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Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease

Nitya Bakshi,*,† Ines Lukombo,* Helen Shnol,‡ Inna Belfer,‡ and Lakshmanan Krishnamurti*,†

**Division of Pediatric Hematology-Oncology-Bone Marrow Transplantation, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.*
†Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.
‡Department of Anesthesiology, University of Pittsburgh, Pittsburgh, Pennsylvania.

Abstract: **Sickle cell disease (SCD) is associated with episodes of severe vaso-occlusive pain beginning in infancy with a subset of patients with SCD transitioning to chronic pain. Response to experimental pain using quantitative sensory testing in these patients suggests altered pain processing. The objectives of this study were to characterize sensitivity to multiple modalities of experimental pain stimuli and to interrogate the relationship of psychological covariates, clinical pain burden, and pain-related outcomes to experimental pain sensitivity in children with SCD compared with healthy individuals of similar age and sex. Cross-sectional assessments of psychological characteristics were performed, and quantitative sensory testing methods were used to measure experimental pain sensitivity in children age 8 to 21 years. Anxiety, depressive symptoms, catastrophizing, and somatization were found to be associated with increased sensitivity to experimental pain stimuli. Increased frequency of painful episodes in SCD was associated with decreased sensitivity to heat pain and decreased mechanical temporal summation. These data suggest that careful consideration be given to psychological factors, age, sex, and clinical burden of pain when studying response to experimental pain in SCD.**

Perspective: ***In this study of patients with SCD, a condition associated with recurrent acute or chronic pain, psychological factors such as depression, anxiety, and catastrophizing are associated with increased sensitivity to experimental pain stimuli. Further study is need to delineate the role of these factors in chronic SCD pain.***

Key words: *Sickle cell disease, pain, quantitative sensory testing, psychological factors.*

Sickle cell disease (SCD) is an inherited blood disorder characterized by episodes of pain due to vaso-occlusion. Pain is often severe and begins in infancy. Although episodic vaso-occlusive pain or vaso-occlusive crisis (VOC) is described as the prototypical pain phenotype in SCD, a subset of individuals transition from recurrent acute to chronic persistent pain.[47] While chronic pain is generally defined as pain persisting beyond the period of healing or beyond a period of 3 to 6 months,[17] there is not yet a generally accepted definition for chronic pain in SCD. The Pain in Sickle Cell Disease Epidemiology Study (PISCES) measured pain using daily pain diaries for a period of 6 months in adults with SCD and reported that approximately a third of patients with SCD had pain on >95% of diary days,[47] suggesting they had chronic pain. The factors that contribute to this transition from episodic pain to chronic pain have not been described in SCD, although like in other chronic pain conditions, this transition is likely facilitated by a combination of biological, psychological, social, and genetic factors. Central sensitization (CS) is defined as an increase in responsiveness of the

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Address reprint requests to Lakshmanan Krishnamurti, MD, Emory University, Division of Pediatric Hematology/Oncology/BMT, Department of Pediatrics, Emory University, 2015 Uppergate Drive, Atlanta, GA; Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA 30322. E-mail: lkrishn@emory.edu
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nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.[26] CS has been implicated in the pain phenotype of chronic painful conditions such as fibromyalgia, osteoarthritis, temporomandibular joint disorders, headaches, neuropathic pain, visceral pain, and postsurgical pain.[58] Clinically, CS is inferred indirectly by the presence of manifestations of pain hypersensitivity such as hyperalgesia, allodynia, aftersensations, and enhanced temporal summation.[26,58] Studying response to experimental pain using quantitative sensory testing (QST) methods may provide insight into mechanisms that play a role in the transition to and maintenance of chronic pain in SCD.

Using QST, children with SCD have been shown to be more sensitive to cold pain[8,38] and heat pain,[8] but not to mechanical pain,[8] compared with race-matched controls of similar age. Adults with SCD have also been shown to have increased sensitivity to experimental pain,[10] and manifest features of either CS or peripheral sensitization, or both.[11,21] Those with a heightened CS profile also experience a greater number of pain episodes, poorer sleep, increased negative mood, and catastrophizing.[11] Correlation of QST responses with clinical pain, pain-related traits, or pain outcomes have not been described in children with SCD. Jacob et al compared children with SCD with a reference historical cohort comprised of children who were predominantly of Caucasian origin.[30] They identified a subset of children with SCD as having an 'abnormal' QST profile if their responses to experimental pain stimuli were outside of the 2.5 to 97.5 percentile of the reference historical healthy cohort. They did not, however, identify any differences in age, sex, genotype, or pain frequency measured at hospital associated pain visits between patients who had an 'abnormal' QST profile versus those who did not.[30] Brandow and Panepinto defined children with SCD as having impaired pain sensitivity threshold if they were >1 SD beyond the median of the control group,[7] however, they did not account for differences in age and sex within the control group. Although healthy children have been shown to have decreased pain sensitivity with age,[4,5] age was associated with increased sensitivity to cold, heat, and mechanical pain stimuli in children with SCD.[8] While these studies indicate the potential existence of altered pain sensitivity in SCD, methodological variations between studies do not allow for a full comparison between these studies. Additionally, effect of factors such as age, sex, and psychological characteristics on experimental pain sensitivity have not been fully addressed in these studies.

The objectives of this study were to characterize sensitivity to multiple modalities of experimental pain stimuli and to interrogate the relationship of psychological covariates to experimental pain sensitivity in children with SCD compared with healthy individuals of similar age and sex. We also studied the relationship of previous pain experience to experimental pain sensitivity in children with SCD.

Methods

Participant Recruitment

The participants in this study were recruited from a comprehensive sickle cell clinic at a large academic pediatric hospital. Eligible patients with SCD were offered participation in the study either at a clinic visit or via telephone. If a potential participant expressed interest in the study, the study was explained in detail and informed consent subsequently obtained in person before any study procedures. Patients with SCD were eligible if they were: 1) between 8 and 21 years of age, 2) had SCD of any genotype, 3) were >2 weeks from the most recent hospitalization (inpatient or emergency room) for an SCD-related pain episode. They were excluded if they had: 1) any other disease or sensory condition that could result in acute or chronic pain, 2) history of stroke, 3) any recent surgical procedures or pain interventional procedure in the previous 3 months, 4) trauma or injury to the proposed testing sites, 5) significant cognitive impairment, or 6) active major psychiatric or mood disorder. To minimize confounding variables, all patients meeting criteria were enrolled but a subset of patients were planned a priori to be analyzed separately from the main cohort because of their clinical characteristics. The characteristics of this subset were: 1) receiving long-term opioids (without change in dosing or frequency of opioids in the month before the study), gabapentin, or other adjunctive medications for pain, 2) receiving chronic transfusion for nonovert stroke indication, and 3) SCD patients who were not African American. Controls were either siblings or other family members of SCD patients usually offered participation at the same time as patients or were unrelated controls offered participation through flyers placed in the community. Controls were healthy (ie, no major self-reported medical, psychiatric, or neurologic diagnoses) African American children age 8 to 21 years without any acute or chronic pain diagnoses and not receiving any pain medications. Participants were recruited from January 2013 until June 2014 if they met eligibility criteria. The study was approved by the institutional review board and written informed consent and assent was obtained before all procedures. Timing of study procedures was on the basis of participant convenience.

Measures of Psychological and Pain-Related Functioning

Measures of patient reported outcomes, psychological functioning, and quality of life (QoL) were completed before QST to avoid any QST-related effects on these measures. Measures relevant to this analysis are described as follows.

Patient Reported Outcome Measures Information System Measures of Pain Intensity, Pain Interference, Anxiety, Depressive Symptoms, Sleep, Fatigue, and Peer Relationships

Patient Reported Outcome Measures Information System (PROMIS) measures are designed to capture