2016

AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain

Carlton Dampier
Emory University

Tonya M. Palermo
Seattle Children's Research Institute

Deepika S. Darbari
Children's National Medical Center

See next page for additional authors

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 18, No 5 (May), 2017: pp 490-498
Available online at www.jpain.org and www.sciencedirect.com

Focus Article

AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain

Carlton Dampier,* Tonya M. Palermo,† Deepika S. Darbari,‡ Kathryn Hassell,§ Wally Smith,¶ and William Zempsky‖

**Emory University School of Medicine, Atlanta, Georgia.*
†Seattle Children's Research Institute, Seattle, Washington.
‡Children's National Medical Center, Washington, D.C.
§University of Colorado School of Medicine, Aurora, Colorado.
¶Virginia Commonwealth University Health System, Richmond, Virginia.
‖Connecticut Children's Medical Center, Hartford, Connecticut.

Abstract: Pain in sickle cell disease (SCD) is associated with increased morbidity, mortality, and high health care costs. Although episodic acute pain is the hallmark of this disorder, there is an increasing awareness that chronic pain is part of the pain experience of many older adolescents and adults. A common set of criteria for classifying chronic pain associated with SCD would enhance SCD pain research efforts in epidemiology, pain mechanisms, and clinical trials of pain management interventions, and ultimately improve clinical assessment and management. As part of the collaborative effort between the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks public-private partnership with the U.S. Food and Drug Administration and the American Pain Society, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy initiative developed the outline of an optimal diagnostic system for chronic pain conditions. Subsequently, a working group of experts in SCD pain was convened to generate core diagnostic criteria for chronic pain associated with SCD. The working group synthesized available literature to provide evidence for the dimensions of this disease-specific pain taxonomy. A single pain condition labeled chronic SCD pain was derived with 3 modifiers reflecting different clinical features. Future systematic research is needed to evaluate the feasibility, validity, and reliability of these criteria.

***Perspective:** An evidence-based classification system for chronic SCD pain was constructed for the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy initiative. Applying this taxonomy may improve assessment and management of SCD pain and accelerate research on epidemiology, mechanisms, and treatments for chronic SCD pain.*

***Key words:** Sickle cell disease, chronic pain, taxonomy, diagnostic criteria.*

Support was provided by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks public-private partnership with the U.S. Food and Drug Administration (FDA), which has received contracts, grants, and other revenue for its activities from the FDA, multiple pharmaceutical and device companies, and other sources. A complete list of current Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks sponsors is available at: http://www.acttion.org/partners. No official endorsement by the FDA should be inferred.
The authors have no conflicts of interest to declare.

Address reprint requests to Tonya M. Palermo, PhD, Seattle Children's Research Institute, M/S CW8-6, PO Box 5371, Seattle, WA 98145. E-mail: tonya.palermo@seattlechildrens.org

1526-5900

http://dx.doi.org/10.1016/j.jpain.2016.12.016

Sickle cell disease (SCD) encompasses a group of related genetic disorders of hemoglobin structure, and is the most common genetic blood disease among individuals in North America. SCD most commonly occurs in individuals whose ethnic origin is from Africa, Middle East, Indian Subcontinent, Southern Europe, South or Central America, or the Caribbean.[35] The hallmark feature of SCD is recurrent episodes of acute pain, presumably ischemic in origin, caused by a remarkably complex process leading to obstruction of blood flow in vulnerable tissue beds by sickled erythrocytes,[72] typically referred to as a vaso-occlusive crisis.[63] From the patient perspective, SCD pain is reportedly worse than postoperative pain,[16,32] as intense as cancer pain,[82] and has a negative effect on all aspects of the individual's health-related quality of life.[21,22] Recurrent pain is the main reason for SCD-related hospitalization, and drives annual health care costs of $1.1 billion.[42] Having frequent or prolonged episodes of pain is a key predictor of morbidity and mortality.[38,60,61] Although as yet poorly studied, clinicians and researchers are increasingly appreciating that for many adolescent and adult patients with SCD these episodes of recurrent acute pain occur in the context of ongoing persistent or chronic pain.[13,69]

Mounting evidence shows that the burden of SCD pain as well as pain-associated health care utilization increase from childhood to adolescence and young adulthood.[19,67,69,70] Diary studies show that children with SCD report pain on 16 to 30% of days and pain becomes more severe in adolescence as evidenced by a marked increase in the use of opioids (57% of days in youth ages 14–19 years old, but only 10–11% of days in younger age groups).[19,67] By adulthood, the prevalence of pain continues to increase. For example, in the Pain in Sickle Cell Epidemiology Study, a daily diary study of 232 adults with SCD, 55% of adult respondents reported pain on more than half of the days and 29% reported pain on 95% of days, suggesting a substantial prevalence of chronic pain.[69] Whereas most of these reported pain days were not described as "crisis" pain, a minority of pain days with more intense pain were described as "crisis"-related. The temporal overlap of these "crisis" and non-"crisis" pain days suggested some individuals experienced a pattern of acute episodic pain superimposed upon chronic pain.

Consistent with other pediatric chronic pain conditions, youth with SCD reporting pain on most days had significantly greater functional disability, depressive symptoms, and inpatient admissions for pain relative to patients characterized as having episodic or no SCD pain.[68] Similarly, adults with frequent days of pain had higher somatic symptom burden and were more likely to be depressed or anxious.[71]

There are no existing consensus-based criteria for chronic SCD pain from which to draw for deriving a formal diagnostic classification. This lack of clarity in what defines chronic SCD pain has hindered research efforts in understanding the epidemiology of chronic SCD pain, mechanisms of chronic SCD pain, and in developing effective pain management interventions in this population. Chronic pain criteria on the basis of the duration of pain persistence from an inciting event, such as used for postoperative pain, is particularly problematic in a condition like SCD in which patterns of frequent recurrent pain occur. The likely overlap of acute and chronic pain suggested the potential utility of a frequency-based criteria similar to the classification system of the International Classification of Headache Disorders,[36] because of the similar episodic nature of headache disorders compared with acute sickle pain and the propensity for frequent headaches to become chronic or daily.

To meet the need for an evidence-based chronic pain classification system, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks public-private partnership with the U.S. Food and Drug Administration and the American Pain Society collaborated to develop the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy (AAPT). The resultant pain taxonomy framework developed through this initiative incorporates knowledge of biopsychosocial mechanisms and classifies chronic pain conditions along 5 dimensions including: 1) core diagnostic criteria, 2) common features, 3) common medical and psychiatric comorbidities, 4) neurobiological, psychological, and functional consequences, and 5) putative neurobiological and psychosocial mechanisms, risk factors, and protective factors. This framework is comprehensively described in Fillingim et al[30] and further background concerning the AAPT initiative is available in a series of additional review articles.[10,27,29,31,48,75,78,80]

The aim of our working group on SCD pain was to apply the AAPT framework to identify chronic pain condition(s) associated with SCD and to propose a diagnostic classification system on the basis of the 5 dimensions of the AAPT.

Methods

A 6-member interdisciplinary work group (WG) of clinicians and clinical scientists with expertise in SCD pain and chronic pain across the lifespan was convened. The WGs met during an AAPT consensus conference in July 2014 in Annapolis, Maryland. Before the meeting, relevant guidelines and literature on SCD pain was searched and compiled to examine pain definitions, epidemiology, and risk factors. In particular, key review articles proposing definitions or conceptualizations of chronic SCD pain were identified (eg, Ballas,[4] Ballas et al,[5] and Taylor et al[73]), and original research presenting data on pain patterns and characteristics available from daily diary studies in the SCD population were reviewed.[69] In several teleconferences before the meeting, this literature was discussed and preliminary definitions of chronic SCD pain were drafted.

The WG made the decision to not perform an exhaustive review of the literature. Systematic reviews conducted recently to inform the 2014 evidence-based report on management of SCD[84] reported little evidence related

specifically to chronic pain of individuals with SCD. Thus, the WG's stance was that proposing another systematic review was not anticipated to yield new findings. Rather, the WG sought to identify key definitions, focusing discussion on significant items pertaining to defining chronic pain in SCD. Background readings provided by the AAPT steering committee relating to multiaxial diagnostic classification systems were also reviewed so that the WG could apply this evidence-based framework to chronic pain in SCD.

During the consensus conference, full details on the AAPT framework were presented by the steering committee, and the WG developed an initial draft version that contained 2 diagnostic categories for chronic SCD pain. Each chronic pain WG presented their draft diagnostic categories to the larger group allowing for additional opportunities to incorporate feedback to refine signs and symptoms proposed in the classification system.

After the consensus meeting, the WG used the AAPT background documents and conducted several teleconferences to further refine the draft diagnostic categories. The WG cochairs (C.D. and T.M.P.) compiled literature to support the diagnostic categories proposed. Because of the lack of available evidence from the literature specifically on chronic pain in SCD to support 2 distinct diagnoses of chronic SCD pain, the WG members unanimously agreed to revise the draft categories to instead propose a single diagnostic category of chronic SCD pain. In line with the evidence-based recommendations for managing chronic complications of SCD[84] the WG proposed 3 subtypes of chronic SCD pain to account for the effect of chronic complications of SCD on the experience of chronic pain. The AAPT steering committee provided the structure for Table 1 and suggested terminology for all WGs to apply. Revisions were made until all WG members agreed on the wording of each of the signs and symptoms listed.

Table 1. AAPT Diagnostic Criteria for Chronic Pain Associated With SCD (Chronic SCD Pain)

Dimension 1: Core Diagnostic Criteria

1. Diagnosis of SCD confirmed by laboratory testing
2. Reports of ongoing pain present on most days over the past 6 months either in a single location or in multiple locations
3. Must display at least 1 sign:
   - Palpation of the region of reported pain elicits focal pain or tenderness
   - Movement of the region of reported pain elicits focal pain
   - Decreased range of motion or weakness in the region of reported pain
   - Evidence of skin ulcer in the region of reported pain
   - Evidence of hepatobiliary or splenic imaging abnormalities (eg, splenic infarct, chronic pancreatitis) consistent with the region of reported pain
   - Evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain
4. There is no other diagnosis that better explains the signs and symptoms

Chronic SCD pain diagnostic modifiers:

We propose 3 diagnostic modifiers to indicate subtypes of chronic SCD pain.

1. Chronic SCD pain without contributory disease complications is used if there is no evidence of contributory SCD complications on the basis of either clinical signs (eg, presence of leg ulcers) or test results (eg, imaging abnormalities)
2. Chronic SCD pain with contributory disease complications should be used if there is evidence of contributory SCD complications on the basis of clinical signs or test results
3. Chronic SCD pain with mixed pain types should be used if there is evidence of contributory SCD complications (eg, avascular necrosis) on the basis of clinical signs or test results and there is pain also occurring in unrelated sites (eg, arms, back, chest, or abdominal pain)

Results

Our proposed classification is for a single pain condition, which we label chronic SCD pain, with 3 subtypes: 1) chronic SCD pain without contributory disease complications, 2) chronic SCD pain with contributory disease complications, and 3) chronic SCD pain with mixed presentation.

Chronic SCD Pain

Dimension 1. Core Diagnostic Criteria of Chronic SCD Pain

The AAPT criteria for chronic SCD pain are summarized in Table 1. The history must include a diagnosis of SCD confirmed by appropriate laboratory testing. Three diagnostic modifiers indicate subtypes of chronic SCD pain to distinguish between the presence or absence of contributory disease complications as a source of chronic pain (eg, leg ulcers, avascular necrosis) and a mixed presentation that includes pain in the presence of local contributory disease complications as well as pain also occurring in other unrelated sites. Differential diagnosis includes distinguishing between chronic SCD pain and other primary pain conditions with specific defined etiologies that individuals with SCD may develop, such as migraine headaches or autoimmune disorders (eg, lupus, rheumatoid arthritis).[39,55,56] Previous research has shown that patients are able to attribute pain to their SCD rather than to other causes (eg, other injuries or illnesses) and to distinguish crisis pain from noncrisis pain (presumably ongoing chronic pain).[19,69,82]

Diagnosis of chronic SCD pain requires that, in addition to ongoing pain, the patient displays at least 1 sign of pain sensitivity on palpation or with movement of the region of reported pain, decreased range of motion or weakness in the region of reported pain, or evidence of chronic disease complications (eg, skin ulcer, splenic infarct, or bone infarction) associated with the region of reported pain.

Dimension 2. Common Features of Chronic SCD Pain, Including Epidemiology and Lifespan Considerations

SCD pain is considered to be chronic SCD pain when such pain is present on most days, and has occurred for at least the previous 6 months. As noted, more than half of adult patients with SCD report pain on more than half of days,

and 29% report pain occurring almost daily.[69] Similarly, 15% of adolescents, and 10% of young children with SCD also report pain on most days lasting greater than 6 months.[68] The daily use of opioids for pain management in older children and adolescents, and in adults, is also reported, consistent with reports of very frequent or daily pain.[17,67] Pain in multiple locations is common[20,32] with an average of 3 or more sites of pain identified by patients,[50] most commonly extremities, back, and abdominal sites. Most patients describe their pain as constant, continuous, or steady.[82] Half of patients also describe/report pain patterns that are intermittent, periodic, or rhythmic.[69,82] In one study, 90% of 145 adults with SCD described their pain using at least some neuropathic pain descriptors on a pain quality questionnaire.[82] Unfortunately, only a few of these studies distinguished between acute and chronic pain, so additional data are needed to identify features unique to chronic SCD pain. Compared with those with infrequent episodic pain, children and adolescents with chronic SCD pain were seen more often for pain management in acute care and hospital settings, reflecting the difficulties of treating combined acute and chronic pain.[66]

Individuals with SCD may experience pain originating from complications in bone or associated structures, soft tissues, and internal organs. Hepatic or splenic enlargement from accumulation of fluid and blood cells may lead to chronic pain from capsular stretch or pericapsular infarction. Other pain symptoms related to disease complications include pain at the site of ulcers that occur in the skin and associated soft tissues on either side of the ankles,[53] and pain at the site of the humeral or femoral heads from avascular necrosis.[51,66] Although uncommon in children, prevalence rates for leg ulcers in adults with SCD range from 5 to 10%.[43] Avascular necrosis can occur in older children, adolescents, and adults in either the hip (femoral head) or shoulder (humeral head) joint and is often bilateral (40–60%).[1,47] The co-occurrence of shoulder and hip involvement is also high. Similarly, persistent back pain from vertebral collapse or fractures occurs in 2 to 5% of individuals with SCD.[65] These SCD complications create persistent or irreversible injury and contribute to significant pain. For example, in a study of adults with SCD, ulcers had been present for a median of 10 months with a range of 2 to 300 months.[52]

Dimension 3. Common Medical and Psychiatric Comorbidities Associated With Chronic SCD Pain

Clinical manifestations of SCD vary by frequency and severity and are hypothesized to have differing pathophysiology. Natural history studies suggest that more frequent acute vaso-occlusive pain and certain disease characteristics (eg, presence of alpha thalassemia characterized by higher hematocrit, lower mean corpuscular volume) are associated with osteonecrosis of the femoral head.[51] In contrast, other disease complications such as leg ulcers are more strongly associated with intensity of hemolysis[41] than with frequency of acute vaso-occlusive pain. Frequent acute pain has also been associated with an increased risk of pulmonary hypertension and subsequent cardiovascular disease,[25] and with an increased risk for acute chest syndrome and subsequent chronic pulmonary disorders.[59,77] Asthma has been associated with an increased frequency of acute pain and chest syndrome episodes.[26] Similar to other chronic pain conditions,[29] chronic SCD pain is also associated with comorbid psychiatric illness, most commonly major depression and anxiety disorders.[40,44,73,83]

Dimension 4. Neurobiological, Psychosocial, and Functional Consequences of Chronic SCD Pain

Although not well characterized, the consequences of chronic SCD pain likely include common psychosocial and functional effects experienced by individuals with other types of chronic pain, which are summarized in Turk et al.[75] In children and adolescents, acute SCD pain is associated with increased impairment in daily activities such as school,[28,64] having fewer friends, and being less physically active.[22] Reductions in health-related quality of life are well documented in adults[21] and children with SCD pain, some of which was likely chronic SCD pain.[58] Activity restrictions because of persistent pain are common in almost all chronic pain disorders.[45] Fatigue,[2] somatic symptoms,[71] and sleep disturbances (including behavioral sleep problems, sleep fragmentation, and increased risk for sleep disordered breathing and periodic limb movements[46,76]) are common and associated with increased pain-related disability in SCD adults, many of whom likely had chronic SCD pain. For example, in one study of 328 adults with SCD, more than 70% had sleep disturbances, which were more common among those adults with frequent SCD pain.[81]

Studies have shown that SCD disease complications are associated with similar effects on function. Children and adolescents with hip avascular necrosis have reduced physical function of the affected hip[1,18] and parents report diminished global physical functioning.[22] Similarly, adults with pain due to either hip avascular necrosis or leg ulcers report effects on their physical functioning.[21]

Because SCD affects predominantly ethnic minorities in the United States and there are substantial disparities in wealth between white Americans and African-American and Hispanic Americans,[62] the relevance of socioeconomic conditions to pain, functioning, and health-related quality of life is high in this population. Lower family income and greater neighborhood socioeconomic distress have been associated with greater pain-related functional disability in children with SCD pain.[37,57] Many people with SCD report experiences of discrimination in health care encounters. The influence of stigma and perceived discrimination on health outcomes has been studied among individuals with SCD, reporting associations between higher levels of perceived disease stigma and discrimination and increased clinical and laboratory pain and health care utilization.[7,49]

Dimension 5. Putative Neurobiological and Psychosocial Mechanisms, Risk Factors, and Protective Factors of Chronic SCD Pain

Multiple mechanisms putatively underlie the experience of pain related to SCD including acute nociceptive pain, inflammatory pain, neuropathic, and central pain processes.[8,23] It has been postulated that multiple inputs including vaso-occlusive pain and chronic nociceptive pain as well as opioid-induced hyperalgesia from chronic opioid therapy, cause central nervous system sensitization leading to the evolution of chronic pain in SCD.[14,70] However, whether persistent pain represents peripheral sensitization at the site(s) of tissue damage and/or central sensitization has not been well studied in humans with SCD. Similar to other chronic pain syndromes in which central pain processing alterations have been shown, individuals with SCD display several features seen in centralized pain states, such as widespread musculoskeletal pain and lower pain thresholds on quantitative sensory testing to thermal and mechanical stimuli compared with healthy control participants,[9,12,33,34,79] altered patterns of functional connectivity of many brain regions,[24] a lack of response to opioid analgesia,[3,85] and susceptibility to other pain syndromes (ie, headache).[55] Research interest has heightened in evaluating whether quantitative sensory testing may predict clinical characteristics in patients with SCD such as chronic pain (eg, Brandow and Panepinto,[9] and Campbell et al[11,12]).

In the absence of published diagnostic criteria, risk and protective factors for chronic SCD pain have not yet been identified. History of mental health diagnoses, somatization, and emotional factors are associated with higher admission rates for vaso-occlusive pain in individuals with SCD.[54,74] In addition, poorer family functioning has been related to increased health care utilization in children with SCD.[6] Similarly, in adults with patterns of frequent hospital utilization for pain management there was a 3-fold higher prevalence of psychiatric illness in family members.[15] These findings may be relevant to chronic SCD pain because of their more frequent health care utilization.[66]

Chronic SCD Pain Diagnostic Modifiers

Three diagnostic modifiers indicate subtypes of chronic SCD pain. The first modifier is labeled chronic SCD pain without contributory disease complications. This modifier is used if there is no evidence of contributory SCD complications on the basis of either clinical signs (eg, presence of leg ulcers) or test results (eg, imaging abnormalities). For example, a typical patient with this type of chronic SCD pain may experience daily widespread musculoskeletal pain. The second modifier is labeled chronic SCD pain with contributory disease complications. This category should be used if there is evidence of contributory SCD complications on the basis of clinical signs or test results. For example, a typical patient with this type of chronic SCD pain may have persistent localized pain at the site of a leg ulcer or bone injury. The third modifier is labeled chronic SCD pain with mixed pain types. This category indicates that there is evidence of contributory SCD complications (eg, avascular necrosis) on the basis of clinical signs or test results and there is pain also occurring in unrelated pain sites (eg, arms, back, chest, or abdominal pain, headache). For example, a typical patient with this type of chronic SCD pain may have persistent pain in the hip due to avascular necrosis but also experience unrelated persistent pain in the back, chest, and arms typical of their widespread musculoskeletal pain. Research is needed to confirm and validate these modifiers and to develop specific strategies for assessment and management of chronic pain that are tailored to each subtype.

Discussion

Chronic SCD pain is a serious complication associated with increased morbidity and mortality, especially in older adolescents and adults with SCD.[38,60,61] Currently, there is not a universally accepted classification system for chronic SCD pain. A common set of diagnostic criteria for classifying chronic SCD pain would improve clinical assessment and management of this complex condition. Indeed, recognition of chronic pain as a distinct syndrome in SCD is a relatively new concept, because of the historical focus on assessment and management of acute vaso-occlusive pain. Over the past several decades, a number of advances in medical treatment of SCD (eg, prophylaxis against infection, improved red cell transfusions, hydroxyurea therapy) have led to improved life expectancy and most patients with SCD live into at least middle adulthood. As patients age, they accumulate tissue damage as disease-related complications leading to an increasing frequency of pain, which has likely led to a change in the symptom experience of individuals with SCD over the decades. At this time, it is critical to address chronic pain and its effect on individuals with SCD.

Many studies have characterized individual complications of SCD, modeled after the SCD natural history studies initiated in the late 1970s, but few studies have tried to describe the co-occurrence of multiple SCD complications. Thus the WG believed there was insufficient evidence to currently support multiple diagnostic types of chronic SCD pain. However, their clinical experience and available literature did suggest that individuals with certain painful SCD complications of significant duration, notably leg ulcers and avascular necrosis of hips/shoulders, could occur, to varying degrees, in the absence of other more generalized SCD pain. Similarly, clinical experience and evolving psychophysical[9,10] and neuroimaging studies[25] suggest the existence of widespread/multifocal pain and overlapping pain disorders in individuals with SCD consistent with central sensitization described in other chronic pain disorders.[48] In this iteration of the AAPT taxonomy, the WG chose to consider these likely subgroups as diagnostic modifiers until the results of further validation studies are available.

The WG suggested the frequency characteristic of "majority of days" for the chronic SCD pain definition corresponding to the 15 or more days per month used in the chronic migraine definition in the International

Classification of Headache Disorders. However, at this time there are not adequate data to support this cutoff in SCD or whether patterns of escalating pain frequency are associated with the subsequent development of chronic pain. An initial review of 3 years of daily pain data from a study by Dampier et al[21] suggests that this cutoff may characterize recurrent episodic pain from chronic pain in a small group of children with SCD but requires further study in larger samples. The consideration of pain duration also was a difficult decision because few longitudinal SCD pain studies were available to inform this criterion. In the absence of appropriate data, a 6-month criterion was selected to be consistent with that used by other AAPT WGs to define chronic pain. Longer time durations may more effectively reduce misclassifying individuals with healing leg ulcers or avascular necrosis, and those with a self-limited period of acute pain exacerbations, but will require further validation in SCD. A shorter duration may be more appropriate in guiding treatment decisions, particularly in children.[84] Future versions of the AAPT taxonomy will be updated to provide more specific definitions of pain frequency and duration when validation data are collected using these diagnostic criteria in SCD.

Our WG applied a 5 axial system to identify critically important aspects of chronic pain assessment and management in SCD, which calls attention to the evidence gaps that exist in chronic SCD pain. The paucity of available research on chronic pain in SCD compared with many other chronic pain disorders significantly limited the WG's ability to apply the AAPT dimensional framework. Because much of the SCD pain literature did not make a distinction between frequent acute or persistent/chronic pain, the WG often relied on expert consensus for domain characteristics. Indeed the Expert Panel on Management of SCD[84] also relied on consensus in its guideline statement on chronic pain management and relied on general literature on chronic pain rather than evidence specifically related to chronic pain in individuals with SCD. However, the study by Sil et al,[66] which grouped children and adolescents with SCD using a pain frequency classification similar to that proposed in this report, observed only quantitative differences in several functional outcomes and psychosocial characteristics between their chronic and episodic pain groups suggesting that existing literature likely underestimates the effects of chronic SCD pain.

Considerable research will be needed to provide evidence of the reliability and validity of the criteria proposed in this report for chronic SCD pain. This iterative process has been extensively described in a companion article and would involve field testing of the criteria during clinical examinations of patients as well as empirical studies of validity.[10] Although we propose 3 diagnostic modifiers to indicate subtypes of chronic SCD pain, at present there are few data that describe the frequency of each of these subtypes of pain, or whether the effect of chronic pain or prognosis differ according to chronic pain subtype. Similarly, it will be important to characterize the frequency and effects of acute recurrent vaso-occlusive pain in these chronic pain subtypes, because this is a particularly difficult combination of pain syndromes to evaluate and treat. Research is needed to distinguish between the presence or absence of contributory disease complications as a source of chronic pain and to understand the effect of chronic SCD pain subtypes on patient functioning and quality of life across the lifespan. Because of the increase in SCD disease complications with age, it is anticipated that developmental differences will be found in the frequency of chronic pain subtypes, highlighting the importance of considering normal developmental processes that affect pain processing.[80] Such studies would also likely identify the typical age of onset for chronic pain. Moreover, it will be critical to focus research attention on developing optimal pain management strategies for individuals with different chronic SCD pain subtypes, and for management of episodic acute pain (crises) in patients with chronic SCD pain. Similarly, research is needed to identify disease management strategies that might reduce the risk of developing chronic SCD pain or improve the likelihood of its resolution.

There are several research priorities that were identified by our WG in applying an evidence-based chronic pain taxonomy to SCD pain. First, we hope this taxonomy will provide consistent criteria for conducting epidemiological studies of chronic pain prevalence and risk factors for chronic pain in individuals with SCD across the lifespan. At present, epidemiological data are drawn from a few key longitudinal diary studies, but larger sample sizes are needed to test a broad range of biopsychosocial risk factors for chronic SCD pain. Second, this taxonomy may spark interest in studies of pain mechanisms in SCD. Although it is clear that chronic SCD pain has multifactorial etiologies, at present there are limited available data on any specific mechanisms to guide treatment decisions. Studies that better characterize chronic SCD pain subtypes and phenotypes might elucidate different mechanisms for pain associated with disease complications versus for chronic SCD pain unrelated to disease complications. Third, therapeutic clinical trials in SCD would also be facilitated by use of standard inclusion/exclusion criteria for individuals with chronic SCD pain. Previous studies have focused on identifying individuals on the basis of frequency of health care utilization for acute pain, likely producing heterogeneous samples. A common set of diagnostic criteria for chronic SCD pain, such as those presented in this report, can enhance the conduct of clinical trials and lead to progress in development and testing of more effective therapies for SCD pain management.

It is important to note that the appropriate use of this classification is for evaluating chronic pain symptoms among persons with SCD. It is not appropriate to use this classification for classifying persons presenting to the Emergency Department for management of acute vaso-occlusive pain. Appropriate guidelines for management of vaso-occlusive crisis pain are available and should be followed.[84] However, when patients present for follow-up care in the outpatient setting, this classification may assist in planning the comprehensive

care for the overall management of the patient's pain characteristics.

Conclusions

This WG synthesized available literature to provide evidence for the dimensions of a disease-specific pain taxonomy for one chronic pain syndrome labeled chronic SCD pain. Future systematic research is needed to evaluate the feasibility, reliability, and validity of the diagnostic criteria, which may lead to improved clinical assessment and management and accelerate research efforts on chronic SCD pain.

References

1. Aguilar CM, Neumayr LD, Eggleston BE, Earles AN, Robertson SM, Jergesen HE, Stulberg BN, Vichinsky EP: Clinical evaluation of avascular necrosis in patients with sickle cell disease: Children's Hospital Oakland Hip Evaluation Scale–a modification of the Harris Hip Score. Arch Phys Med Rehabil 86:1369-1375, 2005

2. Ameringer S, Smith WR: Emerging biobehavioral factors of fatigue in sickle cell disease. J Nurs Scholarsh 43:22-29, 2011

3. Ballas SK: New era dawns on sickle cell pain. Blood 116: 311-312, 2010

4. Ballas SK: Pain management of sickle cell disease. Hematol Oncol Clin North Am 19:785-802, v, 2005

5. Ballas SK, Gupta K, Adams-Graves P: Sickle cell pain: A critical reappraisal. Blood 120:3647-3656, 2012

6. Barakat LP, Patterson CA, Weinberger BS, Simon K, Gonzalez ER, Dampier C: A prospective study of the role of coping and family functioning in health outcomes for adolescents with sickle cell disease. J Pediatr Hematol Oncol 29:752-760, 2007

7. Bediako SM, Lanzkron S, Diener-West M, Onojobi G, Beach MC, Haywood C Jr: The measure of sickle cell stigma: Initial findings from the Improving Patient Outcomes through Respect and Trust study. J Health Psychol 21: 808-820, 2016

8. Brandow AM, Farley RA, Panepinto JA: Early insights into the neurobiology of pain in sickle cell disease: A systematic review of the literature. Pediatr Blood Cancer 62: 1501-1511, 2015

9. Brandow AM, Panepinto JA: Clinical interpretation of quantitative sensory testing as a measure of pain sensitivity in patients with sickle cell disease. J Pediatr Hematol Oncol 38:288-293, 2016

10. Bruehl S, Ohrbach R, Sharma S, Widerstom-Noga E, Dworkin RH, Fillingim RB, Turk DC: The ACTTION-APS Pain Taxonomy (AAPT): Approaches to demonstrating the reliability and validity of core diagnostic criteria. J Pain 9: T118-T131, 2016

11. Campbell CM, Carroll CP, Kiley K, Han D, Haywood C Jr, Lanzkron S, Swedberg L, Edwards RR, Page GG, Haythornthwaite JA: Quantitative sensory testing and pain-evoked cytokine reactivity: Comparison of patients with sickle cell disease to healthy matched controls. Pain 157:949-956, 2016

12. Campbell CM, Moscou-Jackson G, Carroll CP, Kiley K, Haywood C Jr, Lanzkron S, Hand M, Edwards RR, Haythornthwaite JA: An evaluation of central sensitization in patients with sickle cell disease. J Pain 17:617-627, 2016

13. Carroll CP: Chronic and noncrisis pain in sickle cell disease. South Med J 109:516-518, 2016

14. Carroll CP, Lanzkron S, Haywood C, Kiley K, Pejsa M, Moscou-Jackson G, Haythornthwaite JA, Campbell CM: Chronic opioid therapy and central sensitization in sickle cell disease. Am J Prev Med 51:S69-S77, 2016

15. Carroll PC, Haywood C Jr, Hoot MR, Lanzkron S: A preliminary study of psychiatric, familial, and medical characteristics of high-utilizing sickle cell disease patients. Clin J Pain 29:317-323, 2013

16. Crawford MW, Galton S, Naser B: Postoperative morphine consumption in children with sickle-cell disease. Paediatr Anaesth 16:152-157, 2006

17. Dampier C: The management of pain from sickle cell disease. In: Benzon H, Rathmell J, Wu C, Turk DC, Argoff C, Hurley R (eds): Practical Management of Pain. Philadelphia, PA, Mosby, 2014, pp 997-1002

18. Dampier C, Barry V, Gross HE, Lui Y, Thornburg CD, DeWalt DA, Reeve BB: Initial evaluation of the pediatric PROMIS(R) health domains in children and adolescents with sickle cell disease. Pediatr Blood Cancer 63:1031-1037, 2016

19. Dampier C, Ely B, Brodecki D, O'Neal P: Characteristics of pain managed at home in children and adolescents with sickle cell disease by using diary self-reports. J Pain 3: 461-470, 2002

20. Dampier C, Ely E, Brodecki D, O'Neal P: Home management of pain in sickle cell disease: A daily diary study in children and adolescents. J Pediatr Hematol Oncol 24:643-647, 2002

21. Dampier C, LeBeau P, Rhee S, Lieff S, Kesler K, Ballas S, Rogers Z, Wang W, Comprehensive Sickle Cell Centers (CSCC) Clinical Trial Consortium (CTC) Site Investigators: Health-related quality of life in adults with sickle cell disease (SCD): A report from the comprehensive sickle cell centers clinical trial consortium. Am J Hematol 86: 203-205, 2011

22. Dampier C, Lieff S, LeBeau P, Rhee S, McMurray M, Rogers Z, Smith-Whitley K, Wang W: Health-related quality of life in children with sickle cell disease: A report from the Comprehensive Sickle Cell Centers Clinical Trial Consortium. Pediatr Blood Cancer 55:485-494, 2010

23. Darbari DS, Ballas SK, Clauw DJ: Thinking beyond sickling to better understand pain in sickle cell disease. Eur J Haematol 93:89-95, 2014

24. Darbari DS, Hampson JP, Ichesco E, Kadom N, Vezina G, Evangelou I, Clauw DJ, Taylor Vi JG, Harris RE: Frequency of hospitalizations for pain and association with altered brain network connectivity in sickle cell disease. J Pain 16: 1077-1086, 2015

25. Darbari DS, Wang Z, Kwak M, Hildesheim M, Nichols J, Allen D, Seamon C, Peters-Lawrence M, Conrey A, Hall MK, Kato GJ, Taylor JG: Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study. PLoS One 8:e79923, 2013

26. DeBaun MR, Rodeghier M, Cohen R, Kirkham FJ, Rosen CL, Roberts I, Cooper B, Stocks J, Wilkey O, Inusa B, Warner JO, Strunk RC: Factors predicting future ACS episodes in children with sickle cell anemia. Am J Hematol 89:E212-E217, 2014

27. Dworkin RH, Bruehl S, Fillingim RB, Loeser JD, Terman GW, Turk DC: Multidimensional diagnostic criteria for chronic pain: Introduction to the ACTTION-American Pain Society Pain Taxonomy (AAPT). J Pain 17:T1-T9, 2016

28. Dyson SM, Abuateya H, Atkin K, Culley L, Dyson SE, Rowley D: Reported school experiences of young people living with sickle cell disorder in England. Br Educ Res J 36: 125-142, 2010

29. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wassan AD: The role of psychosocial processes in the development and maintenance of chronic pain. J Pain 17(9 Suppl): T70, 2016

30. Fillingim RB, Bruehl S, Dworkin RH, Dworkin SF, Loeser JD, Turk DC, Widerstrom-Noga E, Arnold L, Bennett R, Edwards RR, Freeman R, Gewandter J, Hertz S, Hochberg M, Krane E, Mantyh PW, Markman J, Neogi T, Ohrbach R, Paice JA, Porreca F, Rappaport BA, Smith SM, Smith TJ, Sullivan MD, Verne GN, Wasan AD, Wesselmann U: The ACTTION-American Pain Society Pain Taxonomy (AAPT): An evidence-based and multidimensional approach to classifying chronic pain conditions. J Pain 15:241-249, 2014

31. Fillingim RB, Loeser JD, Baron R, Edwards RR: Assessment of chronic pain: Domains, methods, and mechanisms. J Pain 17:T10-T20, 2016

32. Franck LS, Treadwell M, Jacob E, Vichinsky E: Assessment of sickle cell pain in children and young adults using the adolescent pediatric pain tool. J Pain Symptom Manage 23:114-120, 2002

33. Gil KM, Edens JL, Wilson JJ, Raezer LB, Kinney TR, Schultz WH, Daeschner C: Coping strategies and laboratory pain in children with sickle cell disease. Ann Behav Med 19:22-29, 1997

34. Gil KM, Wilson JJ, Edens JL, Webster DA, Abrams MA, Orringer E, Grant M, Clark WC, Janal MN: Effects of cognitive coping skills training on coping strategies and experimental pain sensitivity in African American adults with sickle cell disease. Health Psychol 15:3-10, 1996

35. Hassell KL: Population estimates of sickle cell disease in the U.S. Am J Prev Med 38:S512-S521, 2010

36. Headache Classification Committee of the International Headache Society: The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33: 629-808, 2013

37. Hoff AL, Palermo TM, Schluchter M, Zebracki K, Drotar D: Longitudinal relationships of depressive symptoms to pain intensity and functional disability among children with disease-related pain. J Pediatr Psychol 31:1046-1056, 2006

38. Houston-Yu P, Rana SR, Beyer B, Castro O: Frequent and prolonged hospitalizations: A risk factor for early mortality in sickle cell disease patients. Am J Hematol 72:201-203, 2003

39. Igbineweka N, Darbari DS, Drasar ER, Steer S, Thein SL: Increased prevalence of autoimmunity and connective tissue diseases in sickle cell disease. J Gen Pract 4:236, 2016

40. Jonassaint CR, Jones VL, Leong S, Frierson GM: A systematic review of the association between depression and health care utilization in children and adults with sickle cell disease. Br J Haematol 174:136-147, 2016

41. Kato GJ, Gladwin MT, Steinberg MH: Deconstructing sickle cell disease: Reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev 21: 37-47, 2007

42. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG: The cost of health care for children and adults with sickle cell disease. Am J Hematol 84:323-327, 2009

43. Koshy M, Entsuah R, Koranda A, Kraus AP, Johnson R, Bellvue R, Flournoy-Gill Z, Levy P: Leg ulcers in patients with sickle cell disease. Blood 74:1403-1408, 1989

44. Levenson JL, McClish DK, Dahman BA, Bovbjerg VE, de A Citero V, Penberthy LT, Aisiku IP, Roberts JD, Roseff SD, Smith WR: Depression and anxiety in adults with sickle cell disease: The PiSCES project. Psychosom Med 70:192-196, 2008

45. Lewandowski AS, Palermo TM, Kirchner HL, Drotar D: Comparing diary and retrospective reports of pain and activity restriction in children and adolescents with chronic pain conditions. Clin J Pain 25:299-306, 2009

46. Long AC, Krishnamurthy V, Palermo TM: Sleep disturbances in school-age children with chronic pain. J Pediatr Psychol 33:258-268, 2008

47. Mahadeo KM, Oyeku S, Taragin B, Rajpathak SN, Moody K, Santizo R, Driscoll MC: Increased prevalence of osteonecrosis of the femoral head in children and adolescents with sickle-cell disease. Am J Hematol 86:806-808, 2011

48. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD: Overlapping chronic pain conditions: Implications for diagnosis and classification. J Pain 17:T93-T107, 2016

49. Mathur VA, Kiley KB, Haywood C Jr, Bediako SM, Lanzkron S, Carroll CP, Buenaver LF, Pejsa M, Edwards RR, Haythornthwaite JA, Campbell CM: Multiple levels of suffering: Discrimination in health-care settings is associated with enhanced laboratory pain sensitivity in sickle cell disease. Clin J Pain 32:1076-1085, 2016

50. McClish DK, Smith WR, Dahman BA, Levenson JL, Roberts JD, Penberthy LT, Aisiku IP, Roseff SD, Bovbjerg VE: Pain site frequency and location in sickle cell disease: The PiSCES project. Pain 145:246-251, 2009

51. Milner PF, Kraus AP, Sebes JI, Sleeper LA, Dukes KA, Embury SH, Bellevue R, Koshy M, Moohr JW, Smith J: Sickle cell disease as a cause of osteonecrosis of the femoral head. N Engl J Med 325:1476-1481, 1991

52. Minniti CP, Delaney KM, Gorbach AM, Xu D, Lee CC, Malik N, Koroulakis A, Antalek M, Maivelett J, Peters-Lawrence M, Novelli EM, Lanzkron SM, Axelrod KC, Kato GJ: Vasculopathy, inflammation, and blood flow in leg ulcers of patients with sickle cell anemia. Am J Hematol 89:1-6, 2014

53. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK: Leg ulcers in sickle cell disease. Am J Hematol 85: 831-833, 2010

54. Myrvik MP, Burks LM, Hoffman RG, Dasgupta M, Panepinto JA: Mental health disorders influence admission rates for pain in children with sickle cell disease. Pediatr Blood Cancer 60:1211-1214, 2013

55. Niebanck AE, Pollock AN, Smith-Whitley K, Raffini LJ, Zimmerman RA, Ohene-Frempong K, Kwiatkowski JL:

Headache in children with sickle cell disease: Prevalence and associated factors. J Pediatr 151:67-72, 72.e61, 2007

56. Palermo TM, Platt-Houston C, Kiska RE, Berman B: Headache symptoms in pediatric sickle cell patients. J Pediatr Hematol Oncol 27:420-424, 2005

57. Palermo TM, Riley CA, Mitchell BA: Daily functioning and quality of life in children with sickle cell disease pain: Relationship with family and neighborhood socioeconomic distress. J Pain 9:833-840, 2008

58. Palermo TM, Schwartz L, Drotar D, McGowan K: Parental report of health-related quality of life in children with sickle cell disease. J Behav Med 25:269-283, 2002

59. Paul R, Minniti CP, Nouraie M, Luchtman-Jones L, Campbell A, Rana S, Onyekwere O, Darbari DS, Ajayi O, Arteta M, Ensing G, Sable C, Dham N, Kato GJ, Gladwin MT, Castro OL, Gordeuk VR: Clinical correlates of acute pulmonary events in children and adolescents with sickle cell disease. Eur J Haematol 91:62-68, 2013

60. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, Kinney TR: Pain in sickle cell disease. Rates and risk factors. N Engl J Med 325:11-16, 1991

61. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C: Outcome of sickle cell anemia: A 4-decade observational study of 1056 patients. Medicine (Baltimore) 84:363-376, 2005

62. Raphael JL, Dietrich CL, Whitmire D, Mahoney DH, Mueller BU, Giardino AP: Health care utilization and expenditures for low income children with sickle cell disease. Pediatr Blood Cancer 52:263-267, 2009

63. Savitt TL, Smith WR, Haywood C, Creary MS: Use of the word "crisis" in sickle cell disease: The language of sickle cell. J Natl Med Assoc 106:23-30, 2014

64. Schwartz LA, Radcliffe J, Barakat LP: Associates of school absenteeism in adolescents with sickle cell disease. Pediatr Blood Cancer 52:92-96, 2009

65. Serarslan Y, Kalaci A, Ozkan C, Dogramaci Y, Cokluk C, Yanat AN: Morphometry of the thoracolumbar vertebrae in sickle cell disease. J Clin Neurosci 17:182-186, 2010

66. Serjeant GR, Serjeant BE, Mohan JS, Clare A: Leg ulceration in sickle cell disease: Medieval medicine in a modern world. Hematol Oncol Clin North Am 19:943-956, viii-ix, 2005

67. Shapiro BS, Dinges DF, Orne EC, Bauer N, Reilly LB, Whitehouse WG, Ohene-Frempong K, Orne MT: Home management of sickle cell-related pain in children and adolescents: Natural history and impact on school attendance. Pain 61:139-144, 1995

68. Sil S, Cohen LL, Dampier C: Psychosocial and functional outcomes in youth with chronic sickle cell pain. Clin J Pain 32:527-533, 2016

69. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, Aisiku IP, Levenson JL, Roseff SD: Daily assessment of pain in adults with sickle cell disease. Ann Intern Med 148:94-101, 2008

70. Smith WR, Scherer M: Sickle-cell pain: Advances in epidemiology and etiology. Hematology Am Soc Hematol Educ Program 2010:409-415, 2010

71. Sogutlu A, Levenson JL, McClish DK, Rosef SD, Smith WR: Somatic symptom burden in adults with sickle cell disease predicts pain, depression, anxiety, health care utilization, and quality of life: The PiSCES project. Psychosomatics 52: 272-279, 2011

72. Steinberg MH: Sickle cell anemia, the first molecular disease: Overview of molecular etiology, pathophysiology, and therapeutic approaches. ScientificWorldJournal 8: 1295-1324, 2008

73. Taylor LE, Stotts NA, Humphreys J, Treadwell MJ, Miaskowski C: A review of the literature on the multiple dimensions of chronic pain in adults with sickle cell disease. J Pain Symptom Manage 40: 416-435, 2010

74. Tsao JC, Jacob E, Seidman LC, Lewis MA, Zeltzer LK: Psychological aspects and hospitalization for pain crises in youth with sickle-cell disease. J Health Psychol 19:407-416, 2014

75. Turk DC, Fillingim RB, Ohrbach R, Patel KV: Assessment of psychosocial and functional impact of chronic pain. J Pain 17:T21-T49, 2016

76. Valrie CR, Bromberg MH, Palermo T, Schanberg LE: A systematic review of sleep in pediatric pain populations. J Dev Behav Pediatr 34:120-128, 2013

77. Vance LD, Rodeghier M, Cohen RT, Rosen CL, Kirkham FJ, Strunk RC, DeBaun MR: Increased risk of severe vaso-occlusive episodes after initial acute chest syndrome in children with sickle cell anemia less than 4 years old: Sleep and asthma cohort. Am J Hematol 90: 371-375, 2015

78. Vardeh D, Mannion RJ, Woolf CJ: Toward a mechanism-based approach to pain diagnosis. J Pain 17:T50-T69, 2016

79. Walco GA, Dampier C, Hartstein G, Djordjevic D, Miller L: The relationship between recurrent clinical pain and pain threshold in children. Adv Pain Res Ther 15:333-340, 1990

80. Walco GA, Krane EJ, Schmader KE, Weiner DK: Applying a life-span developmental perspective to chronic pain: Pediatrics to geriatrics. J Pain 17: T108-T117, 2016

81. Wallen GR, Minniti CP, Krumlauf M, Eckes E, Allen D, Oguhebe A, Seamon C, Darbari DS, Hildesheim M, Yang L, Schulden JD, Kato GJ, Taylor JG: Sleep disturbance, depression and pain in adults with sickle cell disease. BMC Psychiatry 14:207, 2014

82. Wilkie DJ, Molokie R, Boyd-Seal D, Suarez ML, Kim YO, Zong S, Wittert H, Zhao Z, Saunthararajah Y, Wang ZJ: Patient-reported outcomes: Descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease. J Natl Med Assoc 102:18-27, 2010

83. Wison Schaeffer JJ, Gil KM, Burchinal M, Kramer KD, Nash KB, Orringer E, Strayhorn D: Depression, disease severity, and sickle cell disease. J Behav Med 22:115-126, 1999

84. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, Jordan L, Lanzkron SM, Lottenberg R, Savage WJ, Tanabe PJ, Ware RE, Murad MH, Goldsmith JC, Ortiz E, Fulwood R, Horton A, John-Sowah J: Management of sickle cell disease: Summary of the 2014 evidence-based report by expert panel members. JAMA 312:1033-1048, 2014

85. Zempsky WT, Loiselle KA, McKay K, Blake GL, Hagstrom JN, Schechter NL, Kain ZN: Retrospective evaluation of pain assessment and treatment for acute vasoocclusive episodes in children with sickle cell disease. Pediatr Blood Cancer 51:265-268, 2008