Published in final edited form as:

Clin Pediatr (Phila). 2015 October ; 54(11): 1087–1093. doi:10.1177/0009922815594356.

Risk Factors for Attention and Behavioral Issues in Pediatric Sickle Cell Disease

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Abstract

Background—Children with sickle cell disease have an increased risk of neurodevelopmental disorders such as attention deficit hyperactivity disorder, intellectual disability, and specific learning disabilities. Little research has been done to characterize the sickle cell disease–related characteristics associated with neurodevelopmental disorders in the sickle cell disease population.

Methods—This study was a retrospective chart review involving the outpatient records of 2 medical centers, Kennedy Krieger Institute and Johns Hopkins Hospital. Participants in the study included 59 children with sickle cell disease with a documented neurodevelopmental diagnosis, specifically attention deficit hyperactivity disorder, attention issues, behavioral issues, executive dysfunction, specific learning disabilities in math, reading, and reading comprehension, intellectual disabilities, developmental delay, fine motor disorders, language disorders, or autism spectrum disorders.

Results—Children with sickle cell disease type hemoglobin S- β thalassemia plus had significantly higher odds of attention issues than children with sickle cell disease type hemoglobin SS (OR = 17.0, 95% CI = 1.99-145.00, $P < .02$). Children with sickle cell disease and a reported history of asthma had significantly higher odds of behavioral issues than children with sickle cell disease without a history of asthma, after adjustment for gender and sickle cell disease type (exact OR = 19.53, 95% CI = 1.16-1369.72, $P < .04$).

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Author Contributions

EIL and BKS created the study concept and design, participated in data acquisition, analysis, and interpretation, and wrote the initial draft of the manuscript together. AMC assisted with study design, data analysis and interpretation, and critically reviewed and revised the manuscript. MVJ participated in data analysis and interpretation and critically reviewed and revised the manuscript. JFC assisted with study design, data acquisition and analysis, and critically reviewed and revised the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JFC has received an honorarium and travel expenses in the past and presently receives salary support through Johns Hopkins for providing consultative advice to Mast Pharmaceuticals (previously Adventrx Pharmaceuticals) regarding a proposed clinical trial of an agent for treating vaso-occlusive crisis in sickle cell disease. JFC is an inventor and a named party on a patent and licensing agreement to ImmunArray for a panel of brain biomarkers for the detection of brain injury. JFC has filed a provisional patent for a potential treatment for sickle cell disease. The other authors have no financial relationships relevant to this article to disclose.

Conclusion—Children with sickle cell disease may have increased risk for certain neurodevelopmental diagnoses based on their disease characteristics and associated comorbidities. These preliminary study results should be explored in a larger database.

Keywords

sickle cell disease; neurodevelopmental disorders; ADHD

Introduction

Sickle cell disease (SCD) is a genetic hemoglobinopathy with several different disease subtypes and variable severity. Children with SCD are at risk for several neurological and developmental complications. Stroke rates are high, with the incidence rate of first ischemic stroke at 1.02 per 100 patient-years in untreated children with SCD between the ages of 2 to 5 years.¹ In the general pediatric population, stroke incidence is estimated to be 2.3 per 100 000 children per year.² Apart from stroke, neurodevelopmental screening in pediatric SCD is warranted for many other reasons. Children with SCD and no prior history of stroke commonly have difficulties with cognition, language, and fine motor tasks.³ One study found that children with SCD, normal neuroimaging, and no prior history of stroke still had lower full scale, verbal, and performance IQs when compared with age-, race-, and gender-matched controls,⁴ findings which appear to continue into adulthood.⁵ Higher rates of learning disabilities, intellectual disability, cerebral palsy, and other developmental delays in comparison with the general population have also been noted in children with SCD. One study reviewed children from the National Health Interview Survey, and found that black children with SCD had 3.3 times higher odds of reporting intellectual disability than black children of the same age in the survey.⁶ Another study found that children with SCD had 2.7 times increased risk for intellectual disability and 10.8 times increased risk for cerebral palsy than other black children in Atlanta.⁷

Referral of these children to the disciplines of pediatric neurology, neuropsychology, or developmental pediatrics typically is prompted when problems arise in school. This referral pattern and screening model is appropriate in the general population, where there is a lower risk of neurodevelopmental disorders; however, it may not be appropriate in children with SCD who are at higher risk of neurodevelopmental disorders and neurological complications such as stroke. Serial assessments for developmental disorders are regularly recommended in other high-risk chronic pediatric diseases such as prematurity and congenital heart disease.^{8,9}

Despite this known high risk for developmental disorders, many children with SCD are not seen routinely for neurodevelopmental evaluation. Potential explanations include difficulties in assessing young children, infrequent follow-up with primary care providers, and school performance issues incorrectly attributed to poor attendance, medication side effects, or chronic illness. Current National Heart, Lung, and Blood Institute (NHLBI) medical guidelines do not include neurodevelopmental evaluation as part of the standard of care for pediatric SCD unless the child has known cerebrovascular disease or there are academic concerns.¹⁰ The American Academy of Pediatrics recommends review of school

performance at routine visits, with consideration for neurocognitive testing as indicated in children with SCD.¹¹

The objective of this study was to identify risk factors for specific neurodevelopmental disorders in children with SCD. We hypothesized that specific neurodevelopmental diagnoses are associated with certain SCD-related conditions. Faster identification of patients with increased risk for attention deficit/hyperactivity disorder (ADHD), intellectual disability, and specific learning disabilities may allow earlier treatment of these disorders with therapeutic interventions, educational modifications, and medication management. Early intervention has the potential to improve academic performance, activities of daily living, and quality of life of these children and their families.¹²

Methods

This study is a retrospective chart review of children with SCD. The study was approved by the Johns Hopkins Institutional Review board in May 2012. A chart review of subjects with SCD seen at 2 medical centers, Kennedy Krieger Institute and Johns Hopkins Hospital, took place from May 2012 to March 2014. The Kennedy Krieger Institute is an urban pediatric rehabilitation hospital and an ambulatory outpatient care center in Baltimore, Maryland, adjacent to the Johns Hopkins Medical Campus, with shared faculty and research between both hospitals. The Harriet Lane Clinic of the Johns Hopkins Hospital Children's Center is an ambulatory pediatric care center and tertiary care hospital of an urban hospital in Baltimore, Maryland. Charts from both hospitals were reviewed for study inclusion.

Chart Review

For the Kennedy Krieger Institute charts, a list of potential subjects was created by a search of the Institute's medical records for subjects with a diagnosis of "sickle cell disease" seen between January 2007 and March 2012. For the Johns Hopkins Hospital charts, a roster of patients with SCD was provided by the Pediatric Hematology Department in March 2012. Inclusion criteria included age less than or equal to 18 years and documentation of a neurodevelopmental diagnosis, specifically ADHD, attention issues, behavioral issues, executive dysfunction, specific learning disabilities in math, reading, and reading comprehension, intellectual disabilities, developmental delay, fine motor disorders, language disorders, and autism spectrum disorders. Behavioral issues and attention issues are disorders that do not meet full criteria for neurodevelopmental diagnoses such as ADHD but do have concerning symptoms. Subjects with psychiatric diagnoses associated with neurodevelopmental disorders such as anxiety, depression, bipolar disorder, and substance abuse were also included. Subjects at risk for neurodevelopmental disorders were included, if there was documentation of poor academic performance, hearing loss, genetic disorders other than SCD, seizure disorders, or traumatic brain injury. Children in foster care or adopted were excluded from the study.

A total of 58 Kennedy Krieger Institute charts were identified with an SCD diagnosis and reviewed for study inclusion. Neurodevelopmental or neuropsychological evaluations were written, reviewed, and completed by resident physicians/neuropsychology trainees and their attending physicians/PhD neuropsychologists. Subjects were selected for the study if they

had a neurodevelopmental diagnosis in the impression and diagnoses sections of the Kennedy Krieger Institute notes, based on patient history and evaluation results. A total of 343 Johns Hopkins Hospital patients were on the Pediatric Hematology SCD roster and their charts were reviewed for study inclusion. Subjects were selected for the study if they had a neurodevelopmental, neuropsychological, or developmental diagnoses indicated by their hematologist or other medical provider per their medical records.

All charts were reviewed for date of birth, genotype of SCD, disease complication/comorbidity history (stroke, acute chest syndrome, pain crisis, splenic sequestration, infection, dactylitis), sickle cell treatments (hydroxyurea, chronic transfusions), school services (Individualized Educational Plan [IEP], 504 Rehabilitation Plan [504 Plan]), and neurodevelopmental diagnoses (ADHD, attention issues, developmental delay, specific learning disabilities in math and reading comprehension, language disorders, anxiety). Demographic data included age, gender, and SCD type. An IEP is a public school special education services plan, including rehabilitative therapies, used for children with significant neurodevelopmental disabilities. A 504 Plan provides classroom accommodations for children with behavioral and developmental issues. Further information was collected regarding neurological examination findings, neuroimaging findings, and current medications. Data collected from the chart review were input into a Microsoft Access 2010 database created specifically for this study.

Subjects were excluded for a variety of reasons. Of the 58 total Kennedy Krieger Institute charts reviewed, 45 were excluded due to being adopted or in foster care (concern for additional confounding factors due to background), non-English speaking, no SCD diagnosis found on chart, or seen by providers in departments other than neuropsychology, neurology, and child development. Of the 343 total Johns Hopkins Hospital charts reviewed, 297 were excluded due to not having documentation of developmental issues, being adopted or in foster care, not having an SCD diagnosis, not having a hematology visit note in the electronic medical records system, legal issues, or being older than 18 years.

Statistical Analyses

Data were collected using Microsoft Access 2010 and exported into Stata IC-13 (StataCorp, College Station, TX) for analyses. Because of the small sample size, only neurodevelopmental diagnoses, disease characteristics, and complications occurring in at least 5 subjects were included in the analyses. Logistic regression analyses and exact logistic regression analyses (exact) were used with specific neurodevelopmental diagnoses as the outcome variables (ADHD, developmental delay, specific learning disability in math, specific learning disability in reading comprehension, language disorder, anxiety, and behavioral issues). Exact logistic regression was used whenever possible to compensate for the small sample size. Gender and SCD type were included as covariates in the model; only these 2 covariates were used, due to the small sample size. Specific SCD complications and associated comorbidities were used as prediction variables (pain crisis, acute chest syndrome, stroke, splenic sequestration, asthma, infection).

Results

A total of 59 subjects met inclusion criteria and were included in the overall chart review from both hospitals. There were 18 subjects from the Kennedy Krieger Institute chart review and 41 subjects from the Johns Hopkins Hospital chart review. All Johns Hopkins Hospital subjects identified were also searched for in the Kennedy Krieger medical records search and 5 of the 18 total neurodevelopmental evaluations were obtained using this method. Table 1 shows additional subject characteristics in both groups. Of note, there were no hemoglobin S- β null thalassemia patients chosen for the study. Figure 1 shows the reported neurodevelopmental diagnoses in all of the subjects. Figure 2 shows the reported SCD-related complications in all the subjects.

Neurodevelopmental Diagnoses Associations With Demographics and Disease Characteristics

There was a significant difference in the distribution of the types of SCD between children with attention issues and children with other neurodevelopmental disorders. Two of the 36 subjects with hemoglobin SS had attention issues (6%); 3 of the 6 subjects with hemoglobin S- β plus thalassemia had attention issues (50%); none of the 12 subjects with hemoglobin SC had attention issues (0%); 1 of the 2 subjects with hemoglobin SS- α thalassemia trait had attention issues (50%), (Fisher's exact test, $P < .005$). Logistic regression analysis showed that children with SCD type hemoglobin S- β thalassemia plus had a significantly higher chance of attention issues than children with hemoglobin SS (odds ratio [OR] = 17.0, 95% CI = 1.99-145.00, $P < .02$).

There were no additional significant relationships between other neurodevelopmental disorders and demographic characteristics when demographic characteristics were added to the model.

Neurodevelopmental Diagnoses Associated With Sickle Cell Disease Complications

There was a significant difference in the probability of a history of asthma between those with and without behavioral issues. Of the 47 children without a history of asthma, 2 (4%) had behavioral issues; of the 10 children with a history of asthma, 3 (30%) had behavioral issues (Fisher's exact test, $P < .04$). With gender and SCD type as covariates, there were significantly higher odds of behavioral issues in subjects with a history of asthma than in children without a history of asthma using exact logistic regression analysis (exact OR = 19.53, 95% CI = 1.16-1369.72, $P < .04$). The association between behavioral issues and history of asthma diagnosis was no longer significant when gender or both gender and SCD type were removed from the model (exact OR = 9.44, 95% CI = 0.92-132.05, $P > .05$).

There were no additional significant relationships between other neurodevelopmental disorders and disease-related complications.

Discussion

Children with SCD with and without a history of neurological complications are at increased risk for neurodevelopmental disorders in comparison with the general pediatric population.³

However, risk factors for ADHD and other disorders have not been widely researched in the pediatric sickle cell literature, outside of children with a history of stroke. This study is an exploration for associations between specific disorders and disease-related characteristics.

In our study, children with hemoglobin SS and hemoglobin SC were less likely to have attention issues when compared with children with hemoglobin S- β thalassemia plus. The label of attention issues is usually seen in children who do not meet full criteria for ADHD, due to symptoms only in one setting or intact school performance despite symptoms, or who have not been formally evaluated for ADHD. The less common genotypes of SCD, such as hemoglobin S- β plus thalassemia, are usually less severe and may not have as many disease-related complications as homozygous hemoglobin SS SCD. Confounding neurodevelopmental disorders may be easier to uncover during their routine medical care, as opposed to the complex routine assessments of sicker children. Additional research is necessary to determine if better screening processes or targeted assessment methods are needed for this specific population. Better detection of attention issues in all genotypes of SCD will allow implementation of proper educational interventions and potentially improve the quality of life and outcomes of these children.¹²

Another finding was that children with SCD and a reported history of asthma are at higher risk for behavioral issues when compared with children with SCD without a reported history of asthma. Asthma in SCD is difficult to diagnose, as certain complications of SCD, such as acute chest syndrome, share common symptoms with asthma, particularly wheezing and airway hyperresponsiveness.¹³ Asthma also increases the risk of other SCD-related complications, specifically pain crises, acute chest syndrome, and stroke.^{13,14} The association between asthma and behavioral issues in our study is significant, though there is a wide range in the 95% CI, from 1.1 to 960. Despite this imprecision, there is biological plausibility to this finding. Screening for asthma and asthmatic medication is routine during neurodevelopmental evaluations, as certain asthma medications can reportedly cause increased heart rates and behavioral issues similar to hyperactivity.¹⁵ Children with asthma are also thought to be at higher risk for ADHD in the general pediatric population, though the evidence is conflicting.¹⁶⁻²⁰ In addition, both disorders are quite common in this group; 30% to 70% of patients with SCD have asthma, while one study found that 51% of children with SCD had behavioral and emotional issues per parental and teacher report.^{13,21} The relationship between asthma and behavioral issues in our study is also confounded by gender and SCD type, as it is no longer a significant association when these factors are not adjusted for in a model. Subjects with a reported history of both asthma and behavioral issues included 2 males with hemoglobin SS, 2 females with hemoglobin SS, and 1 female with hemoglobin SC. Further exploration of the relationship between behavioral issues and asthma in children with SCD is needed in a larger population with more precise diagnostic information.

No other relationships between SCD-related complications and neurodevelopmental disorders were identified. Specifically, a reported history of stroke was not associated with any specific neurodevelopmental disorders. While all the subjects had a reported history of a neurodevelopmental disorder, only 22% of the subjects in our study had a reported history of stroke. Children with a history of stroke regardless of SCD status are clearly at risk for

motor and cognitive difficulties. However, stroke may be a common risk factor for many neurodevelopmental disorders, thus obscuring relationships between different disease characteristics and specific disorders. This relationship should be explored further in a larger dataset with children with and without neurodevelopmental disorders.

We also did not find any children with a diagnosis of autism in our review. Autism does occur quite commonly in the black population, per population statistics, but many hematology and neurology providers have not seen a single SCD patient with autism or an autism spectrum disorder.²² SCD could confer a protective effect for autism but autism could also simply be underrecognized in these patients. There were also no significant differences between males and females in terms of the prevalence of any of the neurodevelopmental disorders, though ADHD and autism have a clear higher prevalence in male children in the general population.^{23,24} The lack of gender differences in ADHD prevalence suggests that the phenotype and mechanisms of neurodevelopmental disorders may differ in children with SCD in comparison with the general pediatric population.

Because of the subtle presentations of cerebral infarctions and high frequency of neurodevelopmental disorders, serial neurodevelopmental assessments are needed on a regular basis in children with SCD. In situations where the child does not have a previously diagnosed neurological injury, neurodevelopmental office visits are often not covered by insurance; therefore parents may be financially restricted to available government and school providers. In areas with limited access to child neurology, neuropsychology, and developmental pediatric providers, wait times for visits with these specialists may be excessive for both public and private services. In addition, these children have other SCD-related health care needs that require frequent visits with other medical providers for routine health maintenance, which could limit the family's time and resources. However, an increased frequency of visits might also increase rates of diagnoses.

Limitations

There were several limitations to this study. Our study was limited to children in Maryland with SCD seen in a small time frame. We also did not use or confirm standardized diagnostic criteria for SCD-related complications or neurodevelopmental diagnoses. However, our subjects had rates of SCD-related complications similar to the general pediatric SCD population. Information about both types of disorders was not always available in pediatric hematology or neurodevelopmental medical records. Referral bias was also different between clinics, as Kennedy Krieger Institute typically serves as a tertiary referral system for children with neurodevelopmental issues, while the Johns Hopkins Hospital Pediatric Hematology clinic was the pediatric hematology provider for most of the subjects. Many of the Kennedy Krieger Institute subjects were excluded due to lack of documentation of SCD history in the clinic notes, while many of the Johns Hopkins Hospital subjects were excluded due to lack of documentation of neurodevelopmental issues in the clinic notes. We also did not have any Hemoglobin S Beta null thalassemia patients included in the study, which limits generalization to that subtype of SCD. The study was also small, with only 59 participants. With such a small number, it is difficult to draw generalizable conclusions unless there are large differences between groups. To account for these issues,

we only used chi-square and logistic regression analyses on the diagnoses, demographic characteristics, and complications with a subject group greater than 5. While some comparisons reached statistical significance, the large confidence intervals suggested these findings require further exploration.

Future Research

Our results are a preliminary analysis in order to better define our methods, hypotheses, and models. The above limitations can be addressed in a dataset from a large clinical trial with consistent and validated neuropsychological and neurodevelopmental testing and inclusion of children with and without neurodevelopmental disorders to better define our comparison group. The relationship between different types of stroke (ischemic, hemorrhagic, silent) and neurodevelopmental disorders could also be addressed in larger data set, to better screen for subclinical brain injury in the population. Neurodevelopmental disorders are a major complication of pediatric SCD.

Acknowledgments

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: EIL was supported by T32HD007414-20 (Principal Investigator [PI] MVJ) from the National Institute of Child Health and Human Development (NICHD). EIL and JFC were supported by K12HL087169-07 (PI JFC) from the National Heart, Lung and Blood Institute (NHLBI). JFC was supported by U54HL090515 (PI JFC), R01HL091759 (PI JFC) from the NHLBI and U01-NS-042804 9 (PI Debaun) from the National Institute of Neurological Disorders and Stroke (NINDS). BKS was supported by LEND T73MC17245 from the Health Resources and Services Administration.

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Figure 1.
Neurodevelopmental Diagnoses of Subjects (n = 59)

Figure 2.
Sickle Cell Disease-Related Complications of Subjects (n = 59)

Table 1

Characteristics of Pediatric Sickle Cell Neurodevelopmental Subjects.

	Overall Group (n = 59)	Kennedy Krieger Group (n = 18)	Johns Hopkins Hospital Group (n = 41)
Average age, years	16.7		
Gender, n (%)			
Male	34 (58)	9 (50)	25 (61)
Type of sickle cell disease, n (%)			
Hb SS	36 (61)	8 (44)	28 (68)
Hb SC	12 (20)	3 (17)	9 (22)
Hb S- β thalassemia plus	6 (10)	3 (17)	3 (7)
Hb S- β thalassemia null	0	0	0
Hb SS- α Thalassemia	2 (3)	2 (11)	0
Unknown	3 (6)	2 (11)	1 (3)
Ethnicity, n (%)			
Black	57 (97)	18 (100)	39 (95)
Caucasian	1 (1.5)	0	1 (2.5)
Other	1 (1.5)	0	1 (2.5)
School services, n (%)			
Individualized Education Plan (IEP)	26 (44)	11 (61)	15 (37)
None	7 (12)	4 (22)	3 (7)
504 Rehabilitation Act	3 (5)	3 (17)	0
Previous IEP	1 (2)	0	1 (2)
Unknown	22 (37)	0	22 (54)

^a Percentages were out of total group number in top row.