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Authors

Longoria, Jennifer N
Pugh, Norma L
Gordeuk, Victor
et al.

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Patient-reported neurocognitive symptoms influence instrumental activities of daily living in sickle cell disease

Jennifer N. Longoria, PhD[1], **Norma L. Pugh, MS**[2], **Victor Gordeuk, MD**[3], **Lewis L. Hsu, MD**[4], **Marsha Treadwell, PhD**[5], **Allison A. King, MD**[6], **Robert Gibson, MD**[7], **Mariam Kayle, PhD**[8], **Nancy Crego, PhD**[8], **Jeffrey Glassberg, MD**[9], **Cathy L. Melvin, PhD**[10], **Jane S. Hankins, MD**[*,11], **Jerlym Porter, PhD**[*,1]

[1]Department of Psychology, St. Jude Children's Research Hospital, Memphis, TN

[2]Center for Clinical Research Network Coordination; RTI International

[3]Department of Medicine, University of Illinois at Chicago, Chicago, IL

[4]Department of Pediatrics, University of Illinois at Chicago, Chicago, IL

[5]University of California San Francisco Benioff Children's Hospital Oakland

[6]Program in Occupational Therapy and Departments of Pediatrics and Medicine, Washington University, St. Louis, MO

[7]Department of Emergency Medicine and Hospitalist Services, Augusta University, Augusta, GA

[8]School of Nursing, Duke University, Durham, North Carolina

[9]Department of Emergency Medicine, Icahn School of Medicine at Mt. Sinai, New York, NY

[10]Medical University of South Carolina, Charleston, SC

[11]Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Individuals with sickle cell disease (SCD) experience neurocognitive decline, low medication adherence, increased unemployment, and difficulty with instrumental activities of daily living (IADL). The relationship between self-perceived cognitive difficulties and IADLs, including employment, school enrollment, independence, engagement in leisure activities, and medication adherence is unknown. We hypothesized that self-reported difficulties across neurocognitive areas would predict lower IADL skills. Adolescent and adult participants of the multi-site Sickle Cell Disease Implementation Consortium (SCDIC) (n= 2,436) completed patient-reported outcome (PRO) measures of attention, executive functioning, processing speed, learning, and comprehension. Cognitive symptoms were analyzed as predictors in multivariable modeling. Outcome variables included 1) an IADL composite that consisted of employment, participation in school, reliance on others, and leisure pursuits, and 2) hydroxyurea adherence. Participants reported cognitive difficulty across areas of attention (55%), executive functioning (51%),

Corresponding author: Jennifer Longoria, PhD; St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 740, Memphis, TN 38105-3678; jennifer.longoria@stjude.org; Phone: (901) 595-1153.

*Denotes co-authorship

processing speed (57%), and reading comprehension (65%). Executive dysfunction (p<.0001) and sometimes or often experiencing learning difficulties (p<.0001 and p=.0397) and poor comprehension (p=.0002 and p=.0005), controlled for age (p<.0001), pain (p<.0001), and hydroxyurea use (p=.0001), were associated with poor IADL skills. Executive functioning difficulties (p=.0212), controlled for age (p=.0129 for ages 25–34), genotype (p=.0006), and hemoglobin (p=.0039), predicted hydroxyurea non-adherence. Analysis of PRO measures indicated that cognitive dysfunction is prevalent in adolescents and adults with SCD. Cognitive dysfunction translated into clinically meaningful outcomes. PRO of cognitive symptoms can be used as an important adjunct clinical tool to monitor symptoms that impact functional skills, including engagement in societal activities and medication adherence.

Keywords

sickle cell disease; neurocognitive; patient-reported; instrumental activities of daily living; medication adherence

Introduction

Sickle cell disease (SCD) is an inherited hemoglobin disorder that affects approximately 100,000 Americans and causes progressive organ damage, acute and chronic pain, and ischemic brain lesions [1]. As patients age, medical complications and neurocognitive deficits intensify [2,3].

The neurocognitive effects of SCD emerge in the early developmental period and persist into adulthood [4,5]. In addition to reduced global intellectual functioning (i.e., full scale intellectual quotient [FSIQ]), adults with SCD also exhibit specific deficits in processing speed, working memory, and executive functioning skills [6]. Executive functioning skills describe a range of complex mental activities required for goal-directed behavior, including focused attention, cognitive flexibility, strategic planning, and inhibitory control. Although neurocognitive difficulties are exacerbated by cerebrovascular events in SCD, weaknesses also exist in the absence of overt stroke or silent infarct [7].

Engagement in daily living activities relies on various skills that increase in complexity and are supported by neurocognitive processing [8]. Adaptive daily living (ADL) skills describe basic tasks, such as ability to independently eat, dress, and ambulate, whereas instrumental activities of daily living (IADL) include complex skills that support independent living within the community [9]. Examples of IADL skills include money management, responsibility for medications, domestic life activities, learning, self-care, interpersonal interactions and relationships, and community, civil, and social life [8,10]. IADL skills require more complex neuropsychological abilities than ADL skills and are most susceptible to cognitive changes [11]. Executive dysfunction has emerged as the best predictor of decline in IADL skills, even when accounting for health status, age, and education in the general population [12].

Adolescents and young adults with SCD report weaknesses in IADL skills that limit independence and impact participation in societal activities, including money management,

vocational skills, living arrangements, health care knowledge, and emergency preparedness [13]. In a robust international sample, more than a third of individuals with SCD reported that the disease impacted their participation in daily household chores and social activities [14]. Medication adherence, another aspect of IADL skills, is often poor among youth and adults with SCD [15].

Workforce and educational engagement represent another marker of IADL skills. The rate of employment for individuals with SCD in the U.S. is below the general population and estimates of workforce participation span 15–56% [5,16]. Emerging evidence has suggested that reduced intellectual functioning, lower educational attainment, female gender, reduced assertiveness, and perceived impact of disease are all predictors of unemployment in individuals with SCD [5,17]. In several studies, the rate of disabled participants has exceeded the rate of unemployed individuals, with prevalence rates of disability status spanning 28–37% [18,19].

Patient reported outcome (PRO) measures allow patients to directly communicate information regarding disease-related symptoms, as well as symptoms specific to cognitive, psychological, adaptive, and social concerns. PROs facilitate patient-centered care and can be used as primary or secondary outcome measures with patients who have SCD [20]. Incorporation of PROs into clinical care can facilitate patient engagement, support individualized care through shared decision-making, and improve patient outcomes by identifying areas of healthcare and psychosocial needs [21].

The relation of PRO measures of cognitive difficulties and IADL skills in SCD is not well understood. In the present study, we examined PRO measures of cognitive difficulties in areas of attention, executive functioning, processing speed, learning, and comprehension. We report the prevalence of self-reported cognitive difficulties in a large sample of adolescents and adults with SCD and tested the hypothesis that patients who reported daily difficulties across neurocognitive domains had lower IADL skills, including employment, school enrollment, independence, engagement in leisure activities, and medication adherence.

Methods

Procedures and participants

In 2016, the National Heart, Lung, and Blood Institute (NHLBI) established the Sickle Cell Disease Implementation Consortium (SCDIC) with the goal of developing a longitudinal registry for collection of healthcare data, including clinical information and PROs [22]. The SCDIC is a multi-site consortium of eight geographically dispersed academic medical centers and a data coordinating center. All sites enroll participants with SCD into a prospective registry (SCDIC registry) comprising the study population [23]. Approval was received by the institutional review boards at each of the SCDIC study sites prior to any data collection. Written informed consent was obtained from participant or legal guardian before enrollment into the study.

Participants were eligible for recruitment in the SCDIC registry based on the following inclusion criteria: 15 to 45 years of age, confirmed diagnosis of SCD (subtypes Hb SS, SC,

Sβ^0-thalassemia, SO, SD, SG, SE, or SF) by hemoglobin fractionation tests, and literacy in English. Participants were excluded from enrollment if they had a successful bone marrow transplant. Recruitment of participants began in October 2017 at outpatient clinics, hospital inpatient settings, patient support group meetings, conferences, and other platforms left at the discretion of the centers.

After consent was obtained, eligible participants completed an enrollment survey and had baseline data on their disease characteristics abstracted from their medical records [22]. The SCDIC registry contains 2,514 participant records and only baseline results were included in the current analysis. Participants were excluded for missing consent form and diagnosis (n=64) and failure to confirm diagnosis (n=14), leaving 2,436 cases available for analysis [23].

Measures

Demographic and clinical information—The SCDIC enrollment survey was developed by the SCDIC registry committee, which consisted of at least one SCD expert from each of the eight sites. The survey contained a combination of PROs and items specific to demographic (e.g., age, race, gender, native language, marital status, household income, education, and employment), disease (e.g., genotype and stroke history), and treatment related variables (e.g., patient-reported history of hydroxyurea use and days of hydroxyurea use within the past week) [22]. Data for demographic and disease (laboratory and treatment) variables were also abstracted from participant's electronic health records by research staff.

To describe employment, participant responses were condensed into two categories: workforce engagement and workforce disengagement. Workforce engagement was formed by grouping participant responses of 1) "working now", 2) "student", and 3) any combination of "working now" or "student" that also included being "disabled." Student status was classified in the workforce engagement category since educational pursuits function as a primary occupation for many youths and represent intent to join the workforce. Workforce disengagement was formed by grouping 1) "looking for work, unemployed", 2) "only temporarily laid off, sick leave, or maternity leave", 3) "disabled, permanently or temporarily", 4) "keeping house", and 5) "retired". Additionally, there were 114 responses of "other" that included additional information on employment and school activities. We analyzed the responses and recoded these cases into categories that reflected workforce engagement or disengagement. Data for hydroxyurea adherence within the past seven days were collapsed into categories representing adherent (took 6 or 7 days) and non-adherent (took ≤ 5 days). Most studies consider an 80% rate of medication adherence to be acceptable and we selected the threshold of ≤ 5 days (71% or less) adherence to reflect this standard [24].

Patient reported outcomes—The SCDIC enrollment survey included PROs from several NIH-developed HealthMeasures, including the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) and Quality of Life in Neurological Disorders (Neuro-QoL) [25].

Eight items from the Neuro-QoL Item Bank v2.0, Cognitive Function Short-Form assessed cognitive symptoms. Questions assessing perceived cognitive symptoms included current difficulty 1) "Reading and following complex instructions", 2) "Planning for and keeping

appointments that are not part of your weekly routine", 3) "Managing your time to do most of your daily activities", and 4) "Learning news tasks or instructions". Perceived cognitive difficulties within the past seven days were assessed by 1) "I had to read something several times to understand it", 2) "My thinking was slow", 3) "I had to work really hard to pay attention or I would make a mistake", and 4) "I had trouble concentrating". Each question contained a 5-point Likert scale response. Items had different anchors for each endpoint of the scale to represent severity. For example, 'never' and 'very often,' and 'none' and 'cannot do' were endpoints for severity and difficulty. Responses were collapsed into three categories according to the following guidelines: *Never* category included 'never', and 'none'; *Sometimes* category included 'rarely', 'sometimes', 'a little bit', and 'somewhat'; and *Often* category included 'often', 'very often', 'a lot', and 'cannot do'. Across items, a response in the *Often* category was considered to represent high impact or severity of symptoms.

Two items assessing the impact of health on independence and social activities were collected from the ASCQ-Me v2.0 Social Functioning Short-Form. Functioning over the past 30 days was assessed by 1) "How much did you rely on others to take care of you because of your health?" and 2) "How much did your health make it hard for you to do things with your friends?" Items included a 5-point Likert scale response. Anchors for impact of symptoms on daily activities included 'not at all' and 'very much'. Responses were collapsed into the following categories according to these guidelines: *Never* category included 'not at all'; *Sometimes* category included 'a little bit' and 'somewhat'; and *Often* category included 'quite a bit' and 'very much'. Pain impact over the past six months was assessed with a single item from the ACSQ-Me: "How often did you have very severe pain?" Responses were re-categorized according to the guidelines previously described for cognitive items on the Neuro-QoL.

Instrumental adaptive daily living (IADL) composite—We initially explored creating a single IADL composite to be the outcome variable of interest. The composite was to include workforce engagement, medication adherence, independence with daily living tasks, and ability to engage in leisure activities. These four outcomes of interest were examined with an exploratory factor analysis. We looked at a model with one factor and no rotation, as well as a model with two factors and promax rotation. In each instance, the medication adherence variable did not load with the others. Cronbach's coefficient alpha statistics confirmed the factor analysis results. Therefore, we examined medication adherence as a separate outcome measure.

The final construct of our IADL composite included 1) employment and educational status, 2) independence with daily living tasks, and 3) the ability to engage in leisure activities. Employment and educational status were further collapsed as "engaged" (student, employed, and any combination that also included disability status) and "unengaged" (exclusively disabled, unemployed, or retired). These three variables were combined via meaningful grouping, an approach that assists in creating a composite variable from multiple categorical variables. Employment status was given a value of 1 for unengaged participants and a value of 2 for engaged participants. For independence with daily living tasks, participants were given a value of 1 if categorized as 'often a problem', 2 if categorized as 'sometimes a

problem', and 3 if categorized as 'never a problem'. Similarly, for the ability to engage in leisure activities, participants were given a value of 1 if categorized as 'often a problem', 2 if categorized as 'sometimes a problem', and 3 if categorized as 'never a problem'. These values were added together to create the final composite score.

Statistical Analyses

Descriptive summary statistics were generated for predictors and outcomes. Spearman correlations were generated to examine the relationships between all predictors. For the IADL composite, we used univariate models (ANOVA) to examine the relationships between the outcome and demographic and clinical measures. All statistically significant relationships were then included in an initial multivariable model. The final multivariable model was generated by PROC GLMSELECT with backward selection.

Likewise, for medication adherence, we used univariate logistic models to examine the relationships between the outcome and demographic and clinical measures. All statistically significant relationships were then included in an initial multivariable model and the final multivariable model was generated by PROC LOGISTIC with backward selection. All analyses were conducted in SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and clinical information

Among 2,436 participants, approximately half were female (56.9%) and the mean age at time of survey completion was 28 years old (Standard Deviation/SD= 7.9, Table 1). Most respondents identified as Black or African American (97%) and indicated that English was their primary language (99.4%). Most respondents were never married (69%) and had a household income of $25,000 or less (54%). Of those participants who keep house and were also in the lowest income group (n= 30, $25,000 and under), 25 lived in a household with at least one child. Approximately 21% of participants were college graduates (undergraduate or graduate degree) and an additional 33.9% reported some college experience across undergraduate and graduate school. More than a third of the total sample reported being unemployed (17.3%) or disabled (24%).

The HbSS genotype was prevalent (69.3%) in our sample and nearly a quarter (22.2%) of participants reported history of stroke. Average hemoglobin value was 9.6 g/dL and average HbF was 8.4%. Participants had similar rates of chronic transfusion modalities, including simple (9.9%) and exchange (11.6%), and 4.2% of participants reported history of both. Most participants reported being prescribed hydroxyurea (73.8%) at some point in their treatment history and 1,153 (47.3%) were currently treated with hydroxyurea. For participants currently prescribed hydroxyurea, 40.6% missed at least one dose within the past week. Pain frequency within the last six months was reported to be mostly acute (56.2%), although a third of participants (33.6%) endorsed chronic pain (Supplemental Table 1).

More than half of participants reported some degree of recent difficulty (i.e., *Sometimes* or *Often* responses) with reading comprehension (65.1%), slow mental processing (56.5%),

and attention within the past week (55.2 and 60.2%, Table 2). Current problems (i.e., *Sometimes* or *Often*) were also reported with time management (50.7%), planning (43.3%), learning (32.1%), and following complex instructions (25.7%). Within the past month, most participants experienced some degree of interruption to social activities (68.9%) and relied on others for care (53.7%) because of their health problems.

We evaluated correlations between PRO responses and information from participant medical charts. Cognitive symptoms were reverse scored and lower values indicate better functioning. PROs of executive functioning, learning, and comprehension were negatively correlated with educational level (EF: r_s= −.06, p=.006, Learning: r_s= −.08, p< .0001, Comprehension: r_s= −.05, p=.017). Executive function was also negatively correlated with hemoglobin (r_s= −.05, p=.043). PRO of hydroxyurea adherence was positively correlated with hemoglobin, MCV, and HbF values (Hb: r_s= .07, p=.026, MCV: r_s= .24, p< .0001, HbF: r_s= .19, p< .0001).

Univariate analysis identified sickle genotype, history of overt stroke, age, income, and having a college degree as associated with employment for participants age ≥18 years. Participants with a severe sickling genotype (i.e., Hb SS/Hb Sβ0- thalassemia) (p < .001), history of stroke (p< .001), no college degree (p< .001), and an annual income <$25,000/ year (p< .001) were more likely to be unengaged in the workforce (i.e., unemployed, disabled, or retired). Aging was associated with disengagement in the workforce, whereas gender was not a significant predictor (Supplemental Table 2).

IADL skills composite

The mean IADL composite was M= 6.0 (SD= 1.5), with a possible range of 3–8. Higher scores indicated greater participation in daily activities (Figure 1).

In univariate analyses, sickle genotype (p=.028), hemoglobin, age group, gender, household income, education, frequency of pain severity, history of hydroxyurea use at any timepoint, SCDIC site, and cognitive symptoms of comprehension, learning, processing speed, attention, and executive functioning (p< .0001) were all associated with the IADL skills composite. In multivariable modeling, executive functioning, learning, comprehension, age group, frequency of very severe pain (in the past 6 months), history of hydroxyurea use at any timepoint, income, education, and gender were significant predictors of IADL skills ($F(15, 1942) = 57.60$, p< .0001, $r^2 = 0.31$) (Table 3). SCDIC site was not significant in the multivariable model. Gender was not retained in the backward selection process but was retained in the final model because of its potential for clinical importance. Current problems with executive functioning (p< .0001 both *Sometimes* and *Often* groups), learning (p=<.0001 for *Sometimes* group and p=.0397 for the *Often* group), and comprehension (p=.0002 for *Sometimes* and p=.0005 for *Often* group) were significant predictors of lower IADL skills when controlled for age (p=.0184 for ages 18–24 years old and p< .0001 for 25–34 and 35–45 years old), acute or chronic severe pain in the past 6 months (p< .0001 both groups), and history of hydroxyurea use (p=.0001). Having a household income greater than $25,000 (p< .0001), a college or professional degree (p< .0001), and being male (p=.0239) were all associated with a higher IADL skills composite score.

We also analyzed the IADL composite without inclusion of participants who were disabled to determine if these groupings (disabled and working or disabled and not working) impacted outcomes. When excluding participants who were both disabled and working from the engaged category (n=10) in the IADL composite, history of stroke became a significant predictor (p= .0441) in univariate modeling; however, this variable was not retained in the final multivariable model. Executive dysfunction (p<.001) and attention difficulties (p=.0225 for *Sometimes* group and p<.0001 for *Often* group) predicted IADL skills, whereas concerns with learning and comprehension were no longer significant (Supplemental Table 3). Removal of participants who were disabled and not working from the unengaged category (n=556) removed a substantial number of participants with the most severe genotype from analysis. Accordingly, sickle genotype was no longer significant in the univariate model and the final model no longer included history of hydroxyurea, education, executive functioning, learning, or comprehension (Supplemental Table 4). Difficulties with attentional control (p=.0089 for the *Sometimes* group and p=<.0001 for the *Often* group*)* emerged as a significant predictor of IADL skills for individuals with SCD when excluding participants who are disabled and not working.

Hydroxyurea non-adherence

For each cognitive variable, the *Never* category served as the reference group. In univariate analyses, sickle genotype (p=.0158), hemoglobin (p=.0379), age group (p=.0208), household income (p=.0496), and concerns with executive functioning (p=.0052) were associated with hydroxyurea non-adherence (i.e., took ≤ 5 days within the past week). In a multivariable model, difficulty with executive functioning skills (p=.0212 for *Sometimes* group) predicted poor hydroxyurea adherence when controlled for age (p=.0129 for ages 25–34 years old), severe genotype (p=.0006 for Hb SS/Sβ^0-thalassemia/SD/SO/SE), and hemoglobin (p=.0039) (Table 4).

We conducted additional analyses to determine whether SCDIC site location or inclusion of participants with a history of transfusion impacted findings. When including SCDIC site in univariate analysis, location (p=.0001) emerged as an additional predictor of hydroxyurea non-adherence. In a multivariable model, variability in hydroxyurea adherence was associated with SCDIC site (p<.0001) when controlling for other variables and executive functioning was no longer significant. We also examined hydroxyurea non-adherence in a model that excluded participants with history of transfusion since hemoglobin values may have been influenced by a recent erythrocyte transfusion. When removing participants with chronic transfusion (n=422) from univariate analysis, executive functioning (p=.0232), income (p=.0181), genotype (p=.0264), and hemoglobin (p=.0035) were associated with hydroxyurea non-adherence. In a multivariable model, age group (p=.0426 for ages 25–34) and genotype and hemoglobin (p<.001) remained significantly associated with hydroxyurea non-adherence (Supplemental Table 5).

Discussion

In the largest PRO study of individuals with SCD in the United States, more than half of adolescent and adult participants reported contending with cognitive difficulties on a regular

basis, including inattention, poor executive functioning, reduced processing speed, and difficulty with comprehension. Difficulty with executive functioning skills, comprehension, and learning emerged as significant predictors of IADL skills (i.e., workforce engagement, independence, and leisure). Poor IADL skills were also associated with aging, chronic pain, and history of hydroxyurea use, and collectively, these variables appear to represent markers of disease impact and severity. Female gender was associated with worse IADL skills. Attentional difficulties were the only significant cognitive symptom associated with IADL skills when excluding participants who were disabled from analysis, suggesting that the influence of cognitive symptoms on IADL skills was more circumscribed for this subset of participants. These results are among the first to demonstrate that PRO measures of cognitive symptoms in SCD are associated with limited engagement in IADLs.

In the current study, a large proportion (40%) of participants reported missing at least one dose of hydroxyurea within the past week. Executive functioning difficulties, age (25–34 years old), severe genotype (Hb SS/Sβ^0-thalassemia/SD/SO/SE), and hemoglobin concentration were significantly associated with medication non-adherence in multivariable modeling. Recent research has identified unintentional forgetting as a leading factor in hydroxyurea non-adherence and poor executive functioning skills may underlie forgetfulness [26]. Our results indicate that medication non-adherence is a significant challenge for adults with SCD and that symptoms of executive dysfunction play a primary role in predicting non-adherence. Hydroxyurea adherence varied by SCDIC site and our findings suggest differences in behaviors that impact medication adherence may be associated with location.

Cognitive difficulties described on PRO measures in the current study are consistent with normative weaknesses that have been identified on standardized performance-based measures. Reported problems with executive functioning skills were particularly impactful, which was expected given that executive functioning skills rely on attention and support some of our most complex IADL skills. Executive functioning skills undergo rapid development between adolescence and young adulthood when myelination increases in the frontal cortex [27]. Adults with SCD may be especially vulnerable to executive functioning deficits due to delayed or interrupted myelination as a result of chronic, sub-clinical hypoxic-ischemic events, or focal vascular injuries in the frontal lobe. Interestingly, patient-reported history of stroke was not associated with IADL skills or medication non-adherence, suggesting that cognitive symptoms, as opposed to formal neurovascular insult, may be more predictive of functional limitations with societal engagement and medication adherence.

Consistent with previous studies, we found that rates of unemployment in SCD (17%) are nearly three times greater than that of the general population and the prevalence of disability status (24%) is more than twice as high as rates in other racial and ethnic groups [28]. Individuals with severe sickle genotype, history of stroke, and no college degree had greater rates of workforce disengagement (i.e., unemployed, disabled and not working, and retired). Contrary to previous studies, we did not find a significant relationship between gender and specific cognitive symptoms or employment, which we believe is a reflection of our sample size and methodology [17,23]. Our findings indicate that the rate of African American or Black participants with a college degree (21% combined for undergraduate and graduate) is less than national estimates for this group (33.4%), hence suggesting that SCD complications

have detrimental effects on post-secondary educational achievement and earning potential [29].

There are several limitations to the current study. History of stroke was patient-reported and not verified with imaging studies, therefore, the rate of stroke in our study (22.2%) is likely inflated and may be reflecting the participants' other cerebrovascular events (e.g., transient ischemic attacks or silent cerebral infarcts). Although PRO of neurocognitive symptoms was correlated with demographic and medical variables, symptoms could not be validated via performance-based measurement tools. Future studies should examine the concordance between patient-reported symptoms and deficits identified on formal evaluation using standardized measures. Further research is needed to examine additional markers of IADL skills including managing appointments and finances, navigating complex systems (e.g., healthcare and insurance), and community, civil, and social life to further elucidate the effect of SCD on independence and societal engagement. In our study, exploration of medication adherence was limited to hydroxyurea and a brief recall period (i.e., past seven days). Subjective data on medication adherence, as used in our study, is vulnerable to influence from social desirability and may over-estimate adherence [30], thus our findings may not fully capture the extent of non-adherence. Our results suggest medication adherence varied by SCDIC site and future research is needed to elucidate factors that may contribute to these differences. Additional research is also needed to understand how cognitive symptoms and attitudes about medication efficacy impact adherence.

In conclusion, we found that self-reported neurocognitive symptoms predicted reduced IADL skills, including employment and post-secondary education, independence with daily tasks, and ability to engage in leisure activities, as well as poor medication adherence. The neurocognitive burden of SCD is high and IADL skills are particularly vulnerable to symptoms of cognitive dysfunction. Targeted interventions to improve executive functioning skills (e.g., mobile applications that deliver cognitive remediation training) that are cost- and time-sensitive should be prioritized within this population, as this will support societal engagement and medication adherence. Mobile health (mHealth) apps to improve medication adherence and self-efficacy among individuals with SCD are currently being investigated through the SCDIC [31,32]. Further, programming should be developed to support employment and educational pursuits among individuals with risk factors for disengagement. Self-report of neurocognitive difficulties could be considered as an adjunct clinical tool in monitoring patient functional skills that impact engagement in societal activities and medication adherence. When collected prior to transition to adult care, PRO of executive functioning difficulties can be used to proactively guide future interventions to enhance employment and medication adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

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Data Availability Statement:

Data will be publicly available from the NHLBI Data Repository at https://biolincc.nhlbi.nih.gov/home/ starting February 2022. Until that time, please contact byk@rti.org for the original data.

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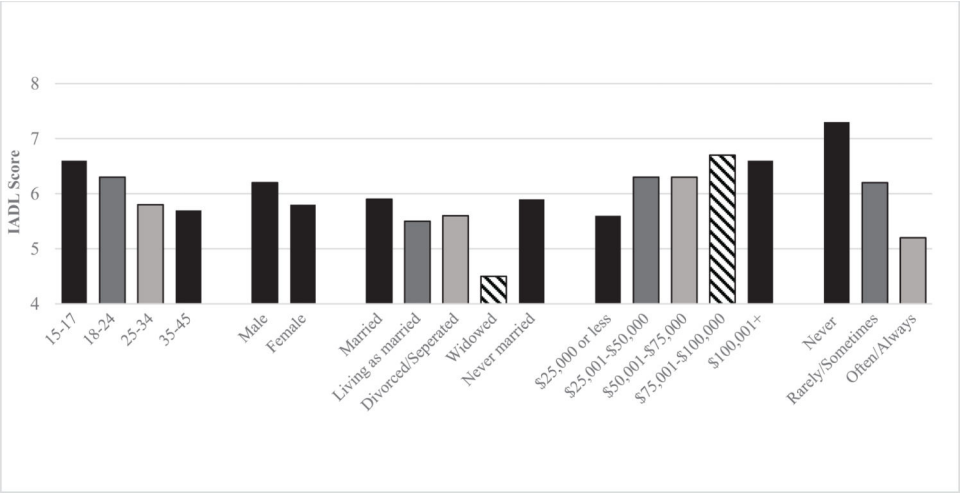

Figure. Instrumental activities of daily living (IADL) composite scores according to age, gender, marital status, household income, and chronic pain.

Values show the average IADL score (range 3–8) for participants in each category, with higher scores indicating increased engagement.

Table 1.

Demographic characteristics of survey respondents

	N (%)
Gender	
Male	1,050 (43.1%)
Female	1,386 (56.9%)
Age Group (years)	
15–17	219 (9.0%)
18–24	676 (27.8%)
25–34	977 (40.1%)
35–45	564 (23.2%)
Race/Ethnicity	
American Indian or Alaska Native	5 (0.2%)
Asian	4 (0.2%)
Black or African American	2,323 (97.0%)
White	13 (0.5%)
Multi-racial	51 (2.1%)
Marital Status	
N/A, subject is a minor	265 (11.1%)
Married	246 (10.3%)
Living as married	90 (3.8%)
Divorced/Separated	130 (5.5%)
Widowed	6 (0.3%)
Never married	1,641 (69.0%)
Highest Level of Education	
Some high school or less	411 (17.3%)
High school graduate / GED	659 (27.8%)
Some college / vocational	760 (32.1%)
College graduate	336 (14.2%)
Some graduate/professional school	43 (1.8%)
Graduate/professional degree	162 (6.8%)

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	N (%)
Household Income	
$25,000 or less	1,146 (54.0%)
$25,001–$50,000	472 (22.2%)
$50,001–$75,000	234 (11.0%)
$75,001–$100,000	118 (5.6%)
$100,001+	153 (7.2%)

Table 2.

Responses from SCDIC survey items assessing cognitive concerns and difficulty with instrumental activities of daily living (IADL)

	N (%)	N (%) Re-Categorized Format	Re-Categorized Descriptive Label
Had to read something several times to understand it [a, e]			
Never	824 (34.9%)	824 (34.9%)	Never
Rarely (Once)	692 (29.3%)		
Sometimes (2–3 times)	573 (24.2%)	1,265 (53.5%)	Sometimes
Often (once a day)	161 (6.8%)		
Very Often (several times a day)	113 (4.8%)	274 (11.6%)	Often
Thinking was slow [a, f]			
Never	1,027 (43.5%)	1,027 (43.5%)	Never
Rarely (Once)	597 (25.3%)		
Sometimes (2–3 times)	486 (20.6%)	1,083 (45.9%)	Sometimes
Often (once a day)	153 (6.5%)		
Very Often (several times a day)	96 (4.1%)	249 (10.6%)	Often
Had to work really hard to pay attention or would make a mistake [a,d]			
Never	1,051 (44.8%)	1,051 (44.8%)	Never
Rarely (Once)	574 (24.5%)		
Sometimes (2–3 times)	441(18.7%)	1,015 (43.2%)	Sometimes
Often (once a day)	164 (7.0%)		
Very Often (several times a day)	117 (5.0%)	281 (12%)	Often
Had trouble concentrating [a,d]			
Never	937 (39.9%)	937 (39.9%)	Never

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	N (%)	N (%) Re-Categorized Format	Re-Categorized Descriptive Label
Rarely (Once)	504 (21.4%)		
Sometimes (2–3 times)	540 (23.0%)	1,044 (44.4%)	Sometimes
Often (once a day)	206 (8.8%)		
Very Often (several times a day)	162 (6.9%)	368 (15.7%)	Often
Reading and following complex instructions [b, g]			
None	1,779 (74.4%)	1,779 (74.4%)	Never
A little	334 (14.0%)		
Somewhat	205 (8.5%)	539 (22.5%)	Sometimes
A lot	64 (2.7%)		
Cannot do	9 (0.4%)	73 (3.1%)	Often
Planning for and keeping appointments that are not part of weekly routine [b, g]			
None	1,351 (56.7%)	1,351 (56.7%)	Never
A little	503 (21.1%)		
Somewhat	348 (14.6%)	851 (35.7%)	Sometimes
A lot	164 (6.9%)		
Cannot do	16 (0.7%)	180 (7.6%)	Often
Managing your time to do most of your daily activities [b, g]			
None	1,173 (49.3%)	1,173 (49.3%)	Never
A little	577 (24.3%)		
Somewhat	394 (16.6%)	971 (40.8%)	Sometimes
A lot	208 (8.7%)		
Cannot do	27 (1.1%)	235 (9.9%)	Often

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	N (%)	N (%) Re-Categorized Format	Re-Categorized Descriptive Label
Learning new tasks or instructions [b, h]			
None	1,613 (67.9%)	1,613 (67.9%)	Never
A little	451 (19.0%)		
Somewhat	223 (9.4%)	674 (28.4%)	Sometimes
A lot	82 (3.5%)		
Cannot do	6 (0.2%)	88 (3.7%)	Often
Rely on others to take care of you because of your health [c, i]			
Not at all	1,106 (46.3%)	1,106 (46.3%)	Never
A little bit	647 (27.1%)		
Somewhat	343 (14.4%)	990 (41.5%)	Sometimes
Quite a bit	191 (8.0%)		
Very much	100 (4.2%)	291 (12.2%)	Often
Your health made it hard to do things with friends [c, i]			
Not at all	736 (31.1%)	736 (31.1%)	Never
A little bit	528 (22.3%)		
Somewhat	467 (19.7%)	995 (42%)	Sometimes
Quite a bit	428 (18.0%)		
Very much	211 (8.9%)	639 (26.9%)	Often
Employment & School [i]			
Student	467 (19.8%)		Engaged
Student + working	8 (0.3%)		Engaged
Student + disabled	5 (0.2%)	1381 (58.7%)	Engaged
Employed	891 (37.9%)		Engaged
Employed + disabled	10 (0.4%)		Engaged

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	N (%)	N (%) Re-Categorized Format	Re-Categorized Descriptive Label
Unemployed	346 (14.7)	973 (41.3%)	Unengaged
Keeping house	59 (2.5)		Unengaged
Disabled	565 (24.0%)		Unengaged
Retired	3 (0.1)		Unengaged

[a] indicates difficulties within the past 7 days

[b] indicates current difficulties

[c] indicates difficulties within the past 30 days

[d] attention composite

[e] comprehension

[f] processing speed

[g] executive functioning composite

[h] learning

[i] IADL composite

Table 3.

Significant multivariable relationships between instrumental adaptive daily living skills (IADL) composite and demographic, disease, and clinical characteristics

Predictor	Estimate	SE	95% CI	P-value
Intercept	7.83	0.14	(7.56, 8.11)	<.0001*
Age group[1]				
18–24	−0.26	0.11	(−0.48, −0.04)	.0184*
25–34	−0.66	0.11	(−0.88, −0.45)	<.0001*
35–45	−0.75	0.11	(−0.98, −0.53)	<.0001*
Frequency of very severe pain, past 6M[2]				
Sometimes	−0.84	0.10	(−1.03, −0.65)	<.0001*
Often	−1.57	0.10	(−1.77, −1.36)	<.0001*
Ever taken hydroxyurea[3]	−0.25	0.06	(−0.37, −0.12)	.0001*
Cognitive symptom: Comprehension[4]				
Sometimes	−0.24	0.06	(−0.36, −0.11)	.0002*
Often	−0.36	0.10	(−0.57, −0.16)	.0005*
Cognitive symptom: Executive function[5]				
Sometimes	−0.28	0.07	(−0.41, −0.15)	<.0001*
Often	−0.74	0.16	(−1.05, −0.43)	<.0001*
Cognitive symptom: Learning[5]				
Sometimes	−0.28	0.07	(−0.42, −0.14)	<.0001*
Often	−0.36	0.18	(−0.71, −0.02)	.0397*
Income more than $25,000[6]	0.43	0.06	(0.32, 0.55)	<.0001*
Education: college graduate/professional degree[7]	0.29	0.07	(0.15, 0.43)	<.0001*
Gender: Male[8]	0.13	0.06	(0.02, 0.24)	.0239*

[1]Compared to the less than 18 group

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[2] Compared to never

[3] Compared to not

[4] Compared to never

[5] Compared to none

[6] Compared to $25K and under

[7] Compared to less than college graduate

[8] Compared to female

* denotes statistical significance at ≤ 0.05.

Table 4.

Significant multivariable relationships between hydroxyurea non-adherence and demographic, disease, and clinical characteristics

Covariate	Odds ratio (95% CI) of non-adherence with indicated covariate	P-value
Age group[1]		
18–24	1.70 (0.993, 2.975)	.0583
25–34	1.96 (1.168, 3.389)	.0129*
35–45	1.31 (0.749, 2.357)	.3497
Gender: Male[2]	1.10 (0.820, 1.469)	.5311
Cognitive symptom: Executive function[3]		
Sometimes	1.42 (1.056, 1.927)	.0212*
Often	1.76 (0.894, 3.427)	.0961
Genotype: Severe sickling SS/S Beta 0/SD/SO/SE[4]	0.45 (0.288, 0.711)	.0006*
Hemoglobin, g/dL	0.87 (0.790, 0.956)	.0039*

[1]Compared to the less than 18 group

[2]Compared to female

[3]Compared to never

[4]Compared to non-severe sickling: SC/S Beta+/S-HPFH.

*denotes statistical significance at ≤ 0.05.