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Review/Overview of pain in sickle cell disease

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Abstract

Sickle cell disease (SCD) is a highly complex inherited disorder of hemoglobin structure. Although the molecular lesion is a single-point mutation, the sickle gene is pleiotropic in nature causing multiple phenotypic expressions that constitute the various complications of the disease. Its manifestations could be acute, chronic, nociceptive, neuropathic that could occur singly or in various combinations. Pain continues to be the major factor of SCD phenotypic complications and the most common cause of admissions to the Emergency Department and/or the hospital. Although progress has been made in understanding the pathophysiology of SCD as well as in developing curative therapies such as hematopoietic stem cell transplantation and gene therapy, effective pain management continues to lag behind. Palliative therapies continue to be the major approach to the management of SCD and its complications. The advent of hydroxyurea made partial success in preventing the frequency of vaso-occlusive crises and L-glutamine awaits post-trial confirmation of benefits. The search for additional pharmacotherapeutic agents that could be used singly or in combination with hydroxyurea and/or L-glutamine awaits their dawn hopefully in the near future. The purpose of this review is to describe the various manifestations of SCD, their pathophysiology and their current management. Recent impressive advances in understanding the pathophysiology of pain promise the determination of agents that could replace or minimize the use of opioids.

Introduction

The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[1-4] This definition implies several important aspects of the pain experience: (1) unpleasantness is a major component; (2) sensation and emotion are two major

aspects; (3) tissue damage may not be a visible factor; and (4) patients may complain of pain in the absence of objective signs. This definition applies well to patients with sickle cell disease (SCD), as will be discussed below. Before IASP introduced this comprehensive definition, several writers and poets made insightful and intuitive remarks about pain that echo certain aspects of the pain experience.

Sickle pain is unique.[5] Polymerization of sickle hemoglobin and sickling of erythrocytes is considered to be the proximate cause of acute vaso-occlusive pain. However, it is becoming clear other cells which are activated such as platelets and neutrophils as well as binding to l- and p-selections and adherence of RBC to the endothelium also play important role in vaso-occlusion. The severity of these events may be different in different parts of the body and hence the variation in the severity and location of the pain. The IASP definition applies to sickle pain, which can be acute, chronic, neuropathic, intermittent, recurrent, or persistent.[5-9] Sensation and emotion in sickle pain are intertwined in an unusually complex manner that is specific to each person and affects behavior in every vaso-occlusive painful crisis (VOC).

Sickle cell pain should not be equated with non-cancer chronic benign pain syndrome (CBPS). Although the two share some characteristics, they have fundamental differences. Major distinctions of SCD include an identifiable etiology, chronic anemia, recurrent acute episodes of severe pain, and progressive organ damage. Unfortunately, some care providers consider sickle cell pain as one type of CBPS and treat it accordingly. This is a tragic mistake because sickle cell VOCs are recurrent attacks of acute, severe pain (of peripheral origin) for which relief often requires the use of opioids. Management of sickle cell pain with opioids, however, must follow two tiers as is the case in the management of other types of pain with opioids. The first tier is to optimize analgesia by prescribing adequate dose to minimize pain severity, and the second

tier is to minimize risk by frequent monitoring and assessment of opioid related adverse effects and outcomes related to substance use disorders.[10, 11] The purpose of this review is to focus on the pathophysiology of sickle cell pain, its types and the principles of their management.

It is important to note that the SCD refers to all types of SCD: homozygosity of sickle gene (Hb SS), Hb SC disease. Hb S-thalassemia, Hb SD, etc. On the other hand, sickle cell anemia (SCA) includes both Hb SS and Hb S-β^0-thalassemia because both are clinically similar despite the fact that they differ at the molecular level.[12]

Pathophysiology of pain

The perception of pain in the prefrontal cortex of the brain after peripheral tissue damage involves several complex inter-related pathways. These pathways function in tandem so that if the pain persists and/or becomes more severe its transmission is handled by the next system in line as if one system gives the baton, so to speak, to a second system for further transmission. The most important of these pathways are listed in Table 1 and shown in Figures 1[13-15] and described below. Pain experience is subjective and self-reported. While many biomarkers have been recently proposed to be studied as markers and possible endpoints for pain none of those have been validated to date.[16]

Na$_V$1.7 – 1.9 channels and Pain

The voltage Na-gated channels (Na$_V$1.7 – 1.9) play an important role in the transmission of painful stimuli from peripheral terminals in the skin to central preterminal and terminal branches in the dorsal root ganglion (DRG) and in the dorsal horn of the spinal cord [17-21]. Transmission of painful stimuli along these nerve fibers is facilitated by glutamate which is an efficient excitatory neurotransmitter throughout the nervous system. Contrariwise, gamma aminobutyrate (GABA) is an inhibitor of the transmission of electrical stimuli.[22, 23]

Na_v 1.7 controls the passage of sodium ions into sensory neurons as shown in Figure 1. Mutation or deletion of Na_v 1.7 causes Congenital Insensitivity to Pain (CIP).[24] Individuals with this mutation are normal with the exception that they do not feel pain. Ironically, a different mutation in the same gene results in an extremely painful condition called erythromelalgia[25, 26] also commonly referred to as "man on fire syndrome" characterized by severe burning neuropathic pain due to hyperfunctioning Na_v 1.7 channel with enhanced and continuous depolarization of membranes (Figure 2A and 2B).

The Dorsal Root Ganglion (DRG)

The DRG is a relay station that sorts the transition of painful stimuli in different directions. Some stimuli are returned to the periphery, others are directed to the sympathetic nervous system and the majority are sent to the dorsal horn of the spinal cord where painful stimuli are processed by a number of channels.

The Dorsal Horn of the Spinal Cord

At the level of the dorsal horn of the spinal cord the transmission of painful stimuli is facilitated or inhibited**.** The pain stimuli received from the DRG cross over to the contralateral side and ascends along the spinothalamic tract to make connections with the brainstem, hypothalamus, thalamus, limbic system (mediator of emotion and memory), reward system (mediator of pleasure and addiction), ~~glia,~~ and the pre-frontal cortex where pain sensation is perceived. Simultaneously, a descending pathway from the nucleus accumbense (modulation) that attempt to prevent or minimize the transmission of painful stimuli via endogenous endorphins.

Activation of the AMPA and NMDA Receptors

Repetitive, severe, painful stimuli play an important role in the transmission and sensation of pain. They exert their effects both at the level of the peripheral and the central nervous systems. At the peripheral level, there is recruitment of dormant nociceptors, which facilitate the transmission of the progressive increase in repetitive painful stimuli. At the level of the DRG, there is communication with and activation of the sympathetic system. At the level of the dorsal horn of the spinal cord, four major events occur in succession over time. These include activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (also known as AMPA receptor or AMPAR), activation of the N-methyl-D-aspartate (NMDA) receptor, central sensitization, and glial activation. The sequence of transmission of painful stimuli from the AMPA to the NMDA receptor is shown in Figure 3.

Central sensitization

Central sensitization is the process by which excessive nociceptive signals bombarding the central nervous system from the periphery cause changes both in the spinal cord and the brain, resulting in continuous amplification of pain sensation.[27-30] Central sensitization indicates neuroplasticity of the nervous system. Clinical manifestations of central sensitization include (1) a reduced pain threshold, in hyperalgesia and allodynia; (2) expanded receptive fields, which refers to hyperalgesia occurring beyond the area of original injury; and (3) aftersensations, in which pain sensation continues after cessation of the original injury. Thus, if a patient with SS develops a VOC with severe pain in the right knee, and within a few hours the same exact pain is felt in another area such as the left knee, the pain in the left knee is not necessarily due to de novo vaso-occlusion in that area but due to central sensitization. It is explained by the convergence-projection hypothesis, in which afferents from one source, usually the viscera, converge on the same pain-projection neurons as afferents from a different source, usually

somatic structures, where pain is perceived.[31, 32] Evidence of central sensitization has been shown in SCD patients using quantitative sensory testing (QST) and neuroimaging. QST studies in adults show increased sensitivity to painful stimuli and aftersensations compared to non-SCD controls.[33] Furthermore, functional neuroimaging studies have shown alternation of brain connectivity patterns which have been associated with burden of pain again suggesting neuroplastic changes in brain.[34, 35]

Individuals receiving opioids occasionally may exhibit the phenomenon of opioid induced hyperalgesia (OIH) where opioid use leads to nociceptor sensitization and make them more sensitive to painful stimuli. This phenomenon could sometimes explain loss of efficacy to opioids in managing pain.[36]

Glial Activation

The glia includes three major cells: oligodendrocytes, astrocytes, and microglia.[37] Glial activation that is associated with sickle cell pain occurs in at least two ways. The first is the facilitation of the transmission of painful stimuli and the second is the activation of the microglia followed by neuroinflammation with the release of excess proinflammatory cytokines and glutamate that accentuate the pain experience.

Classification of Sickle Cell Pain Syndromes

Pain is associated with SCD and the acute painful VOC is its hallmark. Symptoms of pain can start as early as 3-6 months of age typically as an episode of dactylitis and continue to occur through the life span of the individuals with variable frequency. Pain remains the most common cause of health care utilization in this population. Pain in SCD typically described as acute, chronic, neuropathic, due to co-morbidities or a combination of any two or more of these[38]. Recently, a new type referred to as acute pain in the background of chronic pain or chronic pain

in the background of acute pain possibly implying that the pain that occurs between VOCs is chronic.[39] Others refer to the pain between VOCs as persistent but milder acute pain.[38]

The Acute Painful Vaso-occlusive Episodes

These intermittent VOCs are the most common clinical complication of SCD. Per the recent AAAPT criteria to fall under the diagnosis of acute pain, it must be an increased pain of new onset, have a $\geq$ 2-hour duration, but not have been present for >10 days.[39] Additionally signs of acute VOC should include 1) palpation of the region of reported pain elicits focal pain or tenderness, 2) movement of the region of pain elicits focal pain, or 3) a decreased range of motion or weakness in the region of reported pain. AAAPT criteria also proposed 2 possible diagnostic modifiers: acute pain that occurs in the absence of chronic SCD pain, and acute pain that occurs in the presence of chronic pain with or without signs of vaso-occlusion.

Classically, the mechanism of acute pain is considered to be the result of occlusion of microvasculature resulting in hypoxia, tissue damage and inflammation from ischemia−reperfusion injury.[40] Polymerization of sickle hemoglobin (Hb) leading to sickling of the red blood cells initiates vaso-occlusion. The process also involves complex interactions between sickle red cell, vascular endothelium and other blood cells i.e. leukocytes, and platelets.[41] The acute SCD VOC typically has a crescendo−decrescendo course which has been described in 4 phases (Figure 4).[42, 43] *Prodromal Phase* is the first phase of the VOC and lasts 1-2 days. Symptoms typically include numbness, paresthesia, or aches in the areas that subsequently become painful. The next phase *Initial Phase* is associated with increasing pain intensity and accompanying laboratory findings may include decreased RBC deformability, increase in the number of dense cells, red cell distribution width, reticulocyte count, leukocytosis, and relative thrombocytopenia. The next phase, *Established Phase* is associated

with the peaking of the pain intensity with other findings such as increased temperature, white blood cell count, increasing dense cell, and reticulocytes. The last phase, *Resolving Phase* is associated with improvement in the symptoms of pain as well as trends towards normalization of abnormal laboratory findings described above.[42, 44]

Acute episodes of pain can present as early as 6 months of age and often corresponds to age related decrease in fetal Hb levels. Infants typically present with swelling of hand or feet or dactylitis, also known as hand/foot syndrome results from the vaso-occlusion in metacarpal/metatarsal bones or the phalanges[45]. As patients get older, the rates of pain typically increase and acute episodes of pain become one of the most common symptoms[46]. While they remain the most common reason for hospitalization, most of the acute episodes of pain are managed at home. Acute episodes of pain can involve any part of the body but typically affect long bones in the extremities or flat bones in chest/back (ribs and vertebrae) or pelvis.[47] Pattern of chronic pain start to appear as children approach adolescent years and chronic pain becomes common in adults with SCD as described below and as described by the data from the Pain in Sickle Cell Epidemiologic Study (PiSCES).[46, 48, 49]

Frequency of acute episodes of pain varies among patients with SCD.[50] Some patients may experience frequent episodes of pain while others may experience these episodes infrequently. The Cooperative Study of Sickle Cell Disease (CSSD) reported that 39% of individuals had no admissions for pain while 5% had 3-10 admissions per year.[50] Increased rates of hospitalizations for pain are associated with mortality.[50, 51] Typically, patients with SCA (homozygous SS and sickle-β^0-thalassemia) experience the highest whereas sickle-β^+-thalassemia the lowest burden of pain. However, a large variability may exist within each genotype. Many SCD and non-SCD factors can modulate the frequency and severity of VOCs.

These SCD related factors include high levels of Hb whether related to genetics or hydroxyurea therapy and the presence or absence of alpha thalassemia. High Hb F is associated with reduced frequency of VOCs whereas the presence of alpha thalassemia is associated with increased frequency of VOCs.[52,53] Sickle β^S haplotypes have also been proposed to impact the frequency of VOCs. However, this observation could be related to the differences in the fetal ~~hemoglobin~~ Hb levels seen in patients with different haplotypes.[54, 55] Age and female gender have been associated with increasing rates of VOCs and many females experience VOCs with the onset of menstrual cycle.[56, 57] Other triggers for the precipitation for VOCs may include exposure to cold weather, infections, dehydration, pregnancy and mental stress.[58-61] Non- SCD factors such as anxiety and depression which impact perception of pain can contribute to the overall pain experience.[62, 63]

Other acute pain syndromes in SCD

Other complications of SCD that can present with acute pain include acute chest syndrome, acute multi-organ failure, right upper quadrant syndromes, splenic sequestration and priapism.[64] These complications are typically associated with underlying vaso-occlusion. For example, splenic sequestration is associated with trapping of sickled erythrocytes within the spleen and patients presenting with acute anemia with splenomegaly. Enlargement of the spleen and stretching of the capsule is likely the underlying cause of abdominal pain. Similarly, vaso-occlusion of the hepatic vasculature may cause pain in right upper quadrant of the abdomen. Patients typically present with tender, progressive hepatomegaly, acute anemia below baseline, and hyperbilirubinemia. Vaso-occlusion of penile vasculature can lead to priapism or painful erection in absence of sexual stimulation and may be a cause of significant morbidity for males with SCD. Acute pain syndromes described here may have coexisting pathology such as

infection, pneumonia and acute chest syndrome. Accordingly, these complications should be managed by treating the underlying pathology if applicable along with an appropriate pain management plan.

Chronic painful complications of SCD

Sickle cell pain syndromes may be acute or chronic. However, the definition of chronic pain is arbitrary. The distinction between acute and chronic pain is time dependent. The common chronologic markers used to denote chronic pain are 3 months and 6 months since the onset of pain.[65] The 3-month cut-off appears to be used most often by providers. Some providers consider pain lasting for long periods in the presence of ongoing pathology to be persistent or extended acute pain.[65] Such a definition appears to be applicable to VOCs. Acute sickle pain has a duration that varies from hours to months. The VOC is the prototype of acute pain, whereas leg ulcers, avascular necrosis (AVN) of humeral or femoral heads, and bone infarcts cause chronic pain.

Major characteristics of chronic pain include emotional, behavioral, affective, and physiologic responses that differ from those of acute pain. Patients with chronic SCD pain frequently suffer from psychological comorbidities such as depression, paranoia, a feeling of hopelessness, and despair. Many patients with chronic sickle cell pain become preoccupied with their pain and gradually withdraw from social activities. Their existence becomes a circuitous journey from home to the doctor's office, to the pharmacy, and back home.

Patients with SCD who suffer from chronic pain syndromes, and frequent VOCs are seriously disadvantaged. Their management commands infinite patience, understanding, empathy, and long-term follow-up by their medical providers.

Chronic sickle cell pain syndromes include leg ulcers, AVN, bone infarcts, chronic osteomyelitis, osteoporosis/osteopenia and chronic arthropathy due to iron overload.

Leg Ulcers

Leg ulcers are ulceration of the skin and underlying tissues of the lower extremities, especially the medial or lateral surfaces of the ankles. Trauma, infection, and severe anemia may predispose patients to ulcer formation.[64]

Leg ulceration is a common complication of SCD in general and SCA in particular.[66, 67] Representative data from the cooperative study of sickle cell disease (CSSCD) in the United States found active leg ulcers at entry in 2.5% of 2075 patients 10 years of age or older and in none of 1700 patients less than 10 years of age.[68] The prevalence of leg ulcers elsewhere in the world varies from almost none in Saudi Arabia[69, 70] to 4% in London[71] and 10% in Africa.[72-75]

Table 2 summarizes predisposing factors for leg ulcers. Among sickle cell syndromes, SCA is most often associated with leg ulceration, which is rarely seen in patients with Hb SC disease or sickle β^+-thalassemia.[68] Some studies reported that leg ulcers are more common in patients with SCA who were also carriers of the Central African Republic (CAR) β haplotype[57, 76] as shown in Figure 5. Moreover, leg ulcers are associated with genetic polymorphisms in the BMP6, TGFBR3 and Klotho genes.[77, 78]

The pathophysiology of leg ulceration appears to be the result of multiple factors.[79] Leg ulcers may appear spontaneously or after infection or trauma, even minor, to an area of compromised blood supply may initiate an ulcer. Other reported factors that may enhance blood stasis and skin necrosis include reduced red blood cell deformability,[80] adherence of sickle red blood cells to the endothelium,[81] increased blood viscosity,[82] the presence of circulating immune complexes,[83] activated blood coagulation,[84] pulmonary hypertension, abnormal autonomic

control with excessive vasoconstriction when in the dependent position, in situ thrombosis, anemia with a decrease in oxygen-carrying capacity,[85] and decreased nitric oxide bioavailability, leading to impaired endothelial function.[86] Secondary infection of the ulcer, with undermining of the edges, delays healing and causes progressive extension of skin ulceration.

Clinically, leg ulcers occur in areas with less subcutaneous fat, thin skin, and decreased blood flow.[87] The most common site for the appearance of leg ulcers is the distal third of the leg, especially the inner area, just above the ankles and over the medial malleoli. The medial malleolus is more commonly involved than the lateral malleolus. However, no site of the skin is spared from possible involvement, and ulcers have been reported over the dorsum of the foot, Achilles tendon, anterior tibial area, elbows, and thighs.[88] Leg ulcers may be single or multiple, and an estimated one-third occur bilaterally.[67, 68, 89] They vary in size from a few millimeters in diameter to huge ulcers that may circle around the leg. They may be shallow, superficial erosions of the dermis or very deep craters with tendons visible at their base.

Principles of management of leg ulcers include education, protection, infection control, debridement, and compression bandages. Debridement may be surgical, medical or biologic. Optimization of nutritional state is also important especially in the areas where malnutrition is common. Osteomyelitis may complicate chronic leg ulcers, especially those with deep wounds, and it is advisable to rule out this complication with a bone scan or magnetic resonance imaging (MRI) and bone biopsy if needed. Table 3 summarizes various methods of treatment of leg ulcers.[90-98] Autologous stem cell-based therapy for sickle cell leg ulcer is a potentially novel therapy.[99] Amputation is rarely used for severe extensive leg ulcers as shown in Figure 6.[100] Amputation is used more often in South America and Africa.

Avascular Necrosis

Avascular necrosis is necrotic bone tissue due to an interruption in blood supply, most likely as a result of vaso-occlusion. Bones near a joint, especially the hip, are primarily affected; it is also referred to as aseptic necrosis, osteonecrosis, or ischemic necrosis of the bone. Avascular necrosis of the epiphyses is an important complication of SCD. It is second only to the spleen as the most common organ to undergo sickle cell–induced organ failure.[101] Acute diaphyseal infarction of long bones is less common in adults than in children. However, AVN of the epiphyses becomes more common, recurrent, and chronic in adults with SCD and may cause considerable morbidity because of persistent pain and limitation of movement. Avascular necrosis of the hips has been the subject of several studies and reports. Involvement of the shoulder is less common, and the knees and other large joints are rarely involved.[102] Although it tends to be most severe and disabling in the hip area, it is a generalized bone disorder in that the femoral and humeral heads, as well as the vertebral bodies, may be equally affected. The limited terminal arterial blood supply, paucity of collateral circulation, and complete disruption of vascular supply to the articular surfaces and ends of long bones make these three areas especially vulnerable to sickling and subsequent bone damage.[103, 104] Scientific advances in chronic bone disease have lagged behind improvements in survival in SCD, and AVN remains the leading cause of crippling disability in this population.[47, 77, 105]

Risk factors for AVN of the femoral head include genotype, age, frequency of VOCs, Hb/hematocrit level, α-gene deletion, mean corpuscular volume, and serum aspartate aminotransferase (AST) level.[104] There is positive correlation between the α-gene number and frequency of AVN (Figure 7). In the CSSCD[104] that included 2804 patients, those with SCA and α-gene deletion had a higher incidence of AVN because the relatively high hematocrit increases blood viscosity and thus, enhances microvasculopathy in the aforementioned anatomic sites.[104,

[106] The mean corpuscular volume (MCV) and AST levels were reported to be negatively correlated with AVN especially in patients with homozygous alpha gene deletion.[104] In a study involving about 100 patients with SCA, Lemonne et al.[107] found no difference in blood viscosity between patients with and those without osteonecrosis, despite difference in hematocrit/Hb. Together, all these findings suggest that Hb seems to have a negative effect on the frequency of AVN irrespective of its effect on viscosity. The roles of Hb/hematocrit, viscosity, deformability and aggregation in the pathophysiology of certain complications of SCD need further studies.

Medical treatment of AVN is symptomatic and includes providing non-opioid and/or opioid analgesics for pain relief as well as physical therapy. Advanced forms of the disease require total bone replacement. Core decompression in the management of AVN appears to be effective if done in the early stages of AVN.[108] This, however, was not supported by a prospective randomized multi-center comparing physical therapy alone with core decompression and physical therapy for femoral head AVN in 46 patients with SCD.[109] Physical therapy alone appeared to be as effective as hip core decompression followed by physical therapy in improving hip function and postponing the need for additional surgical intervention at a mean of three years treatment.

Results of hip arthroplasty in patients with SCA are not as encouraging as results of arthroplasty performed for arthritic hip.[110] Placement of an internal prosthesis may be difficult owing to the presence of hard sclerotic bone in patients with SCD. Other problems associated with hip arthroplasty in these patients include an increased incidence of infection,[111, 112] a failure rate of about 50% and a high morbidity due to loosening of both cemented and uncemented prosthesis. Recent techniques of arthroplasty may improve the life expectancy of hip Prostheses.[113]

Chronic Osteomyelitis

Chronic osteomyelitis is continuous bacterial infection involving cortical bone, reported in SCD particularly in association with AVN and bone infarcts.[114-116] Acute osteomyelitis may evolve into chronic bone infection, with typical radiographic changes.[117] In SCA, chronic osteomyelitis is rare and may follow acute osteomyelitis associated with insertion of a hip or shoulder prosthesis. The prevalence of osteomyelitis is lower in individuals with the Bantu haplotype, and it may occur as a complication of severe leg ulcers.[118] The most common etiologic organism in SCD is Salmonella, followed by Staphylococcus aureus, Haemophilus influenzae, and enteric Gram-negative bacilli.[119, 120] Inappropriate management can result in significant bone destruction and necrosis, with persistent foci of inflammation. Those sites may continue to re-infect the area, with a progressive bony response characterized by sequestration and involucrum formation. With healing, the shaft will demonstrate increased bone density.[117]

Chronic osteomyelitis in SCA is difficult to treat; prolonged antibiotic therapy may suppress the infection but rarely eradicates it. Persistent infection is one cause for the recurrence of VOCs. The mainstay of treatment of chronic osteomyelitis is a prolonged course of antibiotics. Initial use of parenteral antibiotics against *Salmonella*, *Staphylococcus*, and enteric Gram-negative organisms is prudent to achieve rapid bactericidal blood levels. A 6-week course of antibiotics is recommended for confirmed cases. Physical therapy to improve joint function and avoid muscle wasting should be encouraged once pain improves.

Osteoporosis/Osteopenia

Osteoporosis is systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with resultant increased fragility and risk of

fracture. Osteopenia, or low bone mineral density (BMD), is decreased calcification, bone

density, or bone mass due to impaired osteoid synthesis. Both of these conditions appear to be

more common in SCD than previously thought. The prevalence of low BMD in SCD ranges

from 30% to 80%,[103, 121-125] with a predilection for the lumbar spine. Predisposing factors include

age, sex, severe anemia, frequent VOCs, low Hb F level, high lactate dehydrogenase level, and

body mass index.[126-129] Major etiologic factors include primary or secondary hypogonadism and

vitamin D deficiency. Diagnostic modalities include determination of BMD by dual-energy x-ray

absorptiometry scan. Osteoporosis is usually asymptomatic, but when fractures occur, they can

cause significant morbidity including pain, deformities, and vertebral collapse.[130] Requirements

for long-term analgesia, mechanical support, and surgical interventions increase exponentially

after osteoporosis-related bone complications.

The literature on the prevalence of fracture in SCD is very limited.[130-133] A study by Fung

et al.[134] found the self-report rates of fracture among young adults (median age 25 years) with

SCD to be 32% and 28% for non-transfused and transfused men and boys and 15% and 16% for

non-transfused and transfused women and girls respectively. In that report, most fractures

occurred in the upper extremities (47.4%), lower extremities (29.5%), or spine and pelvis

(11.5%), and fracture rates increased with age. Ebong[135] reported fracture rates of 20% in

patients with SCD and osteomyelitis, the majority of whom were children. As the natural history

of SCD continues to evolve, the prevalence of age-related diseases, such as osteoporosis, will

increase. This is important because hip fractures are associated with a 1-year mortality rate of

36% for men and 21% for women.[136] Prospective studies on the prevalence of fractures and pain

attributable to osteoporosis in SCD are needed in order to generate treatment guidelines and

recommendations for interventions. The management of osteoporosis in SCD is not well

established. Recommendations follow those of the endocrine and thalassemia literature, with emphasis on primary prevention and adequate vitamin D and calcium intake.

Neuropathic Pain

One of the causes of chronic pain in SCD includes neuropathic pain. The current paradigm in pain medicine suggests that persistent acute pain results in chronic pain due to central sensitization[27, 28], and persistent chronic pain in turn causes neuropathic pain, possibly due to glial activation.[137, 138] Sickle cell pain is presumed to follow this sequence, with no well-established scientific evidence.

Neuropathy and neuropathic pain are not the same and not all patients with neuropathy have pain. Neuropathic pain is not well documented as a complication of SCD. The scales to assess neuropathic pain are different than those used in assessing sickle cell nociceptive pain.[139] Neuropathy, especially peripheral neuropathy, has been reported in patients with SCD, albeit uncommonly. Mental nerve neuropathy (AKA numb chin syndrome) is the most commonly reported neuropathy in SCD usually associated with VOC.[140, 141] Other reported neuropathies in SCD include trigeminal neuralgia [142], acute proximal median mononeuropathy,[143] entrapment neuropathy,[144] and acute demyelinating polyneuropathy.[144]

Neuropathic pain is characterized by sensations of burning, tingling, shooting, lancinating, and numbness. These symptoms may occur in the presence or absence of obvious central or peripheral nerve injury. The mechanism of neuropathic pain presumably involves aberrant somatosensory processing in the central or peripheral nervous system.[145-147]

Sickle cell pain could have a neuropathic component.[144, 148] A thorough history and physical examination are essential to determining whether sickle cell pain is associated with a

neuropathic component. While presence of descriptors can be suggestive of neuropathic pain, it is advisable to use a standardized tool to assess presence of neuropathic pain in SCD. Tools such as self-reports on the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANNS) scale and the Neuropathic Pain Symptom Inventory (NPSI) have been utilized where higher scores were indicative of more pain. PainDETECT and PAIN*Report* have also been used. More studies are needed to determine the prevalence of neuropathy and neuropathic pain in patients with SCD using validated tools and to find whether these are complications of the disease itself or due to co-morbidities.[139]

Management of neuropathic pain involves anticonvulsants. Gabapentin and pregabalin seem to be the anticonvulsants that are generally used for this complication.[149]

Pain Due to Comorbidities

Comorbidity refers to unrelated pathologic disease processes that occur concomitantly with SCD. Concomitant disorders can be pain or non-pain comorbidities.[150] They may have a negative, positive, or neutral effect on the primary basic sickling process. Survival of patients with SCA has increased progressively since the 1970's. Newborn screening, prophylactic antibiotics, newer vaccines, newer antibiotics, newer analgesics, safer blood transfusion, chelation therapy and hydroxyurea are some of the reasons for this change in longevity.[151-154] Patients with SCA in their sixth, seventh or eighth decade have been described previously.[155, 156] In 1994 Platt et al.[151] reported that the median age of survival for males with SS was 42 years and for females 48 years and the median age of survival for males with Hb SC disease was 60 years and for females 68 years.

As patients with SCD age, they become more at risk for developing comorbid conditions that were not previously seen or were rare in this patient population. For example, diabetes mellitus, obesity, and end-stage renal disease in SCD are seen more often now than in the 20th century. Cognizance of the complexity of SCD and its polymorbidities and the implementation of preventative, educational, counseling, and prompt intervention measures may ameliorate the associated complexities of the disease and improve quality of life for its victims.

Comorbidities that have been reported in SCD at least once are listed in Table 4. It includes only conditions that have an impact on sickle cell pain and hence, it may not be comprehensive. Most of the comorbidities listed in Table 4 can precipitate VOCs and may have a significant impact on the morbidity and mortality of patients. Details on selected comorbidities according to anatomic and/or pathophysiologic relevance have been recently reported.[157]

Management of sickle cell pain

Management of SCD in general and sickle cell pain in particular advanced significantly since the 1970s and progressed from the simple palliative treatment to specific pharmacotherapeutic therapy within the framework of precision medicine as shown in Table 5. In addition, the sophisticated gene and genomic editing therapies emerged recently to cure SCD, these will not be addressed in this manuscript. Similarly, nonpharmacological approaches such as acupuncture and mindfulness are being evaluated in SCD however the evidence is not yet conclusive and will not be discussed.

Opioids continue to play a major role in the treatment of most sickle cell pain syndromes. They block the transmission of painful stimuli and raise the pain threshold by acting as ligands that bind to receptors (mostly the µ-receptors) in the central nervous system and other tissues.[22, 158, 159] Opioid receptors have a helical structure[160-164] which forms pockets in which the

corresponding opioid fits snugly. Not all opioids fit snugly in the pocket of a certain receptor and, moreover, the structure of the receptor varies greatly among patients due to variations in the OPRM1 gene that codes the specific structure of the receptor. This explains the variability of the analgesic effect of opioids among patients with sickle cell pain.

Buprenorphine is underutilized in the treatment of sickle cell pain. It is a weak agonist/antagonist opioid with a weak partial μ-opioid receptor agonist and a weak κ-opioid receptor antagonist, It is often used for the treatment of severe pain in cancer pain and other types of pain. Its use to treat sickle cell pain may increase in the future. Some centers have already started using it. Buprenorphine can be used sublingually, trans- dermally or parenterally.[165]

Methadone, ketamine and nitrous oxide inhibit the transmission of painful stimuli via the NMDA receptor and hence, they may be used in patients with severe pain not responsive to other analgesics to enhance pain relief.

Another factor that determines the analgesic efficacy of an opioid depends on how that opioid is metabolized. Briefly, the metabolism of opioids includes two major phases[57] as shown in Table 6. Phase I involves the cytochromes P450 (CYPs) enzymes and phase II includes glucuronidation as the major metabolic pathway. The efficacy of the CYP enzymes varies considerably among patients due to variability in their genes. These genes may be deleted, mutated, duplicated or triplicated. Thus, a patient who has duplication or triplication of the enzyme that metabolizes codeine to morphine would have adequate analgesia with codeine alone. On the other hand, a patient who has duplication of the genes that metabolize methadone would have poor analgesia due to the fact that methadone taken would be rapidly metabolized into inactive metabolites.

In addition, the pharmacokinetics of morphine in patients with SCD differ from that in patients with other pain syndromes. Studies of children with SCD treated with intravenous morphine during VOCs found increased clearance of morphine, particularly in prepubertal children which was significantly greater than that in studies conducted in children with postoperative pain or cancer pain. Similarly, increased clearance of morphine was reported in young adults (≥18 years) with SCD in the steady state in the absence of painful VOCs.[57]

The conundrum created by the genetic variations in the metabolism of opioids undermines efforts to establish guidelines to treat patients with certain doses of opioids across the board. Treatment should be individualized plan for each patient. Such a plan should summarize pertinent aspects of the medical history, physical examination, laboratory data, complications, and treatment plans for patients as outpatients, in the day unit, ED, and hospital. In some cases, the treatment plan may be transformed into an identification card to be carried by the patient and presented to the care provider as needed.[166]

Conclusion

The many faces of pain continue to be the hallmark of SCD, and the VOC is the most frequent reason for treatment in the Emergency Department and/or hospital. Pain sensation results from a very complex and interactive series of mechanisms integrated at all levels of the nervous system: from the peripheral nerve fibers to the higher cerebral cortex where pain is perceived. Despite the fact that management of SCD continues to be primarily palliative in nature, the advent of preventative and curative approaches to therapy are promising. Understanding the pathophysiology of pain suggest that pain management should be individualized and coupled with the proper utilization of analgesics in general and opioids in

particular. Early recognition and treatment of organ damage minimizes morbidity and improves

survival.

Legend to Figures:

Figure 1

Schematic of ion channels in nociceptor function. The cell bodies of nociceptors are contained within the dorsal root ganglia and terminate as free endings in peripheral tissues. The peripheral terminals respond to noxious stimuli or tissue damage through receptors and ion channels including TRP channels, acid-sensing ion channels (ASIC), serotonin (5-HT) receptors, ATP-gated P2X receptors, tyrosine kinase receptor A (TRKA), and numerous GPCRs that indirectly activate ion channels. Receptors at the terminals respond to noxious stimuli such as heat or pressure (i). When a defined threshold of depolarization is reached, voltage-gated sodium channels are activated and an action potential is generated (ii). During an action potential, an IFM-inactivating segment moves to block the channel within 0.5–1 ms (iii). In this inactivated state, the channel cannot be opened. Meanwhile, potassium channels open, acting to repolarize the membrane. As the membrane repolarizes, the sodium channel gate is closed and inactivating segment is displaced, returning the sodium channel to a resting closed state (iii). This process is repeated to propagate the action potential along the axon (ii). The action potential is propagated along the axon to the presynaptic terminals synapses ~~wit~~ with second-order neurons in the dorsal horn. Calcium influx through voltage-gated calcium channels (VGCC) triggers the release of neurotransmitters such as glutamate from presynaptic terminals (iv). Glutamate activates ionotropic AMPA, NMDA receptor (NDMAR), and metabotropic glutamate receptors (mGluR) on the postsynaptic terminals in the spinal cord, and the signal is transmitted through the ascending pathways to higher centers in the brain. From *J Clin Invest.* 2010;120(11): 3745-3752. Used with permission.

Figure 2

2A shows a patient with congenital insensitivity to pain. 2B shows a patient with erythromelalgia also known as "man on fire syndrome". Figure 2A rom techfrag.com/2015/05/27/researchers-discover-gene-responsible-for-pain-insensitivity/ and Figure 2B from ayurvedamagazine.org/a-journey-battling-erythromelalgia/ 1/. Used with permission.

Figure 3

A diagram of a model synapse showing the α-Amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-Daspartic acid (NMDA) Na+-gated channels in the dorsal horn of the spinal cord. (A) Shows weak pain stimulus causing weak depolarization by allowing the entry of Na+ through one of the four proteins of the AMPA channel. The NMDA channel is blocked by Mg2+. (B) Continuous weak stimulation allows the entry of Na+ through the other proteins of the AMPA channel but keeping the NMDA channel blocked by Mg2+. (C) Shows that continuous strong painful stimulus causing complete depolarization of the membrane

secondary to maximal entry of Na+ through the four components of the AMPA channel. At this point the NMDA channel is unblocked by the removal of Mg2+ allowing the entry of Ca2+. From *Eur J Haematol.* 2015;95(2): 113-123. Used with permission.

Figure 4

A typical profile of the events that develop during the evolution of a severe sickle cell painful crisis in an adult in the absence of overt infection or other complications. Such events are usually treated in the hospital with an average stay of 9-11 days. Pain becomes most severe by day 3 of the crisis and starts decreasing by day 6 or 7. The Roman numerals refer to the phase of the crisis: I indicates prodromal phase; II, initial phase; III, established phase; and IV, resolving phase. Dots on the x-axis indicate the time when changes became apparent; and dots on the y-axis, the relative value of change compared with the steady state indicated by the horizontal dashed line. Arrows indicate the time when certain clinical signs and symptoms may become apparent. Values shown are those reported at least twice by different investigators; values that were anecdotal, unconfirmed, or that were not reported to occur on a specific day of the crisis are not shown. ISC indicates irreversibly sickled cells; RDW, red cell distribution width; HDW, hemoglobin distribution width; RBC DI, red cell deformability index; CRP, C-reactive protein; SAA, serum amyloid A; LDH, lactate dehydrogenase; CPK, creatinine phosphokinase; and ESR, erythrocyte sedimentation rate. Reproduced from Ballas48 with permission. From *Blood.* 2012;120(18): 3647-3656. Used with permission.

Figure 5

Effect of β-globin haplotypes on the prevalence of leg ulcers. From *Am J Pediatr Hematol Oncol.* 1990;12: 367–374. Used with permission.

Figure 6

Effect of α-globin gene number on avascular necrosis (AVN) in sickle cell anemia. Patients with two α genes have the greatest prevalence of AVN. There is a significant negative correlation between the α-gene number and the prevalence of AVN. From Ballas SK. *Sickle Cell Pain, 2nd Edition*. Washington DC: International Association for the Study of Pain; 2014. Used with permission.

Figure 7

A. Chronic left leg ulcer of over 3 years duration before amputation. B. The stump after amputation below the knee. From *Hemoglobin.* 2014;38(2): 95-98. Used with permission.

Figure 8

Helical structure of the μ-opioid receptor. (A) Morphine-like molecule (yellow) in the deep pocket (blue) of the μ-opioid receptor. (B) μ-Opioid receptors form an intimate pair when crystallized with a ligand (yellow) such as morphine. From *Nature.* 2012;485(7398): 321–326. Used with permission.

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