Neuropsychological assessment, neuroimaging, and neuropsychiatric evaluation in pediatric and adult patients with sickle cell disease (SCD)

Christopher L Edwards
Renee Dunn Raynor
Miriam Feliu
Camela McDougald
Stephanie Johnson
Donald Schmechel
Mary Wood
Gary G Bennett
Patrick Saurona
Melanie Bonner
Chante’ Wellington
Laura M DeCastro
Elaine Whitworth
Mary Abrams
Patrick Logue
Lekisha Edwards
Salutario Martinez
Keith E Whitfield

1Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA; 2American Psychological Association, Science Directorate, Washington, DC, USA; 3Department of Medicine, Division of Neurology, Duke University Medical Center, Durham, NC, USA; 4Department of Society, Human Development, and Health, Harvard School of Public Health, Boston, MA, USA; 5Taub Institute For Research on Alzheimer’s Disease and The Aging Brain, Columbia University, New York, NY, USA; 6Department of Medicine, Division of Hematology, Duke University Medical Center, Durham, NC, USA; 7Department of Radiology, Duke University Medical Center, Durham, NC, USA; 8Duke University, Durham, NC, USA

Abstract: Traditionally, neuropsychological deficits due to Sickle Cell Disease (SCD) have been understudied in adults. We have begun to suspect, however, that symptomatic and asymptomatic Cerebrovascular Events (CVE) may account for an alarming number of deficits in this population. In the current brief review, we critically evaluated the pediatric and adult literatures on the neurocognitive effects of SCD. We highlighted the studies that have been published on this topic and posit that early detection of CVE via neurocognitive testing, neuropsychiatric evaluations, and neuroimaging may significantly reduce adult cognitive and functional morbidities.

Keywords: cerebral vascular event, neuropsychological assessment, sickle cell disease, neuroimaging

In recent years, our understanding of the neuropathophysiology of sickle cell disease (SCD) and its related consequences have progressed significantly (Edwards, Whitfield, Sudhakar et al 2006; Pells, Presnell, Edwards et al 2005). Seminal studies such as The Cooperative Study of Sickle Cell Disease (CSSCD) (Armstrong et al 1996) have highlighted the value of early detection of silent and overt cerebrovascular events (CVE) in populations at risk of complications and morbidity (Brown et al 2000). However, we have yet to fully explore the cumulative influences of early CVE on neurocognitive and adaptive functioning in adults with SCD.

SCD is a class of genetic disorders characterized by sickle-shaped, red blood cells that may cause a variety of clinical symptoms with potentially significant neurological and neuropsychiatric sequelae (Brown et al 1993; Broe 2001; Edwards et al 2005). Central nervous system (CNS)-related complications of SCD include transient ischemic attacks (TIA), seizures, and increased intracranial pressure. The incidence of CNS complications among this population varies from 1.3% to 40% (Izoura et al 1989). Among the most serious neurological complications associated with SCD are clinically symptomatic strokes and “silent infarctions” (Briscoe 2001). A silent infarction is best conceptualized as a CVE in the absence of immediately recognizable signs or symptoms.

Silent infarctions can produce neurocognitive deficits throughout the lifespan. These can result in reduced lifetime capacities for reading and spelling achievement, increased number of absences from school and work, and lower performance on IQ tests (Schatz, Finke et al 2002; Steen et al 2002). Moreover, given the significant adult consequences of these developmental milestones, early detection of silent and perhaps asymptomatic CVEs, may assist to mitigate long-term morbidities and may improve adult neurocognitive functioning (Fowler et al 1988; Powars et al 2001).

In North America, complications associated with the sickle cell diseases (SCDs) have increased over many years. However, clinical management requirements of
patients with SCD vary with some requiring frequent hospitalization, constant narcotic medication management, and frequent transfusions, whereas others require very few medical and support resources. Adult complications and expected longevity may be functional sequelae of neurodevelopmental and childhood hematological crises (Armstrong et al 1996; Cohen et al 2004). As such, understanding the effects of early CVEs on the neurodevelopmental processes may be critical in developing effective management strategies for adult morbidities associated with SCD.

Clinically apparent infarctions or CVEs have been found to occur in pediatric and adult populations with SCD and are associated with diverse sequelae including hemiplegia, aphasia, seizures, deficits in executive function and language, and reduced visuo-perceptual abilities (Izoura et al 1989; Ohene-Frempong et al 1998; Hogan, Kirkham et al 2006). The developmental effects of pediatric CVE on adult neurocognitive functioning are not well defined or understood but are estimated to be consequential (Powars et al 2001). Several studies have found deficits in general intellectual functioning, language and verbal abilities, visual-motor and visual-spatial processing, memory, academic achievement, and processing of subtle prosodic information in pediatric patients with a range of SCD severities and disease-related complicating issues (Kral et al 2001; Treadwell et al 2005).

For example, silent or asymptomatic CVEs in pediatric patients with SCD can produce subtle deficits in attention and concentration, executive function, and visual-motor speed and coordination (Kral et al 2001). However, it is unclear how early and more overt CVEs in patients with SCD affect the life course of academic performance, occupational achievement, adult neurocognitive functioning, mood, and related psychosocial outcomes.

Several earlier studies provide evidence for the impact of SCD on neurocognitive functioning (Steen et al 2002). Fowler et al (1988) noted that children with SCD experienced significantly lower reading and spelling achievement scores than healthy controls. Schatz (2004) noted that children with SCD are more likely to have academic achievement and goal attainment difficulties when compared to their demographically matched peers. Wasserman et al (1991) found that children with SCD, compared with siblings with sickle cell trait or normal hemoglobin, had poorer performance on measures of intellectual, academic, and general neuropsychiatric functioning.

More specifically, and in a sample of 43 patients and 30 sibling controls, siblings with the sickle cell trait performed no differently than the normal hemoglobin group (Wasserman et al 1991). Patients with SCD had a significantly higher absences missed from school and lower performance on IQ tests. Several studies have also noted that children with SCD have significantly poorer cognitive performances on measures of visual-motor integration and attention (Schatz, Finke et al 2002; Hariman et al 1991). Many studies have suggested that these results are at least partially accounted for by the fact that 46% of patients with SCD have remarkable findings on MRI and 64% have vasculopathies detectable on MRA (Steen, Xiong et al 2003).

Representative of a gradual but notable change in scientific thinking, Steen, Emudianughe et al (2003) purported that sickle cell trait may not be as innocuous as once thought, and may predispose African Americans and other populations susceptible to this genetic disease to increased risk of vasculopathies and stroke. Consequently, subtle vascular abnormalities and moderately decreased hematocrit levels are evidenced in many individuals who are trait positive and the impact of this subclinical status on cognitive and psychiatric functioning is relatively unknown (Steen et al 1999).

Consistent with previous research, we propose that there may be a high rate of unidentified brain abnormalities possibly secondary to silent CVE in patients with SCD (Baldeweg et al 2005; Schatz, White et al 2002; Schatz and McClellan 2006; Schatz et al 1999). This conclusion has been partially supported by the work of many researchers including Steen and colleagues (Steen et al 1999; Steen, Emudianughe et al 2005) who have demonstrated that patients with SCD exhibit volumetric growth delays concentrated in gray matter.

Unlike studies related to conditions where neurological finding associated with adults are simply extended to children, SCD represents one of the few diseases about which we have more evidence in pediatric than adult populations as it relates to the sequelae of CVE. For example, using magnetic resonance imaging (MRI) with and without contrasts Wang et al (1998) found that infants and very young children, ages 7 to 48 months, with no reported history of CVE nevertheless had evidence of silent infarctions and major cerebral artery stenosis at rates similar to adults. Wang et al (1998) also found MRI/MRA abnormalities among asymptomatic infants, median aged 18 months.

Several studies have (Briscoe 2001; Steen, Emudianughe et al 2003; Steen, Hankins et al 2003) have reported that children with SCD experience CVE in the absence of historical neurological morbidity and with few, if any, visible short-term symptoms. Grueneich et al (2004) most recently suggested that radiographic imaging evidence of silent strokes may be associated with inconsistent and variable neurocognitive
further reinforce the parallel need for early identification with functioning in patients with SCD as compared to controls, reveal generally poorer neurocognitive and neuropsychiatric chronic illness population. Results from multiple studies that advances to reduce adult neurocognitive dysfunctions in this represent an important goal of medical and psychological symptomatic lesions of the CNS associated with SCD may that early detection of pediatric asymptomatic as well as 

Early detection of cerebral events and entry into rehabilitation services may provide children, and consequently adults who have SCD, with an increased likelihood of avoiding the cumulative effects of CVEs (Steen et al 1998). Because children have greater brain plasticity than their adult counterparts, early rehabilitation efforts may lead to a greater recovery of function, compared to an adult counterpart with the same brain insult (Coelho-Mosch et al 2005). It is notable, however, that patients with SCD may manifest white matter hyperintensities and hypoxia that are less commonly seen in adult stroke victims associated with other diseases. This brings into question whether aggressive behavioral, psychiatric, and rehabilitational remediations that have historically worked effectively for adult victims of stroke could be used in pediatric and adult patients with SCD and yield similar positive results.

In the context of an emerging neurocognitive literature on adults with SCD, the current review reinforces the idea that early detection of pediatric asymptomatic as well as symptomatic lesions of the CNS associated with SCD may represent an important goal of medical and psychological advances to reduce adult neurocognitive dysfunctions in this chronically ill population. Results from multiple studies that reveal generally poorer neurocognitive and neuropsychiatric functioning in patients with SCD as compared to controls, further reinforce the parallel need for early identification with treatment and rehabilitation of cognitive morbidities.

Increasingly, researchers and clinicians have embraced the notion that the absence of symptoms is not synonymous with absence of CVE in patients with SCD (Hogan, Kirkham et al 2006; Hogan, Pit-ten Cate et al 2006; Hogan, Vargha-Khadem et al 2006). It is possible that unidentified and poorly managed CVEs may be associated with difficult to manage or even irreversible neurocognitive consequences. Given the importance of a healthy brain for normal childhood and adult development, and given that brain injury secondary to CVE may produce functional cognitive, social, and interpersonal impairments (Burlew et al 2000), it is important to screen for and manage neurocognitive morbidities as part of routine and standard of care.

This standard of care must begin with more effective disease management in pediatric settings (Thompson et al 2002; Hogan, Pit-ten Cate et al 2006) to include early neuropsychological testing and brain imaging. Neuromaging in early childhood development may identify neuroanatomical substrates of CNS damage before clinical evidence is manifested. Neuropsychological testing may assist in identifying the functional consequences of early silent and overt CVE. Both detection modalities assist to facilitate standards of early intervention and remediation of brain lesions, the reduction of adult cognitive and functional morbidities, and allow for better comparison of treatment options.

Once identified via neuroimaging, young adult patients with SCD who have manifest CVE would likely benefit from rehabilitational services commonly made available to much older stroke populations. Through the use of baseline and subsequent neurocognitive assessment, patterns of developmental delay or impairment in SCD patients may ultimately inform the development of cognitive, behavioral, and psychosocial interventions.

Many states currently conduct brief hematological screenings at birth to identify patients who have the genotype for SCD prior to any manifestation of symptoms. The justification for such programs is that long-term financial and healthcare benefits associated with the identification, anticipation (allocation of financial management and care resources), and management of SCD when conducted at birth offsets the short-term financial cost of early detection. Similarly, the long-term and adult financial cost of unidentified juvenile SCD-associated CVE (lost productivity, reduced cognitive capacities, etc.) may exceed, exponentially, the immediate cost of an early assessment program. Future research that would define additional risk factors for pediatric CVE may yield the ability to image and assess, more selectively, subgroups of patients in their formative years, and further reduce long-term cost (Steen, Emudianughe et al 2003).

Schatz, White et al (2002) proposed that multifactorial quantitative indices of brain functioning (ie, imaging, quantified estimates of lesion volume, neuropsychological testing) may provide a better method to detect silent infarctions. Some patients with SCD manifest CVE asymptotically or with poorly localized effects. Because there are very few cues signaling the need for immediate medical attention, the cumulative effect of “silent” events may be especially problematic. A single silent event may not result in significant long-term deficits. However, the cumulative effects of silent CVE on adult functioning is relatively unknown and worthy of study. In particular, repeated events may deplete...
physiological reserves in key systems and predispose organs to premature failure.

Lastly, the current review reveals that, in comparison to earlier studies of patients with SCD, the neuropsychological literature continues to transition from simply defining morbidity associated with stroke to currently documenting and studying the likely role of “silent” CVE on pediatric functioning and adult development (Bonner et al 1999; Bernaudin et al 2000; Hogan, Pit-ten Cate et al 2006; Schatz and McClellan 2006). It also highlights, in a longitudinal manner, the need for future research to explore SCD-specific factors that may impact cognitive functioning (transfusion, low socioeconomic status and access to preventative care, etc.). We must also seek to differentiate the effects of organic from psychosocial processes on neurocognitive functioning in patients with SCD.

Continued research and clinical collaboration among neuropsychiatrists, hematologists, pediatricians, radiologists, neuropsychologists, and others who provide care to patients with SCD may assist to more effectively identify and reduce the incidence of CVE and the prevalence of CVE-related morbidity. We must continue to re-conceptualize our clinical models of treatment for patients with SCD to include early neuropsychological, neuropsychiatric, and imaging assessments as primary preventative methods.

Acknowledgments
We would like to thank all of those who were instrumental in the construction of this paper to include Linda Weaver, Jude C Jonassaint, and Marilyn Telen for their support and continued guidance.

References


