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AN OVERVIEW OF MANAGEMENT APPROACH TO PAIN CRISIS IN SICKLE CELL DISEASE PATIENT

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Abstract:

Sickle cell disease (SCD) is a hereditary illness characterized by hemolytic anemia, end-organ damage, diminished survival, and discomfort. A literature search was conducted using PubMed, CINAHL, and Embase. Databases were searched for all relevant studies to our topic published up to the beginning of 2022. Recurrent and unpredictable episodes of intense pain due to vasoocclusive crisis requiring hospitalization are one of the distinctive characteristics of SCD. In addition, SCD patients frequently have chronic persistent pain. Presently, opioids are used to treat sickle cell anguish, a method that is limited by unwanted effects. Because pain can begin in infancy and persist throughout life, preventing its onset may be preferable to treating it once it has been triggered.

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INTRODUCTION:

SCD is an autosomal recessive disorder caused by a point mutation in the -globin gene of the hemoglobin gene. It is characterized by repeated vaso-occlusive crises (VOCs), in which interactions between red blood cells (RBCs) carrying sickle hemoglobin and the endothelium result in microvascular blockage and decreased blood and oxygen delivery to the periphery. Clinically, episodes of VOC present as recurring and unpredictable attacks of acute pain [1,2].

SCD affects millions of patients around the world, and although its basic base is a single mutation in the -chain of hemoglobin, its repercussions [3] are multifaceted. Pain is one of the major comorbidities of SCD. With SCD, discomfort can begin in infancy and persist throughout life, frequently resulting in hospitalization and diminished life quality [4]. In SCD, two forms of pain have been identified: acute pain and chronic pain. Vasoocclusion is connected with acute discomfort. Sickle hemoglobin polymerizes into hard filaments and renders red blood cells (RBCs) less deformable when exposed to low oxygen tension. Such rigid RBCs obstruct microcirculation, resulting in VOC, which is characterized by episodic, repeated, and unpredictable intense pain [5]. During VOC, there is decreased tissue oxygenation and ischemic-reperfusion damage. This injury results in acute discomfort due to inflammation, oxidative stress, and endothelial dysfunction [5,6]. In addition to the acute pain associated with VOC, SCD patients may also have chronic discomfort. Persistent pain may come from maladaptive alterations in the pain pathways. Pain in SCD is now believed to be caused by nociceptive, inflammatory, and neuropathic processes. Increasing evidence suggests that multiple pain pathways could be targeted to alleviate or lessen pain [7].

DISCUSSION:

PATHOBIOLOGY OF ACUTE PAIN IN SCD:

Unpredictable and recurrent VOC due to blockage of venules accompanied by ischemia-reperfusion damage, inflammation, hemolysis, and oxidative stress [8,9] is a hallmark and unique feature of SCD. Acute pain, regarded to be worse than labor pain, necessitates hospitalization and is frequently difficult to cure [9]. Under low oxygen tension, sickle erythrocyte HbS polymerizes into hard fibers, causing erythrocytes to assume their characteristic sickle shape [8,9]. As well as circulating leukocytes and platelets, rigid sickle RBCs aggregate and attach to active endothelium. Leukocytes, particularly neutrophils, are activated in both sickle mice and SCD patients [9]. These contacts between sickle RBC and leukocytes and the endothelium of the blood vessel are promoted by adhesion molecules including E- and P-selectin [10]. Vasoocclusion is avoided in sickle mice devoid of E- and P-selectin. Heparin-mediated inhibition of P-selectin increased microvascular blood flow in SCD patients [10,11].

Selectins on the endothelium surface must be upregulated for sickle RBCs and leukocytes to adhere. In vivo, mast cell activation causes leukocyte rolling and adherence reliant on P-selectin in postcapillary venules [12]. In the skin's vasculature, endothelial leukocyte adhesion molecule (ELAM) is expressed when mast cells are activated. In the work by Klein et al. [13], incubation of neonatal human foreskins with morphine, a recognized activator of mast cell degranulation, enhanced the expression of ELAM. Very large clusters of activated mast cells that released extracellular traps were detected in close proximity to the intact vasculature in the skin of sickle mice [13]. Therefore, mast cell activation in SCD may play a significant role in VOC and acute pain, in addition to chronic pain.

Pain continues to be a prominent complication of SCD; people with SCD report acute episodes and/or continuing chronic discomfort. Pain in SCD is caused by nociceptive, neuropathic, and inflammatory processes (**Figure 1**) [14]. Mechanics of pain have yet to be determined, but recent success with mice models suggests participation of both the peripheral and central neural systems [14].

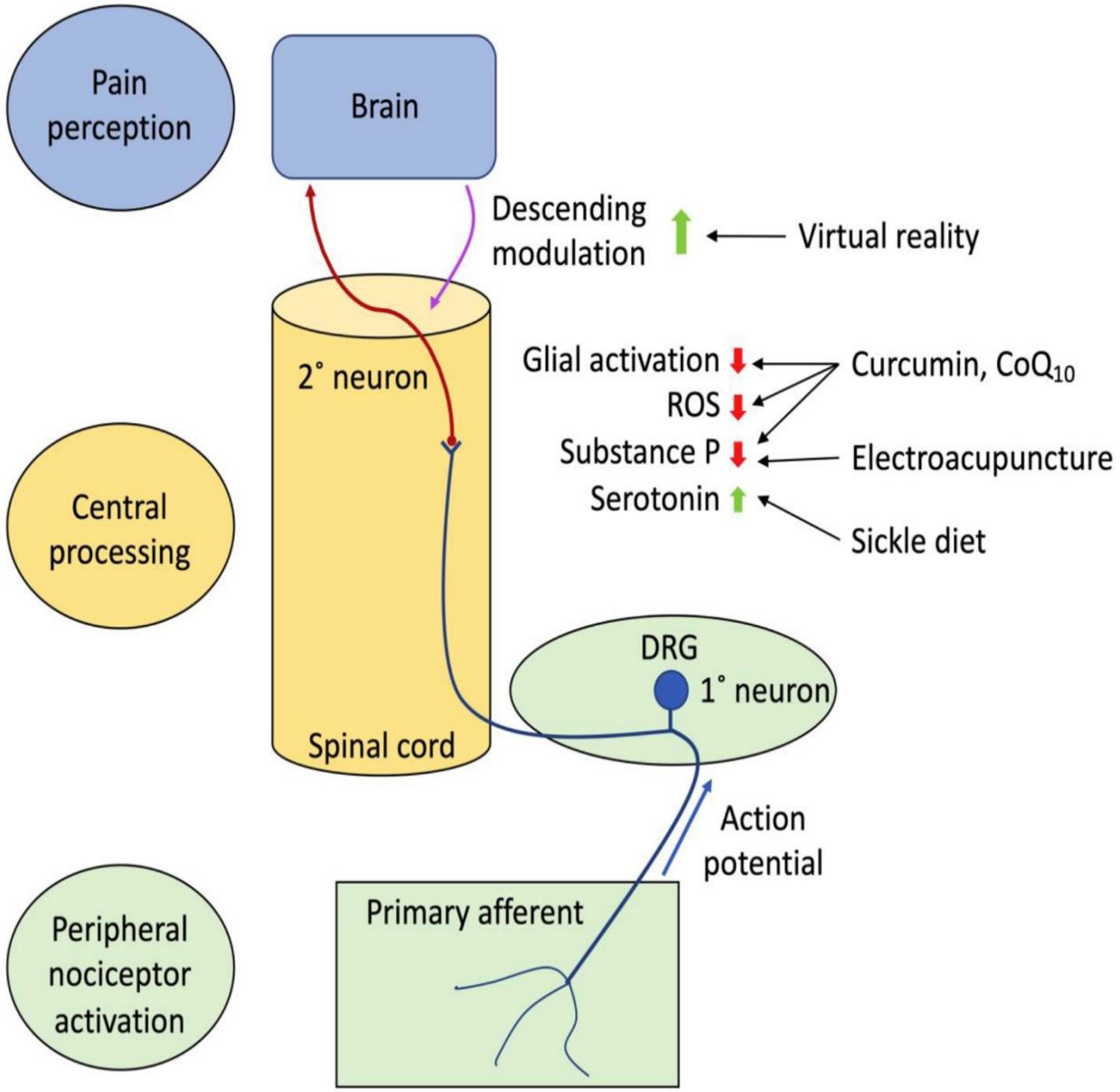

Figure 1: Mechanisms of pain transmission and perception in sickle cell disease.

MECHANISM-BASED STRATEGIES TO TARGET SICKLE CELL PAIN:

Opioids have been the mainstay of symptomatic sickle cell pain therapy. As discussed by Gupta et al. [14], the use of opioids is laden with adverse effects, including hyperalgesia, dependency, and tolerance. In addition, opioids influence RBC rheology negatively by modifying their membrane structure, increase mast cell degranulation-induced inflammation, and influence organ disease via their coactivation of receptor tyrosine kinases, which results in mitogenic signaling [14,15]. Moreover, opioids do not treat the underlying mechanisms that cause pain, and significant concerns about opioid use have led to opioid phobia, which frequently results in inadequate treatment of sickle cell pain. Current understanding of the mechanism-based pain targets discussed above has the potential to lead to improved analgesic therapy for SCD, as outlined in **Table 1** [15].

Table 1: Mechanism-based therapies to target sickle cell pain

Intervention	Mechanism	Known Outcomes and Current Clinical Trials
Crizanlizumab	Anti-P-selectin antibody	Reduced the frequency of painful VOC by 45% and tripled the median time of first VOC in patients with SCD
Sivelestat	Leukocyte elastase inhibitor	Decreased neuronal injury to the DRG and reduced neuropathic pain in BERK sickle mice
Imatinib	cKIT/mast cell inhibitor	Reduced neurogenic inflammation and prevented hypoxia-reoxygenation-induced hyperalgesia in sickle mice; decreased frequency of VOC
Cromolyn	Mast cell stabilizer	Increased the analgesic effect of a suboptimal dose of morphine in BERK sickle mice
Trifluoperazine	CaMKIIα inhibitor; reduces calpain-1 activity	In a phase I clinical trial, ameliorated neurogenic pain and caused 50% reduction in chronic pain in patients with SCD without severe sedation or supplemental opioid analgesics
Simvastatin	Decreases calpain-1 activation?	In patients with SCD, reduced frequency of pain, oral analgesic use, and markers of inflammation, acting synergistically with hydroxyurea; 4 completed clinical trials are cited on the ClinicalTrials.gov website
Rapamycin everolimus	mTOR inhibitor: increases fetal hemoglobin levels	Ameliorated the nociception phenotype in sickle mice; in 1 renal transplant recipient, increased fetal hemoglobin levels from 4.8 to 15% and was well tolerated
Acupuncture	Inhibits inflammation peripherally and in the spinal cord	In awake sickle mice, reduced inflammatory cytokines, substance P, and neurogenic inflammation in the periphery and signaling pathways of nociception in the spinal cord and potentiated the effect of a suboptimal dose of morphine; acupuncture significantly reduced VOC-associated pain in patients with SCD
Hypnosis	Modulates vascular physiology	Decreased pain intensity and increased peripheral blood flow during anticipation and experience of pain in patients with SCD

PRESENTATION OF PAIN AND IT IS MANAGEMENT IN SCD PATIENTS:

Pain in SCD is widespread and complex, with multiple probable different etiologies associated with the pathophysiology of SCD. Differentiating between the many types of pain and their underlying biology in SCD is crucial, especially when it comes to the development of new, targeted therapeutics, which is a major focus of ongoing and future research. With SCD, the pain experienced has both acute and chronic components. Frequently, HbS polymerization, vasoocclusion, and endothelial dysfunction are directly associated to acute pain. Moreover, chronic pain originates from a long-term sensitization of the neural system and sterile inflammation [16]. 55% of adults have chronic pain on more than 50% of days, whereas 29% experience it on 95% of days, according to a study [17]. In adults with SCD, chronic pain is typical and is typically overlaid on intermittent acute pain crises. Adults are able to easily differentiate between SCD-related and unrelated pain, as well as acute pain crisis-related pain and non-crisis pain. The average number of pain areas reported by adults is three, with extremities, back, and abdomen being the most prevalent [18].

Acute pain episodes are a persistent issue for persons

with sickle cell anemia and have been found to be significantly more often than previously believed. 54% (n = 391) of the individuals in the ESCAPED study had at least three acute visits for pain control in the previous year [19]. Many acute therapies and management strategies have been researched due to the incidence of painful episodes in SCD. Analgesia remains the cornerstone of vasoocclusive pain treatment in sickle cell anemia. Whether at home or in the hospital, acute pain episodes are normally managed with analgesics that progress from NSAIDs and acetaminophen to opioids. The doses and administration schedule may vary from hospital to hospital and are also tailored to the pain tolerance and frequency of each individual. 19% of 176 patients who visited an emergency department for pain associated to sickle cell disease received a mix of NSAIDs and opiates, 48% received NSAIDs alone, and 33% received opiates alone, according to a retrospective study [20]. In a cohort study of 219 individuals with sickle cell disease, 78% of home pain days were treated with opioids, with 85% of patients using long-acting opioids and 47% using short-acting opioids. [21] Just 9.6% utilized non-opioids.

Inhibiting Mast Cell Activation:

Mast cell activation plays a crucial role in neurogenic inflammation and nociceptor activation in sickle mice via the production of SP in the skin and DRG. Imatinib, a mast cell inhibitor, inhibits hypoxia-reoxygenation-induced hyperalgesia in BERK sickle mice (P 0.05) [22]. Two patients with chronic myeloid leukemia with SCD reported that imatinib dramatically reduced painful episodes, hospitalizations, and everyday pain in separate case reports [23]. Imatinib is approved by the FDA for multiple indications. We are unaware of any clinical trials of imatinib in SCD at this time, however the justification for such a trial seems clear. We also discovered that the mast cell stabilizer cromolyn sodium enhanced the analgesic efficacy of modest doses of morphine in BERK sickle mice [22]. Thus, it is probable that morphine activates mast cells, thereby contributing to pain, while concurrently acting as an analgesic through its activity in the neurological system. The targeting of mast cells provides a method for lowering the use of opioids in the therapy of sickle cell pain.

Calpain-1 contributes to IgE-mediated activation of mast cells and plays a crucial role in neurotransmission and neurogenic pain [24]. We have shown that genetic ablation of calpain-1 in Townes sickle mice alleviates tonic hyperalgesia in sickle mice, but not hypoxia-reoxygenation-induced hyperalgesia [25]. Trifluoperazine, an antipsychotic drug licensed by the FDA, inhibits CaMKII potently and lowers calpain-1 activity. In a phase I clinical trial, it alleviated neurogenic pain and reduced chronic pain by 50% in SCD patients without requiring significant sedation or additional opioid analgesics. Statins inhibit calpain-1 activation. In a single-center pilot research involving adolescents and adults with SCD, therapy with simvastatin for up to 3 months reduced by 85% the incidence of sickle cell-related pain and oral painkiller use, improved soluble biomarkers of inflammation, and functioned synergistically with hydroxyurea [26]. Despite a significant decrease in the incidence of discomfort, simvastatin had no effect on the degree of pain [26]. To explain this disparate effect of simvastatin on the frequency and intensity of pain, the authors of this study hypothesized that the visual analog scale, which was used as the sole measure of pain intensity in this study, may not have captured the multidimensional nature of pain intensity in SCD [26].

The activation of cannabinoid receptors:

In mast cells, activation of cannabinoid receptor types 1 (CB1R) and 2 (CB2R) has been demonstrated to suppress degranulation and inflammation, respectively. Both CB1R and CB2R are expressed in non-central nervous system tissues, including inflammatory cells [27]. Peripheral CB2R activation produces an antinociceptive response in inflammatory and neuropathological pain. Targeting CB1R produces psychotropic effects, whereas targeting CB2R has no such consequences. CB2R agonists and/or knockout mice provide compelling evidence that CB2R activation alleviates neuropathic and inflammatory pain and is protective against ischemia-reperfusion injury by reducing endothelial expression of adhesion molecules and secretion of chemokines and by attenuating leukocyte adhesion to the endothelium, transendothelial migration, and interrelated oxidative nitrosative damage, which is consistent with Cannabinoids reduce mast cell activation, inflammation, and neurogenic inflammation in BERK sickle mice via both CB1R and CB2R, but CB1R activation is necessary to reduce hyperalgesia [28,29,30]. Among 86 individuals with HbSS, HbSC, and HbS- thalassemia, a controlled, self-administered, and anonymous questionnaire revealed that 36% had used cannabis in the previous 12 months to alleviate SCD symptoms [30].

Elevating Fetal Hemoglobin:

In SCD patients, chronic pain has been observed to be inversely linked with circulating fetal hemoglobin

(HbF). Importantly, increased HbF in SCD patients has been linked to a decrease in the frequency of painful crises [31]. Preclinical investigations have studied HbF-increasing techniques. The mammalian target of rapamycin (mTOR) regulates several essential cellular processes, from protein synthesis to autophagy, and unregulated mTOR signaling has been linked to a number of clinical diseases [32]. In mice with sickle cell disease, rapamycin enhances HbF levels and ameliorates the nociception phenotype [32]. Gaudre et al. [33] described a kidney transplant patient with SCD who was treated with the mTOR inhibitor everolimus.

CONCLUSION:

Almost half of those diagnosed with SCD have chronic discomfort on more days than not. Although the majority of treatment focuses on either resolving or preventing acute crises, conventional medical management gives minimal assistance in terms of chronic pain relief. Nonpharmacological treatments have shown modest benefit in treating chronic pain in these people, with cognitive behavioral therapy (CBT) being the most promising for patients with concurrent anxiety or depression. In addition to resolving chronic pain, stem cell transplantation and genetic therapy have showed efficacy, although their indications are poorly defined and require further investigation. Current research demonstrates conclusively that adequate treatment of concomitant psychiatric problems enhances the quality of life of patients. Although despite the success and potential use of these therapies, there are still numerous unanswered questions regarding their efficacy and generalizability for people with SCD.

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