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Adults with Sickle Cell Disease May Perform Cognitive Tests as Well as Controls when Processing Speed is Taken into Account: A Preliminary Case-control Study

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Abstract

Aims—This study aimed to: 1) evaluate cognitive function among adults with sickle cell disease using a computer-administered neuropsychological test; and 2) replicate previously identified differences in processing speed between patients with sickle cell disease and controls.

Background—Previous evidence suggests that, compared with controls, adult patients with sickle cell disease have poorer cognitive functioning across most domains but the most significant deficits appear to be in the area of processing speed.

Design—Cross-sectional case-control study conducted from June 2008-June 2010.

Methods—Cognitive functioning was measured using computerized, self-administered, neuropsychological tests among 31 patients with sickle cell disease and 17 controls matched for age, gender and race. The assessment averaged 30 minutes and scores were recorded for seven computerized tests: verbal and visual memory, finger tapping, symbol digit coding, Stroop test, shifting attention and continuous performance.

Results—Patients with sickle cell disease scored 10.76 points lower on the CNS Vital Signs processing speed domain than controls. Although non-significant, patients scored 5.73 points lower on the full index than controls but after adjusting for processing speed, mean scores for patients were 3 points greater compared with controls. Differences in executive functioning and attention were not significant and memory did not differ between groups.

Conclusion—Using a brief, computer-administered 30-minute neuropsychological test, we were able to replicate previous findings showing a greater than 10-point deficit in processing speed

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among patients with sickle cell disease. When differences in processing speed are taken into account, patients perform equally well or better than controls on cognitive tasks.

Keywords

Clinical neurology examination; sickle cell disease; disease; case-control studies; nursing

Introduction

Sickle cell disease (SCD) is a mono-genetic disorder that affects millions internationally and is particularly common among those with ancestry from Sub-Saharan Africa, South America, Cuba, Central America, Saudi Arabia, India and Mediterranean countries (Ashley-Koch *et al.* 2000). In the USA, SCD is the most common inherited blood disorder and affects approximately 100,000 Americans, most of whom are of African decent (Hassell 2010, Brousseau *et al.* 2010).

The life expectancy of people living with sickle cell disease (SCD) has significantly increased over the last four decades (Platt *et al.* 1994, Claster & Vichinsky 2003). With increased longevity and age, however, the SCD population experiences a new host of health problems that can add additional complexities to long-term chronic disease care. In particular, neurocognitive health has long been recognized as an issue in SCD but is becoming a much more prominent focus in long-term SCD care due to the potential negative impact of neurocognitive deficits on patients self-management, health care use and quality of life (Anie 2005, Jonassaint *et al.* 2014). However, the costs of extensive neurocognitive testing and brain imaging studies are generally beyond the reach of clinical practice. Therefore, development of a sensitive, accurate, easily administered and cost-effective screening tools for neurocognitive testing in the outpatient setting would be beneficial. To help direct treatment efforts, it will be important to identify markers of early cognitive decline or unrecognized cerebrovascular disease in the SCD population.

Background

People living with SCD experience an alarmingly high risk of cerebrovascular complications. However, even in the absence of overt structural brain damage, people with SCD frequently experience deficits in cognitive function (Hogan *et al.* 2006, Ruffieux *et al.* 2011). Neuropsychological studies in SCD have been predominately conducted among pediatric patients; there is a need for more studies examining whether SCD-related cognitive deficits persist into adulthood and become worse with age.

In the only existing large-scale, comprehensive, neuropsychological, case-control study in SCD adults, Vichinsky *et al.*2010 showed that otherwise healthy patients with SCD (n=149) had poorer global cognitive performance measured by the full-index IQ when compared with controls (N=47). At first glance, it would be easy to make the broad conclusion that patients with SCD are simply less intelligent than their healthy counterparts. However, the most prominant difference between patients and controls in the Vichinsky *et al.* (2010) study was an 11.46-point deficit in patients' processing speeds on the Wechsler Adult Intelligence Scale (WAIS), which was twice their 5.19-point deficit on the full-index IQ. No other

cognitive domain from an extensive neuropsychological battery, including working memory and executive functioning, showed the same magnitude of disparity between patients with SCD and healthy controls as that for processing speed (Vichinsky *et al.* 2010).

It is not clear from earlier studies why processing speed in particular may be the cognitive domain most predominantly affected by SCD. Some evidence suggests that processing speed is one of the primary cognitive domains affected in persons with unexplained anemia (Chaves *et al.* 2006). Further, slower processing speed is thought to account for age-related differences in cognition among healthy adults (Salthouse 1996). Thus, in sickle cell, processing speed may explain at least some of the SCD-related deficits in cognition. If true, this would mean that the cognitive deficits commonly observed in SCD do not mean that this patient population is unintelligent; rather, we may find that although patients with SCD process information equally well as their healthy counterparts, they may process information a little more slowly.

As life expectancy improves and median age increases for medically ill patients, such as those with SCD, there is a growing need for routine neuropsychological assessments in the care of chronic diseases. Unfortunately, testing is time intensive and expensive and access to neuropsychological services is often limited (Eisman *et al.* 2000). The use of computer-administered tests may help overcome some barriers to conducting behavioral and neuropsychological assessments in the medical setting.

The Study

Aim

In this study, we aimed to: 1) evaluate cognitive function among adults with SCD using a computer-administered neuropsychological test; and 2) replicate previously identified differences in processing speed between patients with SCD and controls.

Design

This cross-sectional case-control study was conducted at a large comprehensive care center for patients with sickle cell disease. Recruitment and testing for patients occurred during a regular clinic visit at no additional charge. To control for confounding, a frequency or quota matching approach was used to ensure our samples of cases and controls had similar age and gender distributions. Attempts were made to identify at least one control for each gender/age strata. The age categories were: (19-29), (30-39), (40-49) and (50-59). Participants were not compensated for their involvement in the study.

Participants

We used word of mouth to recruit patients with hemoglobin SS or S beta-zero thalassemia and age- and sex-matched controls, with no history of sickle cell trait or disease of any genotype, from the comprehensive sickle cell center. Participants were ineligible if they had experienced a vaso-occlusive event in the previous three weeks, had visual or physical impairments limiting use of a computer, Mini-Mental Status Exam (MMSE) score < 20, Profile of Mood States depression score > 40, excessive alcohol consumption (14 drinks/

week for females and 21 drinks/week for males), or prior cerebrovascular events. Comorbidities and prescribed medications were documented using medical records. Pain score was patient reported on a scale from 0-10.

Data collection

Data were collected from June 2008 - June 2010. Cognitive performance was measured in an outpatient clinic using CNS Vital Signs (Morrisville, NC) software (Gualtieri and Johnson 2006) self-administered via computer. This CNS Vital Signs testing battery is simple to use, can be initiated by a medical office assistant and completed by any English speaker, age 10 or above, with at least a fourth grade reading level. The assessment averaged 30 minutes and scores were recorded for seven computerized tests: verbal and visual memory, finger tapping, symbol digit coding, Stroop test, shifting attention and continuous performance. In addition to accuracy and errors, several of the tests record reaction times that can also determine domain scores. Domains based on a single test scores were verbal memory, visual memory, reaction time, cognitive flexibility, processing speed, executive function, simple visual attention and motor speed. The multiple test score domains were memory, executive functioning, complex attention and psychomotor speed. A more detailed description of each test and how the domains are scored can be found in a previous report (see Gualtieri and Johnson 2006).

Sample size—Vichinsky *et al.* (2010) reported an 11.5 point difference in processing speed between patients with SCD and controls. For our study, an estimated total sample of 40 participants, 20 cases and 20 controls, was needed to achieve a power of 80% to detect a 11.5 point mean difference between patients with SCD and matched controls, using a .05 type 1 error rate.

Ethical consideration

Participants did not incur any costs for the neuropsychological testing or participation in the study. Patients were informed that their participation or refusal to participate would not affect their care at the comprehensive sickle cell center in anyway. Family members were approached with patients' permission only. Potential participants who were not competent to give consent were excluded. This study was approved by the local institutional review board.

Data analysis

Differences between cases and controls on demographic variables of interest were tested using t-tests and chi-square analysis. For the analyses of the CNS Vitals test scores, only the multiple test domains were included. The full index represents the average score across all measures. Psychomotor speed index and the single-domain processing speed score were averaged to reflect the WAIS-III processing speed index used in the Vichinsky *et al.* (2010) study. Group differences for the full index and four domain scores were tested using separate multivariable analysis of variance ANOVA models. Consistent with Vichinsky *et al.* (2010), age, sex and education were considered as potential covariates. We used a threshold of $p<.50$ for inclusion of covariates in the multivariable models. Significance was set at p-value of .05 for all tests of study hypotheses.

Validity and reliability/Rigor

In a study by Gualtieri and Johnson (2006) the CNS Vital Signs tests was found to have a moderate correlation with conventional neuropsychological tests of memory, perceptual-motor speed and executive function (i.e. Rey Auditory Verbal Learning Test, Logical Memory and Facial Recognition from the Wechsler Memory Test, a mechanical finger tapper, the Stroop Test, Trails B and the Verbal Fluency Test). Further, the CNS Vital Signs correlated with NES2, another validated computerized neuropsychological that includes Finger Tapping, Switching Attention and the Continuous Performance Test. Test-retest reliability of the CNS Vitals Signs tests was high and comparable to conventional neuropsychological testing. Reliability did not differ by age or clinical status. Finally, the Gualtieri and Johnson (2006) study also found that the CNS Vitals Signs test battery was able to adequately discriminate between different cognitive disorders: mild cognitive impairment and dementia, post-concussion syndrome and severe traumatic brain injury, ADHD and depression.

Results

Thirty-one patients and 17 controls participated in the study; 52% of those who participated were female. Patients with SCD were mean age 36.7 year old and controls 33.3 years old. There were no group differences in gender, age, depressive symptoms, or MMSE scores but controls had a higher average education level than patients with SCD. Average reported pain level for patients was 1.9/10. Twenty-three patients were on hydroxyurea and 26 patients had at least one other comorbidity. Patients with SCD scored 10.77 points lower (95% CI, 17.00-4.53) on processing speed than controls. There was a 5.73-point mean group difference (95%CI, 14.56- -3.10) on the full index but this was not significant. Further, executive functioning and attention differed by 6.53 and 4.79 points, respectively, favoring the controls but this also was not significant. There was no difference in memory scores.

Next, we estimated mean full-index scores adjusting for processing speed and although not significant, full-index scores were three points higher for patients compared with controls (Table 1). In contrast, when processing speed was not accounted for, the differences in full-index scores showed a non-significant trend in the opposite direction, favoring controls.

Discussion

Caring for an aging SCD populations has presented new challenges to nursing practice as long-term complications associated with the disease, such as cognitive impairment and dementia, are becoming more common while there continues to be a lack of an evidence-base for screening and treatment of these conditions. Little is known about the potential impact of patient cognitive function on treatment outcomes and often, patient cognitive impairment may be mistaken for volitional maladaptive behaviors or non-compliance (Ballas 2010). Screening for cognitive impairment is not part of current nursing practice or standard SCD care mainly due to the multiple barriers to getting patients traditional neuropsychological testing (Eisman *et al.* 2000). The introduction of new technologies, such as computerize neuropsychological testing, may bridge some of these barriers that have limited nurses' ability to deliver the highest quality care to their patients.

In this study, we introduce a brief, computer-administered, 30-minute test that showed similar neurocognitive findings to the Vichinsky *et al.*2010 study that employed a six-hour battery of tests administered by a trained neuropsychologist. Similar to Vichinsky *et al.* (2010), our data showed a greater than 10-point difference in processing speed between patients with SCD and healthy controls. Further, although not significant, group differences on other cognitive domains (i.e attention and executive functioning) favored controls having better performance and were similar in magnitude to differences that the Vichinsky *et al.* data showed for working memory and perceptual organization. There was not, however, a group difference in memory, a finding that is also supported by the Vichinsky *et al.* (2010) findings showing no group differences between patients and controls on any sub-tests from the Wechsler Memory Scale. Thus, long-term memory, auditory and visual memory may not be impacted by SCD in the absence of an overt neurological event.

Given the stark group differences in processing speed as compared with all other cognitive domains, we hypothesized that processing speed deficits may be accounting for the lower patient scores on other cognitive domains. When we adjusted for processing speed in our analyses, indeed, patients appeared to perform as well as, or better, than healthy controls on our cognitive tests. These preliminary data were trends only and will need to be replicated in a larger case-control study; however, the data suggest that observed deficits in cognitive functioning among patients with SCD may simply be due to slower processing speed rather than global cognitive impairment or lower intelligence.

Three additional messages can be taken from this report. First, slower processing speed is as prevalent in patients with SCD as it is among other adults with chronic diseases (e.g., diabetes) where slower processing speed has been associated with decreased ability to perform instrumental activities for daily living (Christman *et al.* 2010). Second, the SCD populations studied have been much younger than the general populations that show similar processing speed deficits. Perhaps cognitive aging is accelerated in SCD and slowed processing speed may be an early marker of global cognitive decline. Prospective studies are needed to help guide screening practices and interventions and to understand the progression and identify the causes of slow processing speed in patients with SCD. Lastly, computerized neuropsychological measures may be an effective way to detect early cognitive decline by introducing brief cognitive screenings into routine SCD care to measure for deficits in processing speed.

Slower processing speed may not be specific to SCD. Low hemoglobin concentrations from other causes may also lead to similar cognitive deficits. Older individuals with mild disease showed slower processing speed in cross-sectional (Shah *et al.* 2009) and prospective (Shah *et al.* 2011) analyses. In an urban sample of older, mostly African-American adults, lower hemoglobin was associated with poorer processing speed but not poorer verbal memory or executive functioning (Jonassaint *et al.* 2014). Despite evidence linking lower hemoglobin levels and disease to slowing cognitive function, little is known about the underlying mechanisms. The vascular system compensates for lower hemoglobin levels and lower oxygen availability in several ways—namely by increasing vasodilation, cardiac output and oxygen extraction. During periods of psychosocial stress or high cognitive demand (e.g., neuropsychological testing), these compensatory mechanisms may be insufficient and

cerebral blood flow and perfusion may become inadequate, leading to impaired cerebral function and even ischemia (Kramer and Zygun 2009).

It is also possible that slower processing speed is an indicator of unrecognized silent cerebral infarction. In a sample of 38 pediatric patients with SCD, slower processing speed was associated with a higher volume of white matter hyperintensities (van der Land *et al.* 2014). Where global cognitive functioning as measured by the full-scale intelligence quotient values have been inconsistent predictors of cerebrovascular disease in sickle cell (Hijmans *et al.* 2011), future research may find that patients at risk or who have experienced a cerebral infarct may be quickly identified by measuring processing speed using a computerized neuropsychological screening test.

Whatever the mechanism leading to slower processing speed among patients with SCD, the long-term negative impact of sickle cell-related anemia on brain health may extend far beyond just processing speed. Several large studies of older adults have shown that adults with anemia have a higher risk of developing dementia in longitudinal follow-up than adults without anemia (Chaves *et al.* 2006, Deal *et al.* 2009, Hong *et al.* 2013, Lucca *et al.* 2008). There have been no longitudinal studies in SCD that have evaluated changes in cognitive function and incidence of dementia over-time. Men with SCD reported an increase in memory disturbance with age in one study (Feliu *et al.* 2011) but little else is known about the impact of age on cognitive functioning in SCD. Computerized neuropsychological testing tools, such as CNS Vital Signs that are cost-effective and easily implementable into standard practice, may make longitudinal studies of cognitive functioning in SCD more feasible.

Limitations

Our study was limited by a small sample size. Given that this was designed as a feasibility study there was insufficient power (31.2%) to detect the 5.7-point group difference on the full-index score. Further, to truly demonstrate the utility of the computerized neuropsychological testing in the SCD population, a direct comparison with traditional, well-validated, neuropsychological measures would be needed. Finally, with the current test series and administration modality (i.e., self-administered by computer), we were unable to determine whether cognitive processing or motor speed is the primary contributor to the observed cognitive impairment. Despite these limitations, we were successfully able to replicate data showing an association between SCD and processing speed.

Conclusion

We may be able to address cognitive impairment in SCD if processing speed is indeed the primary domain being affected. Although processing speed appears to have a broad effect on cognitive functioning in SCD, the impact of slowed processing on cognitive tasks can be attenuated when time constraints are removed and demands for multi-tasking or simultaneous processing are limited (Salthouse 1996). Further, common low-risk psychostimulant medications have been shown to improve processing speed (Rees *et al.* 2007). We may be able to diminish the impact of SCD on cognition by integrating routine screening and basic treatments for processing speed into routine care. Ultimately, addressing

processing speed may also impact related behavioral outcomes leading to improved patient-provider interactions, medical adherence and day-to-day patient self-management.

Nurses are well positioned and have a central role in assessing, managing and even educating patients who may be experiencing signs of cognitive impairment (Myers 2009). Compared with other medical providers, nurses frequently have more contact and interactions with patients and are more likely to notice the early warning signs of cognitive impairment (Nelson *et al*. 2007). By facilitating the diagnoses of symptoms early in the course of cognitive impairment, nursing practice will help improve patient care and maximize the effectiveness of treatments. Computerized neuropsychological testing, such as CNS Vital Signs, may be a mechanism by which nurses can quickly and easily screen clinic or hospitalized patients for signs of cognitive impairment, such as slower processing speed.

Recognizing that a patient may have cognitive difficulties early will help direct care. Nurses can spend more time with the patients on treatment regimens and medication management on discharge to ensure understanding, explore cognitive enhancement techniques and ways for increasing social engagement, as patients with cognitive impairment may become more isolated (Carstensen and Hartel 2006) and integrate community resources into the plan of care to meet the needs of the patient and family members. Patients with cognitive impairment will have an increased need for formal (specialized long-term care) and informal support (e.g. SCD support groups, churches, family/friends) systems. Improved understanding of cognitive impairment in SCD and having tools in place for nurses to assess functioning will ultimately increase the quality and effectiveness of nursing care in SCD.

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Summary Statement

Why is this research needed?

- Patients with sickle cell disease may experience unrecognized cognitive deficits that can impact their communication with providers, medical adherence and overall quality of life.
- Little is know about the cognitive functioning of adult patients with sickle cell disease.
- Neuropsychological testing is often expensive, not widely available and time consuming and therefore has not regularly been integrated into routine clinical care for patients with sickle cell disease.

What are the key findings?

- Patients with sickle cell disease have poorer performance on cognitive testing compared with healthy controls; however, after adjusting for processing speed, patients perform just as well or better than healthy controls on cognitive testing.
- These findings suggest that the cognitive deficits observed in sickle cell disease do not mean these patients are unintelligent, rather, the data suggest they may just be slow at processing.
- In a sample of patients with sickle cell disease and matched controls, a computerized self-administered neuropsychological testing battery, that can be completed in 30-minutes on average, generated similar findings to a previous study that administered a much longer, 6-hour neuropsychological battery, administered by a trained neuropsychologist.

How should the findings be used to influence policy/practice/research/education?

- Neuropsychological screening should be integrated into routine care for patients with sickle cell disease.
- Computerized neuropsychological testing is a low cost assessment tool that can be delivered, in 30-minutes or less, by nurses or other medical providers in a clinic setting.
- Interventions specifically targeting low processing speed may be effective for improving global functioning and overall quality of life for patients living with sickle cell disease.

Table 1
Demographic and Cognitive Test Performance by Case Status

	Controls (n = 17)	SCD Patients (n = 31)		
Variable	**Mean (SD)**	**mean (SD)**	**Diff**	**P value**
Age	36.71 (11.52)	33.32 (11.07)		0.323
Female, freq. (%)	9 (52.9)	16 (51.6)		0.930
Education (yrs)	16.12 (1.45)	14.13 (1.45)		<.001
Depression	5.62 (6.05)	6.39 (6.88)		0.710
MMSE	30.13 (2.45)	29.35 (0.95)		0.128
CNS Vitals Signs Scores *				
Full Index	89.76 (13.40)	84.03 (15.11)	5.73	0.451
Memory	86.65 (19.34)	85.61 (21.63)	1.04	0.940
Executive Functioning	89.82 (23.64)	83.29 (21.55)	6.53	0.951
Attention	91.47 (24.46)	86.68 (23.55)	4.79	0.961
Processing Speed	95.09 (10.37)	84.32 (10.21)	10.77	0.019
Processing Speed-adjusted Full Index	84.08 (15.66)	87.21 (14.01)	-3.13	0.538

Two sample t-tests were used to determine group differences on age, education, depression and MMSE scores; chi-square analysis tested group differences on gender.

* Mean and SD are based on age-normed standard scores; P values are based on multivariable ANOVA models adjusted for age and education level; MMSE = Mini-Mental Status Exam