014;14:253. [PubMed: 25282338]
22. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010–2050: modeling based on demographics, excess mortality, and interventions. PLoS Med. 2013;10:e1001484. [PubMed: 23874164]

23. Wechsler D WISC-IV Administration and Scoring Manual Wechsler Intelligence Scale for Children-fourth edition. Vol. IV Pearson, San Antonio (TX); 2003.
24. Sattler JM, Dumont R. Assessment of Children: WISC-IV and WPPSI-III Supplement. Sattler Jerome M., La Mesa (CA); 2004.
25. Sattler JM. Resource guide to accompany assessment of children: cognitive foundations. Vol. vi, 5th ed. Sattler JM, La Mesa (CA); 2008: 288.
26. Ryan JJ, Glass LA, Bartels JM. Internal consistency reliability of the WISC-IV among primary school students'. Psychol Rep. 2009;104:874–878. [PubMed: 19708414]
27. Donders J, Janke K. Criterion validity of the Wechsler Intelligence Scale for Children-Fourth Edition after pediatric traumatic brain injury. J Int Neuropsychol Soc. 2008;14:651–655. [PubMed: 18577295]
28. Cohen J Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York: Academy Press; 1988.
29. Steen RG, Fineberg-Buchner C, Hankins G, Weiss L, Prifitera A, Mulhern RK. Cognitive deficits in children with sickle cell disease. J Child Neurol. 2005;20:102–107. [PubMed: 15794173]
30. Wasserman AL, Wilimas JA, Fairclough DL, Mulhern RK, Wang W. Subtle neuropsychological deficits in children with sickle cell disease. Am J Pediatr Hematol Oncol. 1991;13:14–20. [PubMed: 2029072]
31. Swift AV, Cohen MJ, Hynd GW, et al. Neuropsychologic impairment in children with sickle cell anemia. Pediatrics. 1989;84:1077–1085. [PubMed: 2587138]
32. McCoy DC, Zuilkowski SS, Fink G. Poverty, physical stature, and cognitive skills: mechanisms underlying children's school enrollment in Zambia. Dev Psychol. 2015;51:600–614. [PubMed: 25844851]
33. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 2007;85:193–200. [PubMed: 17209196]
34. Novelli EM, Hittner JB, Davenport GC, et al. Clinical predictors of severe malarial anaemia in a holoendemic Plasmodium falciparum transmission area. Br J Haematol. 2010;149:711–721. [PubMed: 20408849]
35. Olney DK, Kariger PK, Stoltzfus RJ, et al. Development of nutritionally at-risk young children is predicted by malaria, anemia, and stunting in Pemba, Zanzibar. J Nutr. 2009;139:763–772. [PubMed: 19225131]
36. Knight S, Singhal A, Thomas P, Serjeant G. Factors associated with lowered intelligence in homozygous sickle cell disease. Arch Dis Child. 1995;73:316–320. [PubMed: 7492195]
37. Puffer ES, Schatz JC, Roberts CW. Relationships between somatic growth and cognitive functioning in young children with sickle cell disease. J Pediatr Psychol. 2010;35:892–904. [PubMed: 20026570]
38. Puffer ES, Schatz JC, Roberts CW. Association between somatic growth trajectory and cognitive functioning in young children with sickle cell disease. J Health Psychol. 1359105314559861, first published online on December 8, 2014.
39. Zemel BS, Kawchak DA, Ohene-Frempong K, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. Pediatr Res. 2007;61(5 Pt 1):607–613. [PubMed: 17413865]
40. Henderson RA, Saavedra JM, Dover GJ. Prevalence of impaired growth in children with homozygous sickle cell anemia. Am J Med Sci. 1994;307:405–407. [PubMed: 8198145]
41. Animasahun BA, Temiye EO, Ogunkunle OO, Izuora AN, Njokanma OF. The influence of socioeconomic status on the hemoglobin level and anthropometry of sickle cell anemia patients in steady state at the Lagos University Teaching Hospital. Niger J Clin Pract. 2011;14:422–427. [PubMed: 22248942]
42. Osei-Yeboah C, Rodrigues O, Enweronu-Laryea C. Nutritional status of children with sickle cell disease at Korle Bu Teaching Hospital, Accra, Ghana. West Afr J Med. 2011;30:262–267. [PubMed: 22669830]
43. King AA, Strouse JJ, Rodeghier MJ, et al. Parent education and biologic factors influence on cognition in sickle cell anemia. Am J Hematol. 2014;89:162–167. [PubMed: 24123128]

44. Vichinsky EP, Neumayr LD, Gold JI, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA. 2010;303:1823–1831. [PubMed: 20460621]
45. Wong HS Edwards P Nature or nurture: a systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. Matern Child Health J. 2013;17:1689–1700. [PubMed: 23135625]
46. Bogale A, Stoecker BJ, Kennedy T, et al. Nutritional status and cognitive performance of mother-child pairs in Sidama, Southern Ethiopia. Matern Child Nutr. 2013;9:274–284. [PubMed: 21806779]
47. Byford M, Kuh D, Richards M. Parenting practices and intergenerational associations in cognitive ability. Int J Epidemiol. 2012;41:263–272. [PubMed: 22422461]
48. Bangirana P, John CC, Idro R, et al. Socioeconomic predictors of cognition in Ugandan children: implications for community interventions. PLoS One. 2009;4:e7898. [PubMed: 19936066]
49. Boyede GO, Lesi FE, Ezeaka VC, Umeh CS. Impact of sociodemographic factors on cognitive function in school-aged HIV-infected Nigerian children. HIV AIDS (Auckl). 2013;5:145–152. [PubMed: 23885180]
50. Noll RB, Reiter-Purtill J, Vannatta K, Gerhardt CA, Short A. Peer relationships and emotional well-being of children with sickle cell disease: a controlled replication. Child Neuropsychol. 2007;13:173–187. [PubMed: 17364573]

TABLE 1

Basic demographic data of participants

	Children with SCA (n = 35–56)	Unaffected children (n = 30–44)	*P*-value
Female sex, n (%)	26.00 (46.43)	18.00 (40.91)	0.581[b]
Age (years), mean (SD)	9.20 (2.75)	9.41 (2.49)	0.690[c]
No. in household, mean (SD)	6.25 (2.78)	5.64 (1.45)	0.298[c]
Parental marital status (married), n (%)	39.00 (100.00)	34.00 (97.14)	0.473[a]
Maternal education, n (%)			0.212[b,d]
<Secondary	29.00 (74.36)	20.00 (60.60)	
≥OND/NCE	10.00 (25.64)	13.00 (39.40)	
Paternal education, n (%)			0.077[b,d]
<Secondary	25.00 (71.42)	15.00 (50.00)	
≥OND/NCE	10.00 (28.57)	15.00 (50.00)	

OND, Ordinary National Diploma; NCE, National Certificate in Education. Both groups include subjects who had missing data for each variable.

[a]Fisher's exact test.

[b]Chi Square test.

[c]Independent sample *t*-test.

[d]*P* values indicate the difference between the two categorical education levels.

TABLE 2

Anthropometric and laboratory data of participants

	SCA(n = 45–52), mean (SD)	Comparisons (n = 37–41), mean (SD)	d	*P*-value[a]
Height (cm)	131.70 (13.60)	138.53 (12.45)	−0.52	0.016
BMI	14.60 (1.64)	17.13 (4.42)	−0.76	0.001
WFAZ	−0.88 (1.44)	0.24 (1.11)	−0.88	<0.001
HFAZ	−0.28 (1.25)	0.56 (1.14)	−0.70	0.001
Peripheral oxygen saturation (%)	96.56 (2.56)	98.08 (1.32)	−0.75	<0.001

WFAZ, weight-for-age *Z* scores; HFAZ, height-for-Age Z scores. Effect sizes (Cohen's d) were calculated by dividing the difference of two sample means by the pooled standard deviation of the two groups. Both groups include subjects who had missing data for each variable.

[a]Independent sample *t*-test.

TABLE 3

Neurocognitive test performance of children with SCA and comparison children

Cognitive measures	SCA(n = 42–53), mean (SD)	Percent missing	Comparisons (n = 27–41), mean (SD)	Percent missing	d	*P*-value[b]	Adjusted *P*-value[c]
Estimated IQ[a]	84.58 (15.32)	25.0	96.10 (18.28)	38.6	−0.68	0.006	0.008
Working memory	88.63 (13.90)	17.9	94.69 (13.90)	34.1	−0.44	0.070	0.174
Processing speed	86.69 (15.72)	14.3	96.91 (18.21)	25.0	−0.60	0.009	0.001
Coding	7.70 (3.14)	5.4	9.95 (3.98)	6.8	−0.63	0.003	<0.001
Symbol search	7.34 (3.47)	10.7	9.15 (3.22)	25.0	−0.54	0.019	0.006
Letter numbering	6.00 (3.30)	16.1	6.67 (3.54)	31.8	−0.20	0.403	0.393
Digit span	10.06 (3.49)	5.4	12.73 (3.60)	9.1	−0.75	0.001	<0.001

[a]Est. IQ was derived from four subtest short forms. The scaled scores of the four subtests and the composite scores of the primary outcomes are reported.[25] Effect sizes (Cohen's d) were calculated by dividing the difference of two sample means by the pooled standard deviation of the two groups.

[b]Independent sample *t*-test.

[c]*P*-value for the association between cognitive measure and presence of SCA, from a linear regression model with each cognitive measure as an outcome and both presence of SCA and father's education ≥OND/NCE as binary predictors.

TABLE 4

Correlations of continuous variables and primary cognitive outcomes among children with SCA and unaffected children

	Est. IQ (n = 36–42)		WMI (n = 36–46)		PSI (n = 42–48)	
Patients with SCA	**r**	***P*-value[a]**	**r**	***P*-value[a]**	**r**	***P*-value[a]**
Age	−0.426	0.005	−0.370	0.011	−0.304	0.036
WFAZ	0.491	0.002	0.426	0.006	0.367	0.016
HFAZ	0.548	<0.001	0.417	0.007	0.332	0.028
Peripheral O_2 saturation	−0.043	0.792	−0.088	0.572	0.037	0.810
Hemoglobin	−0.084	0.620	0.059	0.719	−0.264	0.088
	Est. IQ (n = 25–27)		**WMI (n = 27–29)**		**PSI (n = 30–33)**	
Unaffected children	**r**	***P*-value[a]**	**r**	***P*-value[a]**	**r**	***P*-value[a]**
Age	−0.216	0.279	−0.069	0.721	−0.287	0.106
WFAZ	0.036	0.865	−0.179	0.371	0.160	0.398
HFAZ	0.239	0.250	0.126	0.531	0.450	0.012
Peripheral O_2 saturation	0.086	0.703	−0.157	0.464	0.045	0.823

[a]Pearson correlation.

TABLE 5

Primary cognitive outcomes among children with SCA based on gender and parental education

	Est. IQ (n = 26–42)		WM (n = 29–46)		PS (n = 21–48)	
	Mean (SD)	*P*-value[a]	Mean (SD)	*P*-value[a]	Mean (SD)	*P*-value[a]
Gender		0.388		0.164		0.459
Female	82.4 (14.3)		85.6 (13.8)		84.9 (13.8)	
Male	86.6 (16.2)		91.4 (13.7)		88.3 (17.4)	
Maternal education		0.007		0.064		0.022
<Secondary	80.0 (14.1)		86.4 (13.3)		82.4 (15.3)	
≥OND/NCE	94.9 (10.7)		96.2 (13.3)		94.7 (7.8)	
Paternal education		0.083		0.145		0.414
<Secondary	79.4 (12.9)		85.4 (12.7)		83.1 (15.5)	
≥OND/NCE	89.6 (15.2)		93.6 (15.5)		87.7 (12.3)	

[a]Independent sample *t*-test

TABLE 6

Primary outcomes among unaffected comparison children based on gender and parental education

	Est. IQ (n = 18–27)		WM (n = 20–29)		PS (n = 22–33)	
	Mean (SD)	***P*-value[a]**	**Mean (SD)**	***P*-value[a]**	**Mean (SD)**	***P*-value[a]**
Gender		0.295		0.538		0.816
Female	91.9 (18.6)		92.8 (12.8)		97.9 (16.7)	
Male	99.5 (18.0)		96.1 (14.9)		96.3 (19.5)	
Maternal education		0.264		0.057		0.105
<Secondary	94.0 (20.2)		89.7 (13.8)		97.2 (17.8)	
≥OND/NCE	103.7 (15.9)		100.6 (10.4)		108.2 (10.6)	
Paternal education		0.893		0.546		0.280
<Secondary	97.1 (21.0)		95.8 (12.8)		97.2 (18.3)	
≥OND/NCE	98.3 (18.5)		92.2 (13.3)		105.1 (14.4)	

[a]Independent sample *t*-test.