Neuropsychological Assessment, Neuroimaging, and Neuropsychiatric Evaluation in Pediatric and Adult Patients with Sickle Cell Disease (SCD)

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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. Wassserman 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 (Wassserman 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

functioning as well as possible deficits. Several studies have also demonstrated that cognitive deficits in children with SCD exist in the absence of relevant MRI findings, and that deficits are multifactoral, complex, and arise from multiple etiological factors (Bernaudin et al 2000; Steen, Fineberg-Buchner et al 2005). Collectively, these studies emphasize the need for early detection of CVE in patients with SCD in an effort to reduce and prevent adult neurocognitive dysfunction.

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. Neuroimaging 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 neurocogntive 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 multifactoral 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 asymptomatically 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.

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References

Armstrong FD, Thompson RJ Jr, Wang W, et al. 1996. Cognitive functioning and brain magnetic resonance imaging in children with sickle Cell disease. Neuropsychology Committee of the Cooperative Study of Sickle Cell Disease. *Pediatrics*, 97(6 Pt 1):864–70.

Baldeweg T, Hogan A, Saunders D, et al. 2005. Detecting white matter injury in sickle cell disease using voxel based morphometry. *Annals of Neurology*, 59:662–72.

Bernaudin F, Verihac S, Freard F, et al. 2000. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. *Journal of Child Neurology*, 15:333–43.

Bonner M, Gustafson KE, Schumacher E, et al. 1999. The impact of sickle cell disease on cognitive functioning and learning. *School Psychology Review*, 28:182–93.

Briscoe G. 2001. The cognitive and neuropsychological impact of sickle cell anemia: a review and update. *Journal of Psychological Practice*, 7:88–102.

Broe G. 2001. The Cognitive and Neuropsychological impact of sickle cell anemia: a review and update. *Journal of Psychological Practice*, 7:88–102.

Brown RT, Armstrong FD, Eckman JR. 1993. Neurocognitive aspects of pediatric sickle cell disease. *Journal of Learning Disabilities*, 26:33–45.

Brown RT, Davis PC, Lambert R, et al. 2000. Neurocognitive functioning and magnetic resonance imaging in children with sickle cell disease. *Journal of Pediatric Psychology*, 25:503–13.

Burlew K, Telfair J, Colangelo L, et al. 2000. Factors that influence adolescent adaptation to sickle cell disease. *Journal of Pediatric Psychology*, 25:287–99.

Coelho MS, Max JE, Tranel DA. 2005. Matched lesion analysis of childhood versus adult-onset brain injury due to unilateral stroke: another perspective on neural plasticity and recovery of social functioning. *Cognitive and Behavioral Neurology*, 18:5–17.

Cohen AR, Galanello R, Pennell DJ, et al. 2004. Thalassemia. *Hematology*, 14–34.

DeBaun MR, Schatz J, Siegel MJ, et al. 1998. Cognitive screening examinations for silent cerebral infarcts in sickle cell disease. *Neurology*, 50:1678–82.

Edwards CL, Scales M, Loughlin C, et al. 2005. A brief review of the pathophysiology, associated pain, and psychosocial issues associated with sickle cell disease (SCD). *International Journal of Behavioral Medicine*, 12:171–9.

Edwards CL, Whitfield K, Sudhakar S, et al. 2006. Parental Substance Abuse, Reports of Chronic Pain, and Coping in Adult Patients with Sickle Cell Disease (SCD). *J Natl Med Assoc*, 98(3):420–28.

Fowler MG, Whitt JK, Lallinger RR, et al. 1988. Neuropsychologic and academic functioning of children with sickle cell anemia. *Journal of Developmental and Behavioral Pediatrics*, 9:213–20.

Grueneich R, Ris DM, Ball W, et al. 2004. Relationship of structural magnetic resonance imaging, magnetic resonance perfusion, and other disease factors to neuropsychological outcome in sickle cell disease. *Journal of Pediatric Psychology*, 29:83–92.

Hariman LM, Griffith ER, Hurtig AL, et al. 1991. Functional outcomes of children with sickle-cell disease affected by stroke. *Archives of Physical Medicine and Rehabilitation*, 72:498–502.

Hogan AM, Kirkham FJ, Prengler M, et al. 2006. An exploratory study of physiological correlates or neurodevelopmental delay in infants with sickle cell anaemia. *British Journal of Haematology*, 132:99–107.

Hogan AM, Pit-ten Cate IM, Vargha-Khadem F, et al. 2006. Physiological correlates of intellectual function in children with sickle cell disease: Hypoxaemia, hyperaemia and brain infarction. *Dev Sci*, 9:379–87.

Hogan AM, Vargha-Khadem F, Saunders DE, et al. 2006. Impact of frontal white matter lesions on performance monitoring: ERP evidence for cortical disconnection. *Brain*, 129:2177–88.

Izuora GI, Kaine WN, Emodi I. 1989. Neurological disorders in Nigerian children with homozygous sickle cell anaemia. *East African Medical Journal*, 66:653–7.

Kral MC, Brown RT, Hynd GW. 2001. Neuropsychological aspects of pediatric sickle cell disease. *Neuropsychology Review*, 11:179–96.

Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. 1998. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*, 91(1):288–94.

Pells J, Presnell K, Edwards CL, et al. 2005. Moderate Chronic Pain, Weight, and Dietary Intake in African American Adult Patients with Sickle Cell Disease (SCD). *J Natl Med Assoc*, 97:1622–9.

Powars DR, Wong WY, Vachon LA. 2001. Incomplete cerebral infarctions are not silent. *Journal of Pediatric Hematology/Oncology*, 23:79–83.

Schatz J. 2004. Brief report: Academic attainment in children with sickle cell disease. *Journal of Pediatric Psychology*, 29:627–33.

Schatz J, Craft S, Koby M, et al. 1999. Neuropsychologic deficits in children with sickle cell disease and cerebral infarction: role of lesion site and volume. *Child Neuropsychology*, 5:92–103.

Schatz J, Finke RL, Kellett JM, et al. 2002. Cognitive Functioning in Children with Sickle Cell Disease: A Meta-Analysis. *Journal of Pediatric Psychology*, 27:739–48.

Schatz J, Finke R, Roberts CW. 2004. Interactions of biomedical and environmental risk factors for cognitive development: a preliminary study of sickle cell disease. *Journal of Developmental and Behavioral Pediatrics*, 25:303–10.

Schatz J, McClellan C. 2006. Sickle cell disease as a neurodevelopmental disorder. *Mental Retardation and Developmental Disabilities Research Reviews*, 12:200–7.

Schatz J, White D, Moinuddin A, et al. 2002. Lesion burden and cognitive morbidity in children with sickle cell disease. *Journal of Child Neurology*, 17:891–5.

Steen G, Emudianughe T, Hankins G, et al. 2003. Brain imaging findings in pediatric patients with sickle cell disease. *Radiology*, 228:216–25.

Steen G, Emudianughe T, Hunte M, et al. 2005. Brain volume in pediatric patients with sickle cell disease: evidence of volumetric growth delay. *American Journal of Neuroradiology*, 26:455–62.

Steen G, Fineberg-Buchner C, Hankins G, et al. 2005. Cognitive deficits in children with sickle cell disease. *Journal of Child Neurology*, 20:102–7.

Steen G, Hankins G, Xiong X, et al. 2003. Prospective brain imaging evaluation of children with sickle cell trait: initial observation. *Radiology*, 228:208–15.

Steen G, Hu J, Elliot V, et al. 2002. Kindergarten readiness skills in children with sickle cell disease: evidence of early neurocognitive damage? *Journal of Child Neurology*, 17:111–16.

Steen G, Miles M, Helton K, et al. 2003. Cognitive impairment in children with hemoglobin ss sickle cell disease: relationship to MR imaging findings and hematocrit. *American Journal of Neuroradiology*, 24:382–9.

Steen G, Reddick W, Mulhern R, et al. 1998. Quantitative MRI of the brain in children with sickle cell disease reveals abnormalities unseen by conventional MRI. *Journal of Magnetic Resonance Imaging*, 8:535–43.

Steen G, Xiong X, Langston J, et al. 2003. Brain injury in children with sickle cell disease: prevalence and etiology. *Annals of Neurology*, 54:564–72.

Steen G, Xiong X, Mulhern R, et al. 1999. Subtle brain abnormalities in children with sickle cell disease: relationship to blood hematocrit. *Annals of Neurology*, 45:279–86.

Stringer A. 2003. Cognitive rehabilitation practice patterns. A survey of American Hospital Association Rehabilitation Programs. *Clinical Neuropsychologist*, 17:34–44.

Treadwell MJ, Law AW, Sung J, et al. 2005. Barriers to adherence of deferoxamine usage in sickle cell disease. *Pediatric Blood and Cancer*, 44:500–7.

Thompson RJ, Gustafson KE, Bonner MJ, et al. 2002. Neurocognitive development of young children with sickle cell disease through three years of age. *Journal of Pediatric Psychology*, 27:235–44.

Wasserman AL, Wilimas JA, Fairclough DL, et al. 1991. Subtle neuropsychological deficits in children with sickle cell disease. *American Journal of Pediatric Hematology/Oncology*, 13:14–20.

Wang WC, Gallagher DM, Pegelow CH, et al. 2000. Multicenter comparison of magnetic resonance imaging and transcranial Doppler ultrasonography in the evaluation of the central nervous system in children with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, 22:335–9.

Wang WC, Langston JW, Steen RG, et al. 1998. Abnormalities of the central nervous system in very young children with sickle cell anemia. *Journal of Pediatrics*, 132:994–8.