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AN OVERVIEW OF SICKLE CELL DISEASE VASO-OCCLUSIVE CRISIS AND APPROACHES TO MANAGEMENT

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Abstract:

Early diagnosis, treatment, and prevention of a vaso-occlusive crisis (VOC) are critical to the management of patients with sickle cell disease. Literature search conducted through electronic databases, such as PUBMED, EMBASE. We aimed to discuss the proper management of VOC, after emphasizing the mechanism and complications of VOC in SCD. Vaso-occlusive crisis in people with SCD is a multifactorial process identified by inflammation, attachment, and multicellular aggregation of sickled RBCs, endothelial cells, platelets, and also other blood cells, resulting in vaso-occlusion and acute extreme pain.

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INTRODUCTION:

Sickle cell disease (SCD) is the most common hemoglobinopathy, with approximately 300 000 new cases each year and millions of patients affected globally [1]. It is characterized by a point mutation that results in the substitution of glutamic acid with valine on the sixth amino acid of β-globin. The mutant Hb molecules, hemoglobin S (HbS), polymerize upon deoxygenations, causing the erythrocytes to assume a sickle morphology and reduce the fluidity of the plasma membrane. Sickle erythrocytes adhere to leukocytes immobilized to the endothelium, causing microvascular occlusion, vaso-occlusive crisis (VOC), and tissue ischemia. Recurrent vaso-occlusion causes chronic disabling arthritis because of osteonecrosis affecting the joints, progressive retinopathy, chronic renal disorder, increased risks for strokes, and shortened lifespan [1,2].

Painful vaso-occlusive crisis (VOC) remains the foremost common reason for presenting to the Emergency Department and hospitalization in patients with SCD. Given the complexity of VOC and its feedback mechanism which will further exacerbate the pain crisis and to line up a positive feedback that we now term secondary VOC (sVOC), adequate and aggressive intervention of VOC at the earliest time is crucial. this may break the vicious circle and shorten hospital LOS because of pain, although the component of pain due to tissue infarct might not be rescuable [3]. In addition to erythrocyte sickling, one in every of the hallmarks of SCD is that the continuous presence of basal inflammatory processes. this can be exemplified within the following observations. SCD patients have higher baseline leukocyte counts than those without the disease [4]. Although the elevated leukocytes is also contributed by the overstimulated marrow from the underlying hemolytic process, SCD patients exhibit higher levels of soluble CD62L [5], a marker of neutrophil activation. Neutrophils in SCD also express higher activation molecules, e.g. CD64 and CD11b/CD18 [6]. Monocytes in SCD demonstrate activated phenotypes and better propensity to IL-1β and TNFα [7]. Similarly, platelets in SCD are chronically activated and express higher level of CD40L [8]. the continuing inflammatory processes provide the background on which VOC develops. the continuing inflammatory processes originate from a mixture of membrane damage of erythrocytes carrying HbS and increased intestinal permeability that happens in SCD (**Fig. 1**) [3]. However, once VOC is triggered, ischemia–reperfusion injury that follows further feeds into the inflammatory processes.

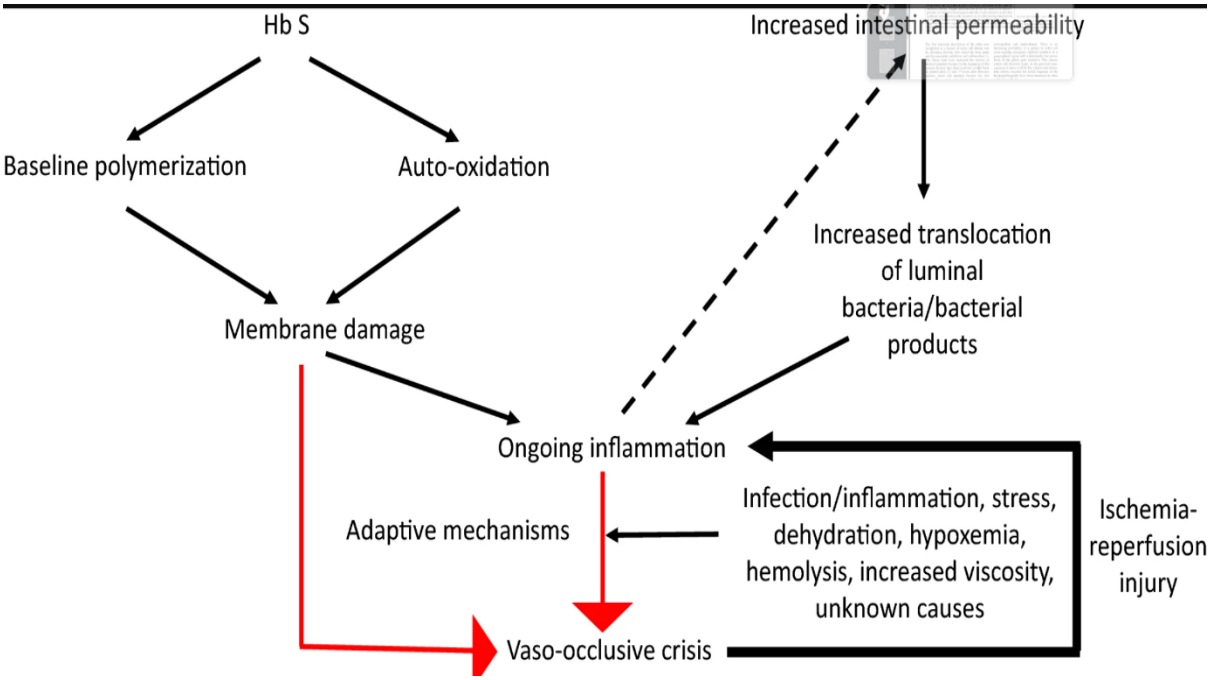

Fig 1: Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events

METHODOLOGY:

Search conducted through electronic databases, such as PUBMED, EMBASE. searching relevant studies that are published in English language up to 2021. MeSH term used in the search strategy as; Vaso-occlusive crisis, VOC, complications, sickle cell disease, SCD.

DISCUSSION:

In order to accurately diagnose, predict, or prevent the onset of VOC and associated pain and other sequelae, it is necessary to understand the underlying mechanisms. Chronic vascular inflammation causes activation of endothelial and blood cells resulting in release of macrophages, mast cells, and platelets, multicellular adhesion, and activation of nociceptors, leading to vaso-occlusion and VOC [9]. Vaso-occlusion may be a multifactorial process involving not only occlusion of small blood vessels by sickled red blood cells (RBCs) and adherent blood cells, but also large-vessel intimal hyperplasia, thrombosis, and bone marrow fat embolization, resulting in hypoxia, ischemia, and tissue damage and inflammation [10]. it's this mixture of hypoxia/reperfusion injury, ischemic tissue damage, and inflammation that produces SCD pain unique.

When diagnosing VOC, the foremost important step is to differentiate it from acute flares of chronic pain that are often of unknown origin, but may be associated with orthopedic complications of SCD, including bone infarction and avascular necrosis. Diagnosis of VOC in children is complicated by the actual fact that VOC affecting the bone is that the most typical acute clinical manifestation of SCD during this population [11]. Vaso-occlusive crisis may additionally be confused with the much less frequently occurring osteomyelitis, which may be an acute or chronic inflammatory process caused by infection with pyogenic organisms thanks to impaired immune function and functional asplenia, resulting in infection of the bone. Osteomyelitis is characterized by localized pain, tenderness, and swelling affecting one site and a limited range of motion, and/or prolonged fever and pain. While the quantity of days of fever and pain before admission, as well as increased C-reactive protein levels and erythrocyte sedimentation rates, is considered to be key differentiators by some, often it is difficult to differentiate the two conditions [12].

- **Polymerization & Adhesion**

Polymerization of deoxygenated sickle hemoglobin leads to decreased deformability of RBCs and is responsible for the characteristic “sickle” shape of RBCs in patients with SCD. Sickled RBCs are rigid and do not easily flow through the microcirculation; they can obstruct the vasculature, resulting in pain episodes and end-organ injury. Recurrent polymerization can lead to multiple RBC and systemic abnormalities, including hemolytic anemia and downstream progressive organ dysfunctions. Recent data suggest that the overall percentage of sickled cells increases 1-3 days prior to the clinical crisis during the evolution of a VOC, which is followed by a decrease in sickled cells as patients recover. Therefore, while overall RBC deformability decreases early in the VOC, it increases later as the percentage of rigid cells decreases [13,14].

Acute VOCs are believed to occur because of adherence of sickled RBCs to the vascular endothelium, adherent leukocytes, and platelets in small blood vessels. This multicellular adhesion, rather than changes in RBC morphology per se, is now thought to be the trigger for VOC and has been shown in animal models to lead to initiation of VOC. Accumulation of sickled RBCs and other adherent cells may contribute to vaso-occlusion in smaller vessels in the absence of an inflammatory trigger.[17] Interaction of a number of adhesion molecules has been implicated in SCD, including α4β1 integrin, CD36 expression on sickle cell vs normal erythrocytes, basal cell adhesion molecule/lutheran protein, and endothelial vascular cell adhesion molecule-1 (VCAM-1) [15].

P-selectin is another adhesion molecule that is implicated in inflammation, coagulation, and atherosclerosis, and appears to be particularly important in SCD [16]. P-selectin is expressed on the surface of both endothelial cells and platelets, and has a role in the adhesion, rolling, and capture of blood cells. Activated platelets bind to neutrophils in a P-selectin–dependent manner to form aggregates, and increased expression of P-selectin on endothelial cells promotes leukocyte adhesion, together contributing to the development of VOC. Possible triggers described for this process include inflammation, stress, increased viscosity, decreased flow, and hemolysis [12].

- **Inflammation**

The inflammatory chemokine CXCL1, which serves as a neutrophil chemoattractant, has been identified as a vital moderator of VOC in humanized SCD computer mice, and also neutrophil activation accompanied by an acute inflammatory response has actually been connected with VOC in patients who experience succeeding ACS [17]. Together, sickled RBCs, triggered endothelial cells, neutrophils, leukocytes, and also monocytes develop a pro-inflammatory and pro-aggregatory atmosphere [18].

Ischemia-reperfusion injury secondary to microvascular occlusions advertises chronic swelling with increased oxidant manufacturing and also increased attachment of leukocytes, which even more contributes to vaso-occlusion and tissue damage. Inflammatory mediators TGF-β and IL-17 have actually been revealed to be considerably raised in individuals with SCD at steady state compared to controls; TNF-α, IL-6, and also IL-8 are also dramatically raised compared to controls in patients with SCD and also VOCs [19,20].

Risk factors for VOC:

Many patient-related and environmental variables have actually been shown to be danger elements for VOC and also may also lead to hyperalgesia (**Table 1**) [21,22]. Individual variables include hypoxia, infection, high temperature, acidosis, dehydration, maternity, menstrual cycle, and obstructive sleep apnea; pain itself can additionally precipitate agonizing crises. Anxiousness, depression, alcohol intake, as well as physical exhaustion can likewise activate beginning of VOC. In addition, comorbidities such as sarcoidosis, diabetic issues, cholecystitis, and also herpes can lead to discomfort crises. It has been recommended that these triggers may really cause pain dilemmas due to a web link in between the free nervous system (ANS) and also VOC. Perturbations in the ANS in reaction to these triggers may trigger ANS-mediated vasoconstriction, tipping the balance from steady state toward VOC. A current study utilizing mathematical designs of biophysical markers suggested that markers relating to raised blood pressure were involved in pain-induced vasoconstriction [23].

Table 1:	**Risk factors that can trigger VOC.**
Triggers	Patient factors: hypoxia, infection, fever, acidosis, dehydration, pregnancy, menstruation, obstructive sleep apnea, pain, anxiety, depression, alcohol consumption, physical exhaustion
	Environmental factors: exposure to temperature extremes, high wind speed, and humidity
	Comorbidities: sarcoidosis, diabetes, cholecystitis, herpes
Biomarkers	Blood parameters: high platelet and neutrophil counts, high hemoglobin levels, unbound extracellular hemoglobin, increased levels of plasma platelet factors 3 and 4, platelet hyperactivity
	Serum factors: high lactate dehydrogenase levels, elevated levels of fractalkine and fractalkine (*Fkn*) gene expression
	Inflammatory factors: reduced interleukin 10 (IL-10) secretion, levels of soluble CD163 > 1400 ng/mL, secretory phospholipase A2
Genetic predictors	Single nucleotide polymorphisms: +191 and +292 in galectin-3 gene (*LGALS3*), mutations in the γ-globin gene promoter that disrupt binding of major fetal globin repressors

Management:

1. Prevention &treatment of VOC:

Hydroxyurea is one of the most typically made use of drugs for the management of unpleasant crises in adult people with SCD. It is suggested for reduction in the regularity of excruciating dilemmas and to lower the requirement for blood transfusions in grown-up patients with SCD with frequent moderate to serious uncomfortable dilemmas (typically a minimum of three VOCs during the preceding 3 months) [24] Additionally, NHLBI also advises its use in people that have discomfort that interferes with everyday activities or lifestyle, in addition to in individuals with a history of severe or reoccurring ACS or severe

persistent anemia that interferes with daily activities or quality of life, and also to consider its usage in infants > 9 months of age, children, and teens to minimize the incidence of SCD-related difficulties [24] Hydroxyurea has actually been shown to enhance degrees of HbF, which seems protective versus VOC. Furthermore, hydroxyurea therapy has been connected with lower white blood cell, platelet and reticulocyte, and dense-cell matters; lower levels of adherent reticulocytes as well as leukocytes that may launch pro-inflammatory cytokines may additionally help to stop initiation of VOC Most importantly, hydroxyurea has been revealed to minimize the number of discomfort episodes in adults with SCD, with an annual rate of VOC 44% less than sugar pill (P <.001) A 9-year follow-up research indicated that hydroxyurea additionally minimized death by 40%The optimum response to hydroxyurea occurs when the dosage is titrated to an optimum endured dose that causes mild myelosuppression, with private pharmacokinetics, pharmacodynamics, and pharmacogenomics adding to the variability [25].

Treatment of pain, especially chronic pain, with opioids does not address the underlying disease processes and may lead to hyperalgesia, dependence, and tolerance. Indeed, opioids may adversely affect the membrane structure of RBCs, increase mast cell degranulation-induced inflammation, and activation of tyrosine kinases, all of which may contribute to VOC. Prevention of pain associated with VOC is a preferred approach whenever possible. Avoidance of VOC triggers such as cold, fatigue, and stress can help to reduce the frequency of VOCs. Another prevention strategy is avoidance of agents that may lead to initiation of VOC. For example, animal studies have suggested that vaso-constrictive agents such as α-adrenergic receptor agonists (including phenylephrine) may precipitate VOC. Such agents should therefore be avoided in patients with SCD [26,27].

CONCLUSION:

Vaso-occlusive crisis in people with SCD is a multifactorial process identified by inflammation, attachment, and multicellular aggregation of sickled RBCs, endothelial cells, platelets, and also other blood cells, resulting in vaso-occlusion and acute extreme pain. While management methods to abort or relieve VOC by administration of opioids have actually been created, the emphasis should shift to prevention of onset and also decrease in frequency of pain situations, specifically in those at greater danger. Research has actually identified a variety of measurable leads for determining those individuals at high threat of VOC. These people may
be excellent prospects for lately authorized therapies in combination with hydroxyurea, such as L-glutamine and crizanlizumab, which benefit from the underlying mechanisms of VOC as well as have been shown to decrease the regularity of this incapacitating repercussion of SCD.

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