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Sensory and Thermal Quantitative Testing in Children with Sickle Cell Disease

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Abstract

Very little is known about pain processing in sickle cell disease (SCD). We examined the mechanical and thermal sensory patterns in children with SCD. Children ages 10–17 years ($n=48$; mean 13.7 ± 2.0 ; 22 females) participated in quantitative sensory testing (QST) procedures and completed a quality of life (PedsQL) and anxiety and depression scale (RCADS). Thirteen children showed evidence of abnormal pain processing, indicated by decreased sensitivity to heat or cold sensations (hypoesthesia), and pain experienced with non-painful stimuli (allodynia). Pain ratings associated with cold and warm sensations were significantly higher in the subgroup with abnormal QST compared to the 35 SCD children with normal QST ($p=0.01$ and $p<0.0001$,

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respectively). The presence of hypoesthesia and allodynia in children with SCD may represent abnormal changes in the peripheral and central nervous system. Clinicians need to be aware that sickle cell pain may not only be inflammatory or ischemic secondary to vaso-occlusion and hypoxia, but may also be neuropathic secondary to nerve injury or nerve dysfunction. Neuropathic pain in SCD may be the result of tissue damage after vaso-occlusion in neural tissues, whether peripherally or centrally. Future studies are needed to determine the presence of neuropathic pain in children with SCD.

Keywords

children; sickle cell disease; quantitative sensory testing; neuropathic pain

INTRODUCTION

The most frequent reason for hospital admissions in children with sickle cell disease (SCD) is the acute pain crisis related to vaso-occlusion.^{1–3} Dampier and colleagues⁴ found that pain at home in children with SCD varied widely, from less than 1% to more than 99% of diary days, and some children were reporting persistent pain. Persistent pain is not well studied in patients with SCD, but was previously described as pain between crises or chronic pain that is intractable without obvious pathology.⁵ Persistent pain may be perceived with non-painful stimuli (also known as allodynia), or a hypersensitivity to painful stimuli may be felt (also known as hyperalgesia). Persistent pain in SCD may be secondary to nerve injury or nerve dysfunction, as a result of tissue damage after vaso-occlusion in neural tissues, whether peripherally or centrally, or be associated with stroke.⁵

Very little information is available about persistent pain and abnormal pain processing in SCD. Therefore, we investigated the mechanical and thermal sensory patterns in children with SCD. Quantitative sensory testing (QST) procedures are widely regarded as the “Gold Standard” for evaluating small-caliber A-delta & C-fibers--the primary transmitters of thermal and pain sensation. It is the only test that quantitatively assesses function of somatic small fibers - from peripheral receptors through their central nervous system connections.

We hypothesized that children with SCD have abnormal mechanical and thermal sensory patterns due to the repetitive vaso-occlusive events. Children with abnormal sensory patterns were defined as having any tested sensory thresholds outside the ranges defined by the 95% reference intervals (i.e. below the 2.5th and above the 97.5th percentiles) that we previously published for healthy controls of similar age.⁶

METHODS

The Institutional Review Board of University of California, Los Angeles approved the study. Parents and children provided consent and assent respectively. Children with SCD were recruited through the Sickle Cell Disease Foundation of California. Children completed questionnaires on rating 1) pain using a 10 cm visual analog scale (VAS),⁷ 2) anxiety and depression using the Revised Child Anxiety and Depression Scale (RCADS),⁸ and 3) quality of life using the PedsQL.⁹

Mechanical sensation was tested randomly on either left or right forearm using a cotton ball, brush, and pinprick.⁶ Thermal sensation was tested randomly on either left or right thenar eminence for cold, warm, cold pain, heat pain, and heat pain tolerance.⁶ The following data were also collected: 1) number of pain episodes requiring hospitalization during the previous 12 months, 2) presence of average and worst pain during the previous month, and 3) pain at the time of testing. Demographic and health related information was collected at the time of enrollment. Children received \$30 gift cards for partaking in the study.

Inclusion Criteria

Children were included if: 1) age was 10–17 years old, 2) known diagnosis of SCD, 3) read and write in English, 4) can use a pen/pencil, 5) did not have cognitive or neurological impairment that precluded completion of testing instruments or following instructions for quantitative sensory testing, 6) not receiving analgesics (opioids and anti-neuropathic agents) within 1–2 weeks of the scheduled testing time, and 6) the child assented and a parent consented for the study.

Nonpainful Mechanical Stimulus

Tactile sensation was applied in 5 strokes using a cotton ball and hand-held soft brush on the right or left forearm randomly and over 3–5 cm distance. The intensity of perceived pain for each stroke was rated using the VAS. The procedure took less than two minutes.⁶

Painful Mechanical Stimulus

Five non-penetrating pinpricks were applied randomly on the right or left forearm. A Neuropen (NT0100) with a Neurotip (NT5405) delivered a force of 40g at 90° angle to the skin. The intensity of perceived pain was then rated using the VAS. The procedure took less than two minutes.⁶

Thermal (Heat/Cold) Detection Thresholds

Quantitative thermal detection thresholds were determined using the Medoc TSAII NeuroSensory Analyzer device (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel). The TSAII NeuroSensory Analyzer device is an essential Quantitative Sensory Testing (QST) tool for evaluating nerve impairment and sensory testing. It generates and documents responses to thermal stimuli (such as warm, cold, heat-induced pain, and cold-induced pain), and is used for identifying thermal pain thresholds (temperature when heat and cold are felt as painful).

All QST procedures were performed using reliable and standardized methodologies described in detail in our previous publications.⁶ A 3 cm × 3 cm (9cm²) contact thermode was strapped to the thenar eminence of the hand and secured with a Velcro band. The thermode baseline temperature was 32°C, with testing temperatures between 0–52.5°C. The thermode temperature increased at a range of 1°C/second for cool and warm sensations, and 1.5°C/second for cold pain and heat pain. The thermode temperature returned to baseline (32°C) at a rate of 1°C/second for cool and warm sensation and 10°C/second for cold and heat pain.⁶

Testing was done in a quiet room with the participant seated comfortably and without access to computer screen. The thermal probe was applied to one hand and the subject was asked to use the computer mouse control button with the other hand. The subjects were instructed to press the control button as soon as they felt a particular sensation (cold, warm, cold pain, heat pain). Activation of the button discontinued the stimulus and then the subjects were asked to rate the pain perception on VAS. The cold and warm sensations were applied in a series of 4 stimuli, the cold and heat pain were applied in a series of 3 stimuli. The mean value of each series of stimuli was taken as the mean detection threshold. The thermal detection testing procedures lasted 20 to 30 minutes.⁶

Statistical Analyses

All data were analyzed using SPSS (Chicago, IL, version 20.0) and SAS (Cary, NC). Descriptive statistics (means, standard deviations) were used to describe pain intensity ratings and thermal thresholds. Similar to statistical procedures reported by Meier and colleagues,⁶ the median (50th percentile) was calculated and normal ranges were defined by the 95% reference intervals determined from the 2.5th and 97.5th percentiles. Children with SCD were considered as having abnormal sensory patterns when any thermal thresholds were outside the ranges defined by the 95% reference intervals (i.e. below the 2.5th and above the 97.5th percentiles). Nonparametric statistics were used to compare medians, and t-tests were used to determine significant differences in pain intensity ratings and thermal detection thresholds between those with normal and abnormal findings on the QST.

RESULTS

Demographics

Forty-eight children ages 10–17 years (mean 13.7 ± 2.0) participated in the study; 22 (45.8%) were female. There were no differences in demographics between the two groups (Table 1). There were 21 (43.8%) children (8 to 12 years) and 27 (56.2%) adolescents (13 to 17 years). None of the patients had experienced VOC crises in the upper extremities. The hemoglobin types were: 1) Hgb SS (n=24; 50%), 2) HgbSC (n=15; 31.3%), 3) Hgb Beta Thalassemia (n=3; 6.3%), and 4) unknown (n=6; 12.5%). Patients were classified in to three groups based on Nebor and colleagues¹⁰ as follows: 1) patients experienced VOE requiring 3 or more hospitalizations in the previous 12 months (n=7; 14.6%); 2) requiring less than 3 hospitalizations the previous 12 months (n=22; 45.8%), and 3) no VOE hospitalizations (n=19; 39.6%). At the time of testing, most (n=41; 85.4%) did not have pain. More than half of the children (n=30; 62.5%) reported having pain the previous month. No child withdrew from the study protocol after enrollment before or after participation in the QST and other sensory testing. The duration of the testing was 20 to 30 minutes.

Comparison Between Patients With Normal and Abnormal Pain Patterns

We identified 13 patients with abnormal QST findings. The 13 patients had at least one of the detection thresholds the cold and warm sensations and cold and heat pain thresholds, that was outside the values of normal reference intervals of 2.5th to 97.5th percentiles of the healthy controls. The differences in median 50th percentile between these 13 subjects and the normative reference data are shown in Table 2.

Compared to those patients with normal QST sensory testing, there were no statistically significant differences noted by age, gender, and Hgb genotypes. The overall mean pain reported by the patients was within the moderate range and was not significantly different between the groups with and without abnormal QST (Table 3).

Pain Intensity Ratings Associated with Non-painful and Painful Mechanical Stimuli

There was significant pain with brush stimulus (indicating allodynia) in the group with abnormal QST compared to those with normal QST ($p=0.04$). There were no differences between the groups with respect to cotton stimuli ($p=0.4$). While no group differences were apparent in pinprick pain ($p=0.05$), there was a consistent trend for patients in the abnormal QST group to rate higher pain intensity with pinprick than in the normal QST group (Table 3).

Pain Intensity Ratings Associated With Thermal (Heat/Cold) Detection Thresholds

Patients in both groups reported pain to thermal stimulation. The thermal pain intensity was lower for innocuous than for noxious stimulation and heat pain tolerance. The pain to cold and warm sensation was significantly greater in the group with abnormal QST ($P=0.01$ and $P<0.0001$ respectively) (Table 3).

Pediatric Quality of Life measure

The PedsQL scores were not significantly lower in the group with abnormal QST vs those with normal QST (Table 4). The mean quality of life scores were within the range of values previously reported for healthy controls and children with other chronic conditions.^{11–17}

Revised Child Anxiety and Depression Scale

There were no significant differences in the RCADS median scores between the two groups (table 4). The median scores were within normal range and did not reach the clinically significant threshold of 65 for both anxiety and depression as defined by DSMIV.

DISCUSSION

The main findings of this study are that 27% of the children with SCD in our cohort exhibited decreased sensitivity (hypoesthesia) to thermal sensations and pain. The thermal hypoesthesia was associated with significant brush allodynia. In general, these patients did not differ from those children with SCD who had normal QST testing in age, gender, SCD genotypes, pain frequency or in frequency of VOC episodes. None of these patients were on opioids or anti-neuropathic pain agents that are known to affect the sensory perception and QST testing. The patients in the abnormal QST group exhibited significant mechanical pain to brush stimuli (dynamic mechanical allodynia) compared to those with normal QST.

Patients in both groups reported higher pain intensity with painful thermal (heat/cold pain) stimulation compared to non-painful (cotton, brush) stimulation; however, the pain rating with non-painful thermal (warm/cool) stimulation was significantly higher in the abnormal QST group (Table 2). The presence of dynamic mechanical allodynia to brush (A-beta fibers) suggests peripheral and/or central sensitization while thermal hypoesthesia to

innocuous cold and warm stimuli as well as to noxious pain stimuli (A-delta and C-fibers), suggests impaired processing of the thermoreceptors function.

Both increased (hypersensitivity) and decreased (hyposensitivity) sensitivity to thermal sensations and pain have been reported in children exposed to single severe or repetitive painful exposures early in life.^{18–21} A study by Brandow and colleagues²² found that children with SCD had increased sensitivity to thermal sensation and pain tests on the thenar glabrous skin of the hand using similar methods of limit paradigm. They defined increased sensitivity (hypersensitivity) to heat and cold pain, as the sensation of cold pain at a higher temperature and the sensation of heat pain at a lower temperature compared to controls with both stimuli detected closer to the starting temperature of 32°C.²³ Contrary to these findings, O’Leary and colleagues, found that SCD patients were less sensitive to cold and warm sensations compared to ethnicity matched controls. They also found no significant differences with cold and heat pain sensitivity between SCD and controls. Interestingly, O’Leary et al. demonstrated increased sensitivity to cold pain at the contralateral forearm (hairy skin) compared to controls. The unexpected finding in their study was the lack of difference between groups for perceptual heat sensitization (an index of peripheral and/or central sensitization) at the thenar glabrous or forearm hairy skin. Our data showed that some patients had cold or cold pain detection thresholds at temperatures lower than the 2.5th percentile for healthy controls, and heat or heat pain detection thresholds at higher than the 97th percentile for healthy controls, indicating decreased sensitivity (hyposensitivity) to thermal stimulation. This finding is important because those children with decreased sensitivity (hyposensitive) to heat are potentially at risk for heat burns from heating pads, a typical nonpharmacologic intervention for pain during VOE. Implication for patients with decreased sensitivity to cold is the potential for VOE when exposed to cold environment.

Several limitations in the study include a small sample size and recruitment in one community based site, and therefore the findings could not be generalizable to hospital or clinic based samples. We examined only one body site. The control reference values for the thermal QST were not performed in age matched African-American population. Lastly, six children with SCD did not have the hemoglobin genotype status available, thus, we were not able to determine the effects of disease severity. Therefore, this calls for cautious interpretation of our preliminary results.

In view of the *psychophysical* nature of thermal and mechanical quantitative sensory studies, testing subjects at different developmental stages and severity and duration, SCD might account for the discrepancies among human studies and may reflect other factors that modulate pain and sensory processing including emotional and ability to activate the conditional pain modulation system among other yet unknown factors.⁴⁰ We also agree with the detailed discussion by Brandow and colleagues, that the psychophysical thermal sensitivity testing may not have mechanistic link to pain in SCD. There are also possible biological differences in animals vs. humans that may account for the discrepancies between animal and human studies. Therefore, there is a need for further exploration of more rigorous quantitative sensory testing paradigms such as validated in patients with neuropathic pain.⁴¹ Longitudinal studies tracking QST and pain ratings from childhood to adulthood may provide valuable information about the impact of somatic and neural tissue

injury resulting from recurrent VOEs. Future studies are needed to determine whether effective pharmacological interventions targeting neuropathic pain, such as NMDA antagonists, would alter aberrant nervous system processing in patients with frequent VOEs. 25–33

Although the consequences of neural tissue damage from repeated VOE have not been fully investigated in SCD,^{34–36} it is conceivable that the recurrent VOE compromise the blood flow through vasa nervosum, leading to irreversible tissue damage following recurrent VOE in various body tissues including cerebral strokes.²⁶ This probable pathophysiology may explain the various peripheral and cranial nerve neuropathic pain conditions reported in SCD.^{26–28} Future research is needed to determine if neuropathic pain is a feature of chronic sickle cell disease or frequent VOE, and if pain management strategies for neuropathic pain would effectively mitigate the development of SCD related nervous system sensitization.

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Table 1**Demographics**

	Normal QST (n=35)	Abnormal QST (n=13)
Age	13.9 ±1.9	12.8 ±1.9
Gender		
Females	16 (45.7%)	6 (46.2%)
Males	19 (54.3%)	7 (53.8%)
Hgb Genotype		
Hgb SS	18 (51.4%)	6 (46.2%)
HgbSC	10 (28.6%)	5 (38.5%)
Others	7 (20.0%)	2 (15.3%)
Hydroxyurea Treatment	8 (22.8%)	4 (30.7%)
Pain Frequency		
None	16 (45.7%)	3 (23.0%)
1 – 2 / year	15 (42.9%)	7 (53.8%)
3 / year	4 (11.4%)	3 (23.1%)
Pain (Day of Testing)		
No	21 (60%)	9 (69.0%)
Yes	14 (40.0%)	4 (30.8%)
Mean Pain *	2.5 ± 1.9	1.3 ± 0.8
Overall Pain Past Month		
No	13 (37.1%)	5 (38.5%)
Yes	22 (62.9%)	8 (61.5%)
Mean Overall Pain *	4.7 ± 2.4	4.3 ± 2.4
Pain Sites **		
Head/Neck	6 (17.1%)	4 (30.8%)
Chest	6 (17.1%)	3 (23.1%)
Abdomen	6 (17.0%)	3 (23.1%)
Low Back	3 (8.6%)	3 (23.1%)
Upper Extremities (Muscular)	7 (20.0%)	3 (23.1%)
Lower Extremities (Muscular)	9 (25.7%)	2 (15.4%)
Bones [sternum/femur/tibia/spine]	4 (11.4%)	4 (30.8%)
Joints [shoulder, elbows, knees, ankles]	6 (17.1%)	2 (15.4%)

* Mean Pain on 0 to 10 Visual Analog Scale

** Number of Pain sites on the Body Outline Diagram of the Modified Adolescent Pediatric Pain Tool^{42,43}

Table 2

Comparison of Thermal Thresholds between 13 Patients with SCD and Abnormal QST to A Historical Healthy Controls (Meier et al. 2001)*

Method of Limits Tests	Median 50 th Percentiles		Normal Reference Interval 2.5 th to 97.5 th Percentiles*	Normal Reference Interval 2.5 th to 97.5 th Percentiles
	HC*	SCD (n=13)	HC*	SCD (n=13)
Cold (°C)	30.5	23.9	28.5 – 31.3	1.2 – 30.9
Warm (°C)	33.7	37.8	33.0 – 36.1	33.8 – 46.4
Cold Pain (°C)	14.9	3.4	0.0 – 28.0	0.0 – 22.1
Heat Pain (°C)	41.7	49.7	35.8 – 50.0	38.5 – 50.0

HC= Historical Control

SCD= Sickle Cell Disease

Table 3**Pain**

	Normal QST (n=35)	Abnormal QST (n=13)	p-Value
Overall Mean Pain			
Past Month (VAS)	2.9 ± 3.0	2.9 ± 2.8	0.74
VOE Frequency			
Previous 12 months			
0	16 (45.7%)	3 (23.1%)	
<3	15 (42.9%)	7 (53.8%)	
3	4 (11.4%)	3 (23.1%)	
Pain at Testing (VAS)			
No Pain (0)	21 (60.0%)	9 (69.2%)	
Mild (1 to 3)	9 (25.7%)	4 (30.8%)	
Moderate (4 to 6)	5 (14.3%)	0	
Severe (7 to 10)	0	0	
Mechanical Pain			
Cotton	0.1 ± 0.2	0.1 ± 0.2	0.40
Brush	0.1 ± 0.1	0.4 ± 0.8	0.04*
Pinprick	1.8 ± 2.0	2.9 ± 1.7	0.05
Thermal Pain			
Cold Sensation	0.1 ± 0.2	0.9 ± 1.7	0.01**
Warm Sensation	0.2 ± 0.5	1.8 ± 2.4	<0.0001**
Cold Pain	2.4 ± 2.2	2.7 ± 2.1	0.63
Heat Pain	3.5 ± 2.3	4.5 ± 1.7	0.14
Heat Pain Tolerance	5.3 ± 2.8	6.1 ± 2.8	0.39

VAS: 0 to 10 visual analog scale; VOE: number of vaso-occlusive episodes of acute pain requiring hospitalization the previous 12 months

Table 4

Quality of Life and Revised Child Anxiety & Depression Scores

	Normal QST (n=35)	Abnormal QST (n=13)
PedsQL		
Range	67 – 98	50 – 97
25 th	67.0	58.0
50 th	84.0	72.0
75 th	87.0	82.5
RCADS		
Range	34 – 59	35 – 67
25 th	34	39
50 th	35	49
75 th	43	56

PedsQL: Quality of Life (0 to 100; higher number indicates higher QOL).

RCADS: Revised Child Anxiety & Depression Scores (> 65 requires further evaluation for clinical anxiety and depression, as defined by DSMIV).