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Sickle cell disease: a natural model of acute and chronic pain

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Typical sickle cell pain case

A 19 year old female with severe sickle cell disease (SCD) presents to her hematologist with severe pain. Prior to age 16, she reported four hospitalizations and two emergency department visits for acute pain management. Her pain significantly increased in frequency and severity between ages 16–19 with 10 hospitalizations and she reported almost *daily* pain. Her pain descriptors included radiating, burning, tingling, electric shocks, numbness and she reported cutaneous pain with slight skin pressure and with cold temperatures. Pain locations included chest, lower back, knees, feet and "all over." At age 18, she started hydroxyurea which induces the production of fetal hemoglobin and ameliorates some SCD complications, including acute pain. Despite a positive hematological response, significant pain persisted, severely impacting her quality of life. Her pain regimen included almost daily oxycodone, tramadol and ibuprofen. Questions raised by this common case include: What is the underlying mechanism(s) causing the pain? Why did her pain transition from acute and intermittent as a young child to chronic, almost daily pain as an adolescent? What alternative pain treatments can be used? What deleterious effects does chronic opioid treatment cause?

Sickle cell disease (SCD) is a global public health challenge

Over 5 million individuals and over a quarter million live births annually are affected by SCD world wide[49] and the United Nations and World Health Organization have recognized SCD as a global health problem that is projected to increase in future decades..[2] In the US, 90,000–100,000 individuals live with SCD[1; 10], 1 in 365 African American babies are born with SCD, and 1 in 13 African Americans carry sickle cell trait.[1] This costs an estimated $460,000 in the US for each individual with SCD.[27] Both SCD and trait are diagnosed on newborn screening in the US and many developed countries. Far greater numbers are affected in West and Central Africa where as many as 18% have sickle cell trait and 1–2% of babies are born with SCD; few of these countries have newborn screening or basic health care.[48] SCD also affects individuals from the Mediterranean basin, Middle

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East, Saudi Arabia, India, Asia and South/Central America. Millions of people suffer from SCD world-wide; however, the universal prevalence is unknown due to lack of newborn screening in many countries.[1; 48] SCD is clearly an under-recognized major international health problem.

Pathophysiology of SCD

Homozygous inheritance of hemoglobin S (sickle hemoglobin, HbS) gene results in the most common and severe form of SCD (HbSS). [53] However, other sickle genotypes occur with compound heterozygosity when HbS is co-inherited with other beta-globin gene variants, such as HbC or β-thalassemia. The HbS mutation is the result of a single base pair change in the β-globin gene responsible for synthesis of the β-globin polypeptide of the Hb molecule ($\alpha_2\beta_2$). This change results in replacement of the normal glutamic acid with valine at position 6 of the β-globin chain. The hydrophobic valine is at the surface of hemoglobin and when deoxygenated, hemoglobin binds to a hydrophobic pocket, formed by βPhe85 and βLeu88, which then forms large insoluble aggregates. Similar interactions between many HbS molecules lead to long polymerization that is promoted by hypoxia or dehydration. Red blood cells (RBCs) with normal hemoglobin (HbA) are flexible biconcave discs that flow easily through blood vessels. In contrast, the aggregation of HbS polymers leads to the pathognomonic sickle RBC shape. Sickle RBCs are rigid, fragile, and have decreased deformability and increased adherence to endothelial cells resulting in increased microvasculature congestion and inflammation. The severe pathophysiology triggered by sickled RBCs includes: 1) blood vessel obstruction resulting in tissue ischemia (vaso-occlusion)[13]; 2) reperfusion injury after vaso-occlusion [13]; 3) shortened RBC survival resulting in severe chronic hemolytic anemia and release of free heme[55] and other RBC intracellular contents[26; 52]; and 4) chronic inflammation.[28; 30] SCD is a multi-organ system disease due to the chronic and ongoing effects of repeated vaso-occlusion and subsequent ischemia-reperfusion injury.[53] [74]

Clinical manifestations of SCD include severe acute and chronic pain[6; 46; 51; 59], pulmonary pathology[21; 66], splenic impairment resulting in life-threatening pneumococcal infections[37; 38], strokes resulting in motor and cognitive impairments[15], renal failure[42], vision loss[34], bony infarcts, joint osteonecrosis[36], priapism[3], and leg ulcers.[40] The mean age of death for patients with HbSS disease is 38 for males and 42 for females (55 years for all SCD genotypes).[31].[16; 43] Although newborn screening, pneumococcal prophylaxis and increased hydroxyurea utilization[61; 62; 64; 67; 70] have increased patient survival and decreased morbidity, the survival and outlook remain significantly impaired.

Severe pain during acute vaso-occlusive crisis

The hallmark of SCD is the acute vaso-occlusive pain crisis manifesting as abrupt onset of severe, debilitating pain in any part of the body. Vaso-occlusive crises are the most common cause of emergency department visits and hospitalizations and crises profoundly impact quality of life.[6; 39] Triggers of vaso-occlusive crises (VOCs) include illness, dehydration, cold temperatures [54; 58], increased wind speed[44], and higher barometric pressure.[58]

However, often no precipitating factor occurs and pain crises start abruptly without warning, adding to the severe impact on patients' quality of life. Children can begin having pain crises as early as 6 months of age when fetal hemoglobin (HbF) is replaced by abnormal adult hemoglobin, HbS. Acute vaso-occlusive crisis pain is described as aching, drilling, pounding, sharp knives or throbbing and can last a week or longer.[18; 68; 69; 71] Pain crises increase in number, duration and intensity as patients age.[46] Patients with more frequent pain crises have a higher mortality rate.[50] The backbone of acute pain crisis treatment includes intravenous opioids.[74] SCD patients often require large opioid doses due to increased opioid metabolism and clearance, as well as tolerance from receiving life-long opioid therapy[14] such that their pain becomes increasingly refractory to opioids.[65] Further, some SCD patients display opioid-induced hyperalgesia.[63]

Transition from acute to chronic pain in SCD

In addition to intermittent acute vaso-occlusive pain, SCD patients also develop *chronic pain*. Chronic pain transpires with increasing age as illustrated in the patient case above and in Table 1. Chronic, almost daily pain occurs irrespective of an acute vaso-occlusive crisis in 29.3% of adults.[59] In addition, 40% of children and adolescents (ages 8–18 yrs) have chronic pain with 35% reporting daily pain.[57] Chronic SCD pain is also associated with more functional and psychosocial morbidity[20; 33; 56; 57], unemployment[4; 5], and school [33; 56; 57; 59; 60] and work absenteeism.[20]

Patients describe SCD pain using both nociceptive (i.e., throbbing, wrenching, tearing, pulsing, piercing, crushing, cramping) and neuropathic descriptors (i.e., aching, cold, hot, penetrating, shooting, and stabbing).[18; 68; 69; 71] The broad pain descriptors suggest that SCD pain is multifaceted in etiology. Neuropathic pain questionnaires demonstrate that 30% of adult patients have neuropathic pain.[7; 17] Quantitative sensory testing in SCD patients reveals they have increased sensitivity to thermal and/or mechanical stimuli, and fMRI changes and windup suggest that there are both peripheral and central nervous system abnormalities.[8; 9; 17; 25; 45] These data suggest a complex etiology to SCD pain including ischemic, inflammatory and neuropathic components. The tissue sources of pain range from cutaneous to deep foci. Although tissue sources can include bony infarcts, avascular necrosis of the femoral/humoral heads and leg ulcers, most SCD patients with chronic pain do *not* have an obvious anatomic source making the etiology of chronic pain even more challenging to identify. Whereas physicians who treat SCD patients are aware of the immense suffering, the pain remains poorly understood and the pain research community has only begun to appreciate the wide-spread chronic pain and multifactorial etiology that occurs with SCD.

While hydroxyurea can prevent some acute SCD complications including acute pain crises and acute chest syndrome (ACS), its effectiveness at alleviating chronic SCD pain is not well known.[72] This is illustrated by our patient case where her pain was not relieved by hydroxyurea despite a good hematologic response to the drug. Furthermore, some patients who have undergone bone marrow transplantation to cure their SCD continue to have chronic opioid requirements at least 6 months post-transplant.[24] This suggests that different mechanisms are likely driving the development and maintenance of *chronic* pain.

High dose opioid-based regimens are the backbone of treatment for both acute and chronic SCD pain[74]; however, chronic opioid use is often associated with well-known side effects including sedation, dizziness, nausea/vomiting, constipation, physical dependence, tolerance and opioid-induced hyperalgesia.[32] Therefore, non-opioid based treatments for chronic pain are critically needed.

Animal models of SCD replicate clinical pain

Several transgenic SCD mouse models exist that exclusively express human sickle hemoglobin.[47; 73] Berkeley sickle transgenic mice have a knockout of all mouse alpha and beta globins and express a transgene with either normal or sickle human hemoglobin.[47] Townes sickle mice have a knockout of mouse hemoglobin and a site-directed knockin of human hemoglobin.[73] The transition from fetal to adult hemoglobin occurs prior to birth in Berkeley mice, whereas in Townes mice, pups are born with expression of gamma globin at birth which gradually decreases to <1% HbF during the first week post birth.[73] Both SCD mouse models have vascular and organ pathologies that closely mimic patients with severe SCD. Like patients, mice have sickled, rigid and fragile RBCs, severe hemolytic anemia, increased hematopoiesis, and extensive multi-organ damage.[35]

Sickle mice exhibit prominent, chronic evoked and ongoing pain behavior

SCD mice display chronic pain-like behaviors at “baseline” when not in an apparent sickling crisis. Stimulus-evoked pain behaviors include pronounced hypersensitivity to cutaneous mechanical stimuli with decreased von Frey thresholds and hypersensitivity to very light touch.[19; 23; 29] Sickle mice also have marked hypersensitivity to cold stimuli and show avoidance of even very mild cool temperatures.[75] This cold allodynia mimics the most prominent phenotype in SCD patients who display increased cold pain sensitivity in quantitative sensory testing[9; 45] and increased numbers of acute pain crises during cold temperatures and cold water exposure.[8; 54; 58] SCD mice also express heat hypersensitivity similar to SCD patients who have lower heat pain thresholds.[9] Anecdotally, many patients prefer warmth using heating pads, high room temperatures and blankets during an acute pain crisis and between crises.

SCD mice also express deep tissue, non-stimulus evoked pain, and musculoskeletal pain measured by decreased grip force strength, decreased voluntary wheel running[22; 29], altered grimace, body length and stature scores associated with chronic pain[41], and anxiety and depression-like behaviors[29; 31] which correlate the comorbidities of depression and anxiety in SCD patients.[57; 60] Female and male mice exhibit similar magnitudes of hypersensitivity[23], consistent with both female and male patients enduring the severe pain. These data suggest cutaneous and deep afferents and CNS pathways may be sensitized in SCD. As in SCD patients, mouse pain behaviors become exacerbated with increasing age[11; 75] suggesting that repeated acute sickling episodes transition to worsened chronic pain. Mimicking acute vaso-occlusion in mice using experimental hypoxia exacerbates the hypersensitivity, indicating RBC sickling worsens the pain.[23]

Peripheral sensory and spinal cord neurons are sensitized in SCD mice

Cutaneous C fiber and Aδ fiber nociceptors exhibit prominent, long-lasting sensitization to mechanical stimuli in the form of increased suprathreshold firing to sustained pressure.[23] C fibers also exhibit sensitization to cold stimuli displayed as warmer cold activation thresholds and enhanced cold-evoked responses.[75] Low threshold, light touch Aβ afferent fibers that innervate Merkel cells and hair follicle afferents also display prominent mechanical sensitization.[19] The mechanical and cold afferent sensitization occurs by 8 weeks of age, however, the timeframe in development when this afferent sensitization develops is not known. Thus, a diverse range of cutaneous afferent fibers are sensitized in SCD. While the extent of sensitization of deep muscle, joint or bone afferents is unknown, the findings that isolated dorsal root ganglion neurons that project to all peripheral targets exhibit sensitization [23; 75] suggests that afferents that innervate deep tissues are sensitized. Importantly, chronic sensitization of primary afferent neurons can lead to enhanced, summated input to the spinal cord pain pathways in SCD patients.

Nociceptive spinal dorsal horn neurons (nociceptive specific and wide dynamic range neurons) exhibit sensitization in the form of enlarged receptive fields, increased spontaneous activity, lower mechanical thresholds, increased suprathreshold mechanical responses and prolonged after discharges following mechanical stimulation[12], suggesting that central sensitization contributes to chronic SCD pain. Higher level brainstem, thalamic and cortical ascending or descending pathway relay neurons that are essential components of chronic pain have not yet been investigated in SCD models.

Neuronal and non-neuronal cellular and molecular mechanisms drive sensitization in SCD

Table 2 outlines supporting data for neuronal and non-neuronal mechanisms that drive sensitization and pain in SCD at both the peripheral and central levels.

The power of SCD models for pain research

The value of SCD mouse models for mechanistic pain research is that the chronic pain develops over time naturally from the underlying disease. This is in contrast to pain that is artificially induced in many persistent pain models such as Complete Freund’s Adjuvant injection or nerve lesion or ligation. While these induced models provide mechanistic insights into inflammatory and neuropathic pain in well-controlled models, there are some underlying concerns with these models, including their relevance and translatability to human patient pain conditions which are more complex in etiology and longer in duration. The SCD mouse models comprise preclinical models where the chronic pain develops naturally from the endogenous disease. Further, in these models, the development of acute pain and its transition to chronic pain can be studied at every level of the pain pathway including the PNS, CNS ascending and CNS descending control, as well as interactions between neuronal and non-neuronal cells (endothelial cells, mast cells, microglia, astrocytes). In addition, the parallel study of patients and mouse models of SCD should

reveal what aspects of this preclinical model will and will not translate into true clinical relevance.

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Table 1

Time course of clinical pain expression over the lifespan of patients with sickle cell disease

	Infancy (0–23 months)	Toddler (2–4 yrs)	Childhood (5–12 yrs)	Adolescence (13–18 yrs)	Adulthood (≥19 yrs)
Clinical Pain Expression	• HbF elevated • Minimal pain • Acute intermitent pain and dactylitis("hand-foot syndrome") • Splenic sequestration	• HbF reaches nadir • Acute, intermittent pain events resulting in emergency department visits and hospitalizations	• Continued acute, intermittent pain events resulting in emergency department visits and hospitalizations	• Acute pain events increase in frequency • Length of hospital stay becomes longer • Chronic pain starts • Pain affects school attendance	• Chronic daily pain is the norm • Acute intermittent pain crises continue, superimposed on chronic pain • Pain affects work attendance and employment • Higher rate of pain associated with increased mortality
Potential Pathophysiology	• HbF protective against effects of HbS • Acute vascular occlusion and tissue ischemia by sickled cells	• Decrease in HbF accompanied by increased HbS • Acute vascular occlusion and tissue ischemia by sickled cells • Chronic inflammation	• Continued acute vascular occlusion and tissue ischemia by sickled cells • Chronic inflammation	• Continued acute vascular occlusion and tissue ischemia by sickled cells • Chronic inflammation • Sensitization of peripheral and central nervous system develops	• Continued acute vascular occlusion and tissue ischemia by sickled cells • Chronic inflammation • Continued Sensitization of peripheral and central nervous system

Table 2

Neuronal and non-neuronal mechanisms that drive sensitization in SCD at peripheral and central levels

	Mechanism	Supporting data
Peripheral Mechanisms	Substance P (SP)	• Increased in cutaneous sensory neurons of SCD mice[28] • NK1 receptor increased in sensory ganglia from SCD mice[76] suggesting elevated SP receptor signaling • Plasma levels higher in SCD patients at baseline health (vs. controls) and increases further during acute pain[9; 39]
	Calcitonin Gene-Related Peptide (CGRP)	• Increased in cutaneous sensory neurons of SCD mice[28]
	Mast cell activation	• Increased activation in SCD mice contributes to peripheral, neurogenic inflammation-mediated release of CGRP, SP and tryptase[66]
	Endothelin-1 (ET1)	• Elevated in plasma in mice and patients at baseline and in crisis[21] and expression is elevated in sensory ganglia from SCD mice[76]
	Transient Receptor Potential Vanilloid 1 (TRPV1)	• Shown to mediate mechanical hypersensitivity in SCD mice suggesting afferent sensitization[23]
	Cannabinoid receptors 1 and 2 (CB1 and CB2)	• Expressed on mast cells and CB1 and CB2 receptor agonists alleviate cutaneous and deep tissue pain behavior in SCD mice[65]
Central Mechanisms	Increased cellular signaling cascades in spinal cord	• Phosphorylated mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinase (JNK), extracellular signaling-related kinase (ERK) and p38 kinase.[12]
	Other cellular and inflammatory mechanisms increased in spinal cord	• COX-2, IL-6 and TLR4 receptors[28] and second messengers PKC and CaMKII activation are increased in the spinal dorsal horn [71], and inhibition of PKCδ attenuates the SCD pain behavior[22]