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COVID -19 Pandemic: A Grim Ongoing Challenge for Sickle Cell Disease Patients

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ABSTRACT

Novel coronavirus disease (COVID-19) pandemic is a major global illness caused by acute respiratory syndrome coronavirus (SARS CoV-2) which primarily causes pulmonary infection. Sickle cell disease (SCD) patients if get infected, has been found to be at higher risk to develop life threatening complication, acute respiratory distress syndrome (ARDS) due to COVID 19. Diagnosis and management of SCD becomes challenging due to its complexity and unrecognizable symptoms associated with sickle cell trait. Definitive diagnosis requires multidisciplinary approach, and chest X ray images usually show peripheral ground glass opacity or consolidations indicative of severe pulmonary involvement. Management strategies should be selected with an aim to prevent polymerization of abnormal sickle haemoglobin HbS in erythrocytes, so as to reduce frequency and severity of infection in SCD. Hydroxychloroquine/ chloroquine, an anti-malarial drug has shown promising results in reduction of COVID 19 symptoms however cardiovascular and gastrointestinal side effects due to them have raised a controversy that demands future clinical trials on evaluation of its safety. Besides this, limited literature evidence necessitates the need of more clinical trials in a quest of search of appropriate therapeutic regimen to prevent complications in SCD patients.

KEYWORDS:

COVID 19, Challenge, Diagnosis, Management, Sickle cell disease

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INTRODUCTION

COVID 19 outbreak, is a devastating global illness caused by novel RNA coronavirus Severe Acute Respiratory Syndrome Coronavirus (SARS CoV -2) and had affected over millions of people worldwide since November 2019. 1 Although population worldwide was at risk acquisition of infection, but patients with haematological disorders particularly Sickle Cell Disease (SCD) became the major concern. SCD is an autosomal recessive genetic disorder, and occurs due to single base pair point mutation (GAG to GTG) in β globin chain by substitution of glutamic acid residue with a hydrophobic valine residue at sixth position of β globin chain that leads to formation of abnormal haemoglobin (HbS). 2 According to Global Burden Disease Study, each year around 3.2 million people are affected with SCD, 43 million people are carriers, and 176,000 million die due to SCD induced complications that include vasoocclusive crisis, thromboembolism and acute chest syndrome. 3 Literature has revealed that high proportion of cases are found in Sub Saharan Africa, Western America and few Mediterranean countries. Homozygous genotype

HbS referred to Sickle Cell Anaemia (SCA) is the predominant form, and its prevalence in India has been studied to vary from 2 to 34%, with high majority of cases in central region [1].

SARS CoV 2 has been found to particularly infect lungs, and patient presents with typical symptoms of high fever, dry cough, breathlessness, and myalgia. Presence of underlying systemic disease such as diabetes mellitus, cardio pulmonary abnormalities, SCD, and malignancy increases risk of severe complications of COVID 19 infection; thereby resulting in poor disease outcome. Moreover, hypoxia is an important factor that affects the COVID -19 progression thereby resulting in severe pulmonary complications and subsequent death. SCA patients are immunocompromised and are more likely to suffer from severe vaso-occlusive crisis and acute respiratory distress. Therefore, these patients require personalized and comprehensive treatment for better prognosis. 5 To the above consideration, this review aims to discuss the potential of SCD patients to develop severe COVID 19 infection and the management strategies to be adopted for prevention of life threatening COVID 19 complications.

PATHOGENIC MECHANISM OF SICKLE CELL DISEASE

The basic pathogenic mechanism is polymerization of HbS, that is following Deoxygenation Mutated Haemoglobin (HbS) polymerize to form bundles resulting in impaired rheology of blood. Morphological alteration of biconcave shaped red blood cells (RBC) to irregular, rigid sickle shaped cells occurs that adhere to vascular endothelium along with leukocytes and platelets, eventually leading to stasis of blood, referred as vaso-occlusion, ischaemic-hypoperfusion injury and hypoxia. The rate of polymerization increases concentration of HbS and decreases of HbF in erythrocytes. Secondly, sickle RBCs have a shorter life span about 10 days than 50 days of normal RBCs, and they undergo intravascular haemolysis during their transport through blood vessels with release of haemoglobin into the plasma. These vascular events increase the turnover rate of RBCs with increase in concentration of reticulocytes. Another important feature is endothelial dysfunction caused due to interaction of circulating sickle RBCs with platelets, leukocytes and molecular and cellular components in the vascular endothelium. In SCD interaction involves adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), E-selectin, and P-selectin to increase the adherence of sickle RBCs to endothelial cells in comparison to normal RBCs. 7 In addition, increased production of reactive oxygen species (ROS) has been observed in SCD patients that contributes to further increase of vascular adherence and finally vascular occlusion. As a result, tissues and mitochondria are deprived of blood supply, become deoxygenated and undergo hypoxic injury. After this, reperfusion phase ensues due to which tissues undergo further damage on exposure to oxygen, and there is increase in production of free radicals. Hypoxia has been studied to regulate the production of adhesion molecules, particularly VCAM -1 and nuclear factor NF-ƙB that increase the interaction of sickle cells with both micro and macro vasculature, thereby worsening vaso-occlusive crisis and ischemic pain (Figure 1).

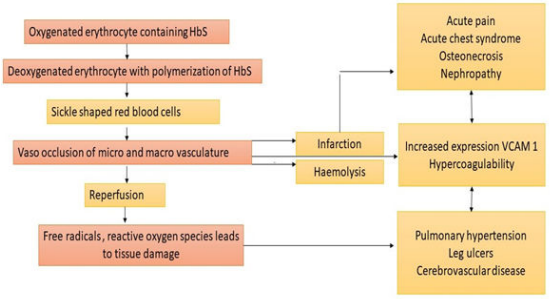

Figure 1: Pathogenesis of Sickle Cell Disease.

COVID 19 INFECTION IN SICKLE CELL DISEASE

Scientific evidences have shown increase risk of SCD patients, and with sickle cell trait who are carriers of the mutation, to develop severe pneumonia like illness and associated complications. Survey done from March to May 21, 2020 in United States on 178 SCD patients with mean age 28.6 years revealed that 122 (99%) SCD patients were hospitalized, 19 (11%) were admitted to intensive care unit and 13 (7%) died due to COVID 19 infection.8 Thiam et al stated that children are more susceptible to severe SARS-CoV 2 infection and require intensive management strategy. Children with SCD had been found to have higher hospitalization rates in the age groups of 0 to 4 years (4.2%) and 5 to 17 years (26.2%). In general population, higher rate of hospitalization of 59.7% was observed in age group of 18 to 49 years. Results concluded that age was a main contributing factor towards progression of COVID 19 infection in SCD patients.9 COVID 19 infection has been found to increase the hypercoagulability state of SCD and patients suffer from severe thromboembolic events with poor outcomes. SARS-CoV 2 may trigger complications in SCD patients by i) hyperinflammation, ii) immunosuppression, iii) deep vein thrombosis, and iv) life threatening multiorgan failure, especially patients with kidney or liver damage have high fatality rate. 10 The major complication of vaso-occlusion is Acute Chest Syndrome (ACS), that occurs 2-3 days after the onset of ischaemic pain. It has been hypothesized that ACS is a hyperinflammatory response in the lungs triggered by infectious agents. As a result of pathogenic stimulus, release of cytokines and inflammatory drugs neutrophils ensues leading to disruption of endothelial-epithelial barrier, and oxygen exchange. Few studies have found platelet thrombi in microvasculature of lung as cause of ACS in 17% of cases and these patients have poor prognosis. Disseminated intravascular coagulation may occur in serious patients, leading to multiorgan failure [2].

Richardson et al in their case series on hospitalized patients with confirmed COVID-19 observed that 14.2%

required Intensive Care Unit (ICU) admission, 12.2% received mechanical ventilation, and 21.0% died, and stay in hospital was of 4.1 days. It is conducted a retrospective analysis to assess the pathophysiological characteristics of COVID-19 in 24 patients with SCD or with trait seen at the Henry Ford Hospital, Detroit, MI, USA, between March 1 and April 15 2020. Results revealed that 13 (54.0%) patients required hospitalization, four patients developed acute pain crisis and one patient developed acute pulmonary embolism. Additionally, three (13.0%) patients underwent packed red blood cell transfusion, and one patient was admitted to the intensive care unit (ICU), mechanical ventilation was done, but unfortunately patient died. They stated that lower proportion of SCD patients with COVID-19 require ICU admission and mechanical ventilation, but may require slightly longer hospitalization. It is reported a case of 48-year-old SCD patient tested positive for COVID-19, he was on hydroxyurea; although close monitoring was done, but patient developed painful crisis and severe haemolysis after few days. Patient was transferred to ICU care and his condition improved after RBC exchange, to this consideration it was suggested that RBC exchange can assist in improving the prognosis of SCD patient infected with COVID-19 without need of mechanical ventilation.

DIAGNOSIS OF COVID 19 INFECTION IN SICKLE CELL DISEASE PATIENTS

Diagnosis of COVID 19 infection in SCD, is challenging for oral physicians due to complexity of disease and unrecognizable symptoms of COVID 19 infection in patients exhibiting sickle cell trait. Patients presenting with complications such as chronic organ failure, or psychosocial problems require detailed evaluation with regular recall visits. Proper diagnosis requires evaluation of clinical symptoms, recording of vital signs, haematological investigations, oxygen saturation by pulse oximeter, and throat and nasopharyngeal swabs. Real time reverse transcriptase polymerase chain reaction RT-PCR is considered as a gold standard to arrive at definitive diagnosis and two positive RT-PCR taken at 24-hour interval are suggestive of COVID 19 positive status [3].

Besides aforementioned investigations, imaging plays a crucial role as a diagnostic support, in detection of SARS CoV-2 associated complications in SCD patients, for formulation of proper treatment plan and in monitoring of treatment response. Chest CT has been found to have more diagnostic utility in detection of pulmonary complications and presence of peripheral ground-glass opacity or consolidations, on CT images indicates severity of pulmonary infection. It is suggested that on high resolution CT images more extensive lesions involve bilateral multiple lobes predominantly in the subpleural areas, often with vascular enlargement and lesions may even extend to whole lung, appearance known as “white lung.” Currently, salivary fluid has become a reliable marker in detection of COVID 19 in initial stages and studies have suggested elevation of proinflammatory cytokine interleukin (IL 6) in salivary samples. 21 Most important is regular follow up of patients for 4 to 6 months to evaluate clinical improvement and pulse oximetry should be done at each follow up session.

MANAGEMENT

SCD patients infected with SARS-CoV 2 should be managed by personalized approach, pre-exposure prophylactic measures such as physical distancing, wearing of protective mouth masks, gloves, personal protective equipment, and disinfection of used instruments after each patient should be strictly adhered during clinical examination. 22 High risk SCD patients should be managed by standard protocols and patients with renal tubular acidosis, proteinuria, hypertension, existing pulmonary disease and multiorgan damage require intensive management strategies. Individuals with sickle cell trait are not considered as a major health problem due to absence of vaso-occlusive symptoms, but if found positive then they should be counselled about implications of disease. 10 Therefore, neonatal screening should be done with an assumption that if new born child is declared positive, then there is probability that at least one parent will have sickle cell trait. Secondly, prenatal screening of pregnant women with particular racial groups with high prevalence of sickle cell gene should be done. It has been reported that chronic pain resulting from avascular necrosis, leg ulcers and other complications is the major cause of morbidity in SCD patients [4].

Patients with SCD suffer from both acute and chronic pain , and should be managed by both non pharmacological methods and pharmacological agents. Non pharmacological methods include patient education and counselling that assist patients in coping with painful episodes and to recognize the source and intensity of pain. Pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and narcotics should be prescribed for uncontrollable pain. 17

Early detection and management of SCD is vital to prevent the life threating complication, that is ARDS, and in COVID positive patient, acute chest syndrome is the primary cause of hospitalizations which is often misdiagnosed due to overlapping symptoms with pneumonia. Palliative treatment with fluids, oxygen therapy and broad-spectrum antibiotics have been found to be beneficial in reducing the count of sickle RBC. 22 Pharmacological therapies for COVID 19 infection such as hydroxychloroquine or chloroquine may worsen the SCD by concomitant G6 PD deficiency and methemoglobinemia. Hydroxyurea (HU) in treatment of acute chest syndrome in SCD have gained attention, with an aim to prevent the polymerization of sickle HbS in erythrocytes. Hydroxyurea (HU) has been found to be effective at an initial therapeutic dose of 10 mg/kg orally in reducing frequency and intensity of vaso-occlusive symptoms and acute chest syndrome associated with SCD. Dose escalation of HU should be done after proper haematological assessment of patients to reduce morbidity. HU increases HbF, decreases intracellular

concentration of HbS, and expression of cell adhesion molecules leading to reduction in red cell sickling. 19

Red blood exchange in SCD is another treatment modality with successful outcomes, however in COVID 19 pandemic risk of transmission of infection from blood donor has limited its use. It has been found that COVID 19 infection in SCD patients can result in cytokine storm, and increase of pro inflammatory cytokine IL-6 levels and to this concern, tocilizumab a monoclonal antibody should be given in initial stages that reduces the IL-6 levels and prevents the development of ACS. 21 During peak of COVID 19 pandemic, physicians have practiced telemedicine to treat SCD patients and medications were delivered at home. Figure 2 shows triage of SCD patients during COVID 19 pandemic. It is recommended that phone triage should be followed unless patient reports with acute symptoms that require thorough medical evaluation or hospitalization. In addition, patients should be educated and made aware of possible complications of SCD and to seek medical care if found to have concomitant COVID 19 symptoms [5].

Conclusion

Impact of COVID 19 infection on SCD patients has become an emerging concern and needs to be addressed to prevent pulmonary complications in SCD patients taking into account different geographical regions, patient age groups and genotypes of SCD.

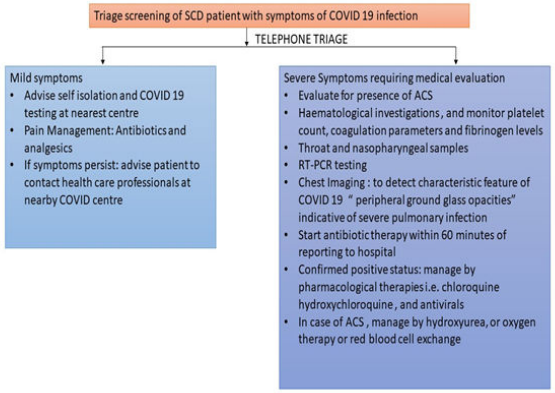

Figure 2: Shows Triage of SCD Patients During COVID 19 Pandemic.

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