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An Evaluation of Central Sensitization in Patients With Sickle Cell Disease

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Abstract: **Central sensitization (CS), nociceptive hyperexcitability known to amplify and maintain clinical pain, has been identified as a leading culprit responsible for maintaining pain in several chronic pain conditions. Recent evidence suggests that it may explain differences in the symptom experience of individuals with sickle cell disease (SCD). Quantitative sensory testing (QST) can be used to examine CS and identify individuals who may have a heightened CS profile. The present study categorized patients with SCD on the basis of QST responses into a high or low CS phenotype and compared these groups according to measures of clinical pain, vaso-occlusive crises, psychosocial factors, and sleep continuity. Eighty-three adult patients with SCD completed QST, questionnaires, and daily sleep and pain diaries over a 3-month period, weekly phone calls for 3 months, and monthly phone calls for 12 months. Patients were divided into CS groups (ie, no/low CS [n = 17] vs high CS [n = 21]), on the basis of thermal and mechanical temporal summation and aftersensations, which were norm-referenced to 47 healthy control subjects. High CS subjects reported more clinical pain, vaso-occlusive crises, catastrophizing, and negative mood, and poorer sleep continuity (*Ps* < .05) over the 18-month follow-up period. Future analyses should investigate whether psychosocial disturbances and sleep mediate the relationship between CS and pain outcomes.**

Perspective: ***In general, SCD patients with greater CS had more clinical pain, more crises, worse sleep, and more psychosocial disturbances compared with the low CS group.***

Key words: *Sickle cell disease, clinical pain, laboratory pain, quantitative sensory testing, central sensitization, sleep, catastrophizing.*

Sickle cell disease (SCD), an inherited blood disorder, is associated with significant morbidity including severe episodic pain and, in a sizeable subset of patients, chronic pain.[47] Although the mechanisms of SCD pain remain poorly understood, recent reports have implicated a process of central sensitization (CS). CS is a process whereby nociceptive signals coming from the periphery assault the central nervous system and alter the spinal cord and brain producing a chronic amplification of pain sensations.[57] This manifests clinically in a number of ways, including hyperalgesia and allodynia, enlarged area of hyperalgesia beyond the initial area of injury, and aftersensations following cessation of the initial insult.[57] Rewiring of pain transmission occurs in patients with CS and a growing body of literature documents augmented central nervous system processing in SCD. Transgenic mice models of SCD (expressing sickle hemoglobin) suggest that CS occurs through aberrant heightened spinal and supraspinal processing that is demonstrated by increased sensitivity to cold, heat, and mechanical stimuli as well as musculoskeletal pain behavior compared with control animals.[15] Ballas and

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colleagues[3] note that the best example of this phenomenon observed in patients with SCD is the continuation of severe pain, even after successful bone marrow transplantation, which essentially "cures" the patient of SCD. They note that resetting the aberrant wiring of the brain back to normal may take an extended period of time.

CS in humans can be assessed through the application of quantitative sensory testing (QST) using standardized, calibrated, consistently applied noxious stimuli to measure pain processing. Typical QST measures of CS include the measurement of painful aftersensations or temporal summation, which is heightened perceptual responses to repeated stimulation of identical intensity.[22,57] QST is often used to measure patient characteristics that might be associated with pain-related outcomes,[28] and increased sensitivity to painful stimuli has been shown to incur risk for poor outcomes. For example, in non-SCD chronic pain conditions, lower levels of pain tolerance[20,24] and higher levels of temporal summation[2] are associated with more frequent, intense, and disabling episodes of recent pain. The few studies that have examined QST in adults with SCD generally reported enhanced sensitivity of thermal detection and reduced pain thresholds in patients with SCD.[5,26,27] A recent study reported evidence of CS in 60% of patients with SCD tested and a combination of central and peripheral sensitization in an additional 32%.[23] The goal of the current study was to use the extant literature to categorize patients with SCD as either showing no/low CS or high CS on the basis of responses derived during QST and examine differences in clinical characteristics between these 2 groups. We hypothesized that those in the high CS group would endorse greater pain, worse psychosocial/behavioral comorbidities, and a more severe symptom experience than those in the no/low CS group.

Methods

The current analyses are part of a larger ongoing project designed to examine pain and crises in patients with SCD and compare them with healthy matched control participants. All subjects were recruited for participation from the Sickle Cell Center for Adults at Johns Hopkins Hospital or through posted advertisements. The current analyses focused on 38 adult patients with SCD, derived from a larger sample of 83 patients with SCD and classifying CS on the basis of QST responses observed in 47 healthy controls (see Table 1 for demographic data and QST used for categorization). Major inclusion criteria for the SCD group included age 18 years or older, formal diagnosis of SCD (by confirmed genotyping or confirmation by study hematologist), no changes in dose of long- and short-acting opioids, nonsteroidal anti-inflammatory drugs or acetaminophen 1 month before pain testing (if receiving any of these medications) and self-identifying as black or African American (for matching purposes in the larger study). Exclusion criteria included chronic transfusions, active alcohol or substance abuse/dependence, significant cognitive impairment, unstable psychiatric illness, HIV infection, viral hepatitis, or other current infection. Although not the focus of the current analyses, additional exclusion criteria for healthy controls included any acute or chronic pain, regular use of anti-inflammatory medication, opioids, or antidepressant medication, and smoking >1 pack/d. Although not the specific focus in the current analyses, CS data from healthy controls were used to categorize SCD patients into groups. In brief, control participants were healthy African American individuals, 65% were women, and the group mean age was 33 (SD = 9.5) years with a body mass index (BMI) of 26 (SD = 4.8).

Table 1. Demographic Variables

Demographic Variables	Low CS (N = 17)	High CS (N = 21)	P
Age, y	35.6 (10.6)	42.8 (13.1)	.08
Female sex	70.6% (12)	76.2% (16)	.49
Education level			
≤High school/GED	11.8% (2)	23.8% (5)	.24
Some college/technical school	35.3% (6)	42.8% (9)	
≥Bachelor's degree	53.0% (9)	33.4% (7)	
Occupational status			
Employed (full or part time)	70.6% (12)	42.9% (9)	.11
Marital status			
Single/divorced/separated	64.7% (11)	81.0% (17)	.34
Married/living with partner	35.3% (6)	19.0% (4)	

Abbreviation: GED, General Educational Development.
NOTE. Data are presented as mean (SD) or % (n).

Procedures

After initial telephone screening to ensure eligibility criteria were met, participants attended an in-person visit. Participants were asked to attend only when their pain was typical of their SCD pain and at no greater intensity than 5 of 10 and they had not experienced a vaso-occlusive crisis in at least the previous 3 weeks. After informed consent procedures, participants completed a standardized laboratory pain testing protocol between 9 and 11 AM; upon completion they were instructed in the use of electronic diary monitoring via personal digital assistant (PDA) and informed they would receive follow-up calls for a total of 18 months (see Fig 1 for a timeline). Participants were allowed to stop or refuse any procedure at any time and all study-related procedures were approved by the Johns Hopkins University School of Medicine institutional review board. Additionally, clinical characteristics (eg, history of acute chest syndrome, presence of avascular necrosis) were obtained from the medical record.

QST

Pain Threshold/Tolerance

Heat pain threshold (HPTh) was assessed via a Peltier element-based stimulator (Medoc, Pathway, Advanced Thermal Stimulator thermode), on the dominant ventral forearm, using an ascending method of limits paradigm with a 9-cm^2 probe and .5°C/s rate of rise. Subjects underwent 2 trials and indicated when they first felt painful (HPTh) via button press which turned the device off.