Review Article

Crisis in sickle cell disease

Abstract –

Sickle cell disease is a very common inherited disorder of the hemoglobin. It is inherited in an autosomal recessive manner. Most affected are the people of African, Indian and Arabian origin. It occurs due to change in the single base pair gene wherein thymine replaces adenine in the 6^{th} codon of the beta-globin gene. This result in the sickling shape of the red blood cells. Sickle cell disease includes a variety of phenotypes like the SS, AS, Sickle-thal, SC patterns, etc. Sickle cell- SS pattern also termed as sickle cell anemia is the most common of the lot and also the cause the most mortality, morbidity and decrease in the quality of life. The sickling pattern of the red blood cells occludes the blood vessels and leads to a wide range of complication in the affected individuals. These complications can be seen in number of different systems of the body and also multiple systems at the same time. These complications are termed as crisis, which then include the vaso-occlusive crisis, acute chest syndrome, splenic sequestration crisis, etc. These crises can negatively affect the quality of life to a large effect, but are also largely controllable or rather delayed and effectively managed as far as possible with reduced effect in the normal well being. Hence the knowledge about these crisis and their treatment is an important aspect of medical practice, especially in the countries where this disorder is commonly seen. Here in this review article we aim to highlight the major crises seen in sickle cell disease and their treatment in brief.

Introduction –

Sickle cell disease (SCD) is a group of inherited disorder of the red blood cell. It is commonly seen in the population of the Indian, African and Arabic regions. (1) Sickle cell disease can lead to anemia and various crisis associated with it known as the sickle cell crisis. Acute painful crisis also known as the vasocclusive crisis is the clinical feature that often leads to hospitalization of the affected. The various forms of sickle cell crises include the vaso-occlusive crisis (VOC) , splenic sequestration crisis, aplastic crisis, hepatic crisis, hemolytic crisis, acute chest syndrome and dactylitis. Some other complications of sickle cell disease include venous thromboembolism, priapism, stroke, avascular necrosis, osteomyelitis, pneumonia, meningitis and sepsis. In this article we review the evaluation and treatment of sickle cell crisis and also will discuss the role of the multidisciplinary approach in evaluating and treating this condition.(2)

Etiology-

An autosomal recessive disorder resuting due to gene mutation is the sickle cell disease.A nucleotide mutation on chromosome 11 causes glutamic acid to be replaced with valine at 6^{th} position of the beta-globin unit. The physical characteristics of globin chain are thereby changed. The co-factors that incite this change in red blood cells include dehydration, hypoxia, stress, infections and cold weathers.(2)

Pathophysiology-

The sickling of the red blood cells in the homozygous form of sickle cell occurs due to the polymerization of the hemoglobin caused by the risk factors mentioned above. The rigidity of the erythrocytes increases. The sickled red cells then interact endothelium by the virtue of release of the adhesion molecules.(3) The heterocellular aggregates are then formed which then causes the occlusion of the small vessels and thus then result in hypoxia. By virtue of this pathophysiology a vicious cycle is the triggered which leads to increased formation of hemoglobin S and then also the release of free radicals and inflammatory mediators which then promote the reperfusion injury. Oxygen is then released by virtue of hemoglobin binding to nitric oxide (NO), which is a potent vasodilator. The pathophysiology is also associated with increased adhesiveness of neutrophil, increased activation of platelets, hypercoagubility and nitric oxide binding. The activated neutrophils then causes occlusion of the microvasculature. The inflammatory mediators released lead to a pro inflammatory state that further adds on to the complications of vaso-occlusion. The microbiome of intestine is also postulated to a potential trigger for the VOC.(4) While few of the triggers for pain like dehydration, cold temperatures etc are identifiable, the triggers for many episodes go unnoticed.(5)

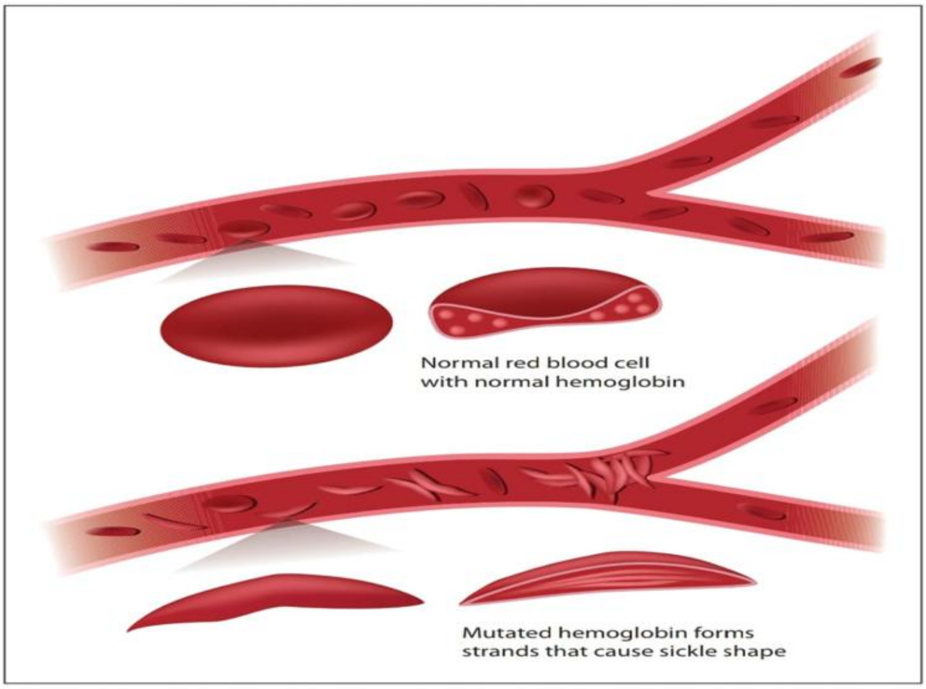

Figure-1(6)

Normal red blood cells are round and flexible and move easily through blood vessels. In sickle cell disease, abnormal hemoglobin causes red blood cells to become sickle (or crescent) shaped and rigid. The misshapen cells can easily become lodged in smaller blood vessels, depriving tissues of oxygen and triggering painful episodes. Illustration by Alila Medical Media.

Clinical features-

Sickle cell disease in many countries of North America and Europe by virtue of multiple studies, has been identified by chronic and prolonged anemia, hemolysis, sepsis and recurrent episodes of VOC. The last of which presents with pain and a systemic inflammatory response.

Vaso-occlusive crisis and bone disease-

The most common cause of hospitalisation of a sickle cell patient is the painful condition known as vaso occlusive crisis. Some children might present with bony infarction of digits or dactylitis, swelling of toes and fingers with or without irritability. The infarction may also act like osteomyelitis and can affect any joint or bone.(7) The infarction of the long bones along their articular surfaces and heads can result into avascular necrosis, as a consequence of repeated episodes of vaso-occlusive crisis.(8) The avascular necrosis can also be associated with hemoconcentration and a suoer added presence of alpha-thalassaemia.(9) A total incidence of 12 percent of septic arthritis and osteomyelitis, was noted by a cohort study in the metropolitan, France, which were mainly caused by *Salmonella* spp, Gram negative enteric bacilli and Staph.*aureus* and Gram negative enteric bacilli.(10) Osteoporosis and osteopenia are commonly seen patients in of sickle cell by virtue of their vertebral collapse.(11)

Acute chest syndrome –

The 2nd most common reason for hospitalisation of a patient of sickle cell disease is the Acute chest syndrome (ACS). Its features include systemic hypoxia, intrapulmonary ischemia and infarction. The chest xray will reveal pulmonary infiltrates.(12) Its pathogenesis may also include fat embolism caused by fat embolism and community acquired pneumonias. 50% of sickle cell children according to a recent study were reported with recent pulmonary events when they were studied under follow up over a mean period of 21 months. It was also seen that the ACS was twice as common in children suffering with a super-added asthma.(13) The other risk factors that promoted ACS include a raised tricuspid regurgitant jet velocity (TRV) and a high total leukocyte count.(14) Raised TRVs have not been reported to increase the chances of morbidity in children as the contrary in adults, but in of the studies done recently, having raised TRVs did result in having a lesser tolerance to exercise, which eventually meant that the valve condition might as well progress during childhood (15)(16).

Septicemia-

Early in the age there are evidence of a decreased functioning of the spleen. Usually there is a functional asplenia by around six months to three years of life. This also renders them to have an increased chance of having infections, with the cause most likely being malaria and the encapsulated bacteria.(17) In countries with high income, the deaths due to sepsis were significantly decreased once screening of newborn along with the vaccination with prophylactic penicillin were introduced. The morbidity and mortality were further reduced following the introduction of vaccination against *Streptococcus pneumoniae and Haemophilus influenza*e.(18) None the less, there still is are high chances of contacting with bacterial infections and increased risks for morbidity and morbidity in certain sections of world due to development of resistance to penicillin and poor compliance to these vaccinations and newborn screening along with hyposplenism.(19)

Sequestration crisis –

It can be defined as the acute increase in the size of spleen with a reduction in the hemoglobin concentration by at-least 2 gm% from baseline with a raised or normal retic count.(19) Splenic sequestration can also lead to hypovolemic shock followed by death within a short span of time. It may present between 3 months to 6 years of age, but rarely noticed beyond six years of age with a chance of recurrence seen in around 50 percent of them.(20) Early transfusing of blood can act as a life saviour.(21) Another sequestration that can be life threatening is the hepatic sequestration. It can be caused by the blocking of the blood flow of the sinusoids of the liver due to the sickled RBCs. These patients usually present with a tender and enlarged liver along with reduced hemoglobin count and reticulocytosis.(22) The mainstay of the treatment though is supportive care, administration of analgesia and along with/without blood transfusion can relieve pain and symptoms and reduce danger to life.(23)

Aplastic Crisis

Aplastic crisis in sickle cell patients may present with a sudden fall in hemoglobin levels along with sudden onset of weakness along with reticulocytopenia. It is seen to occur following an infection by the viruses like parvovirus B19 and few others, which supress the production of RBCs by supressing the bone marrow functioning. The infection usually last for seven to ten days and is usually self limiting.(18)

Hemolytic Crisis

An sudden fall in the hemoglobin concentration present the hemolytic crises, commonly seen in the patients suffering from a super-added deficiency of G-6-PD enzyme.(24)

Others

Some other presentations of the VOC include the avascular necrosis of the head of femur, priapism, renal complications and proliferative retinopathy.

Evaluation –

Evaluation of a patient having sickle cell crisis includes routine investigations such as complete blood count, differential blood count with peripheral smear, reticulocyte count to check ongoing hemolysis, metabolic panel like LFT (liver function test), etc. Inflammatory markers like C-reactive protein, serum ferritin, procalcitonin and Cultures such as blood and urine cultures can also be sent to identify and the source for fever and infection. The diagnosis of ACS can be done and supported by a chest x-ray. In case cholelithiasis is suspected an abdominal ultrasound can be done. Arterial blood gas can be evaluated in case of impending respiratory failure and hypoxemia.(25) In the case that a stroke is suspected neuroimaging should be done.

Treatment –

Vaso-occlusive Crisis Management

Early assessment of pain along with the initiation of pain-killers like analgesics offers relief of symptoms. The analgesics can be administered either orally, intravenously (IV), intramuscularly or even intranasally, etc. depending upon the clinical condition of patient. Many of the protocols prefer administration of parenteral opioid pain killer, like the morphine at a dose of 0.1 mg per kg per iv or subcutaneous (SC) every twenty minutes, followed by maintaining its effect by dose of 0.05-0.1 mg per kg every two to four hourly, either intravenous or subcutaneous or per oral. In case the pain persist even PCA pump can be used. The general vitals of the patient which will also include the oxygen saturation levels of the patient should be closed monitored along with increase or decrease in the pain sensation.(25) If the general condition has improved and the patient has no signs of infectivity along with reduction in the pain intensity the patient can be discharged from hospital.(26) But if there is no resolution of the intensity of pain or there are signs of infection, the patient requires a prolonged hospital stay along with increased or stronger dosage of analgesics. At times he/she may even require exchange transfusion. Tinzaparin, in a randomized control study, was found to reduce the duration of pain with its effect being attributed to its effect on the cellular factors. It has been also seen to have very less side effects along with reduced need to do close monitoring. The other adjuvant therapies include the use of hydroxyurea, anxiolytics, anti-emetics and anti- histaminics.(27) But, despite all these measures, maintaining hydration and also identifying other cause of pain remain of utmost importance.

The other crisis like sequestration crisis and ACS, supportive management with judicious use of fluid, oxygen and transfusing of blood products may be needed. The monitoring of the patient will be needed along with also preventing excessive sedative effect of the drugs.(28)ACS may need the administration of antibiotics empirically along with analgesics with/without exchange transfusion. Incentive spirometry will also help in the cause.

Splenic sequestration and aplastic crisis will require aggressive management with hydration and transfusion of blood products along with other supportive therapy.(25)

Hemoglobin F Production

Hydroxyurea

The patients of the Arab-Indian origin had high levels of Hemoglobin F (HbF) with a mild clinical form of the disease. While those heterozygotes who had high levels of Hb F by virtue of their hereditary persistence also had mild forms of the disease. Hence, it was interpreted that the induction of HbF in patients who's HbF production had been reduced naturally might as well benefit these patients and reduce the severity of the disease.(29)

This drug, hydroxyurea is seen to induce the HbF production which then reduces the polymerisation of the HbS and with the ultimate result being the reduced sickling. Hydroxyurea were well in use by the early 1990s. It also causes the reduced expression of the adhesion molecules on the RBCs and reduction in the numbers of monocyte, neutrophil, platelets and reticulocyte counts which may result in reduced viscosity of blood, with lesser damaging cell to cell interactions along with lesser hemolysis. All this ultimately leads to the reduction in the episodes of vaso-occlusive crisis or ACS, which till then reduce the need of hospitalizations and blood transfusions. (30)

noted in a discussion of hydroxyurea use in sickle cell disease, "true effectiveness [of any drug] is dependent upon utilization in real clinical practice." In one study, conducted by Brandow and Panepinto, they noted that only 30 percent of the individuals eligible to take the drug were actually receiving it. This decreased use of the drug was attributed to the fear of its side effects like bone marrow suppression, effects on fertility, increased risk of malignancy and teratogenesis.(31)

The criteria for starting of hydroxyurea is as follows : (32)

- Patients who have ≥3 moderate to severe pain episodes in a 12-month period
- Patients who have a history of stroke and a contraindication to chronic transfusions (as an alternative to receiving no transfusion)
- Children who have a history of acute chest syndrome or symptomatic anemia
- Infants and children 9 months of age or older who are asymptomatic or have infrequent pain episodes

Differential diagnosis-

Since the Vaso-occlusive crisis will present with severe pain and a relative paucity of objective clinical signs. Its Differential diagnosis will include clinical conditions specific to the site of the pain like for example a patient presenting with abdominal pain can mimic acute abdomen and other conditions like that of acute pancreatitis, acute appendicitis, pyelonephritis, hepatobiliary diseases and pelvic inflammatory disease. Persistent local bone pain may also mimic the Avascular necrosis and acute osteomyelitis.

Conclusion:

This review article thus interprets how the recent knowledge of the disease's pathophysiology and its treatment methods intersect. Even though the research on sickle cell has blossomed heaps and bounds, but there still is lots of scope for clinical trials to be conducted and subjected to more strenuous examination and analysis than have been used in the past.

References –

1. Lim SH, Fast L, Morris A. Sickle cell vaso-occlusive crisis: it's a gut feeling. J Transl Med. 2016 Dec 1;14(1):334.

2. Hiran S. Multiorgan dysfunction syndrome in sickle cell disease. J Assoc Physicians India. 2005 Jan;53:19–22.

3. Jeremiah ZA. Abnormal haemoglobin variants, ABO and Rh blood groups among student of African descent in Port Harcourt, Nigeria. Afr Health Sci. 2006 Sep;6(3):177–81.

4. Mehta SR, Afenyi-Annan A, Byrns PJ, Lottenberg R. Opportunities to improve outcomes in sickle cell disease. Am Fam Physician. 2006 Jul 15;74(2):303–10.

5. Porter M. Rapid Fire: Sickle Cell Disease. Emerg Med Clin North Am. 2018 Aug;36(3):567–76.

6. Tanabe P, Spratling R, Smith D, Grissom P, Hulihan M. CE: Understanding the Complications of Sickle Cell Disease. AJN Am J Nurs. 2019 Jun;119(6):26–35.

7. Berger E, Saunders N, Wang L, Friedman JN. Sickle cell disease in children: differentiating osteomyelitis from vaso-occlusive crisis. Arch Pediatr Adolesc Med. 2009 Mar;163(3):251–5.

8. Mahadeo KM, Oyeku S, Taragin B, Rajpathak SN, Moody K, Santizo R, et al. Increased prevalence of osteonecrosis of the femoral head in children and adolescents with sickle-cell disease. Am J Hematol. 2011 Sep;86(9):806–8.

9. Adekile AD, Gupta R, Yacoub F, Sinan T, Al-Bloushi M, Haider MZ. Avascular necrosis of the hip in children with sickle cell disease and high Hb F: magnetic resonance imaging findings and influence of alpha-thalassemia trait. Acta Haematol. 2001;105(1):27–31.

10. Neonato MG, Guilloud-Bataille M, Beauvais P, Bégué P, Belloy M, Benkerrou M, et al. Acute clinical events in 299 homozygous sickle cell patients living in France. French Study Group on Sickle Cell Disease. Eur J Haematol. 2000 Sep;65(3):155–64.

11. Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol. 2005 May;129(4):482–90.

12. Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med. 2012 Jun 1;185(11):1154–65.

13. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood. 2006 Nov 1;108(9):2923–7.

14. Paul R, Minniti CP, Nouraie M, Luchtman-Jones L, Campbell A, Rana S, et al. Clinical correlates of acute pulmonary events in children and adolescents with sickle cell disease. Eur J Haematol. 2013 Jul;91(1):62–8.

15. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004 Feb 26;350(9):886–95.

16. Gordeuk VR, Minniti CP, Nouraie M, Campbell AD, Rana SR, Luchtman-Jones L, et al. Elevated tricuspid regurgitation velocity and decline in exercise capacity over 22 months of

follow up in children and adolescents with sickle cell anemia. Haematologica. 2011 Jan;96(1):33–40.

17. McAuley CF, Webb C, Makani J, Macharia A, Uyoga S, Opi DH, et al. High mortality from Plasmodium falciparum malaria in children living with sickle cell anemia on the coast of Kenya. Blood. 2010 Sep 9;116(10):1663–8.

18. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood. 2010 Apr 29;115(17):3447–52.

19. Ellison AM, Ota KV, McGowan KL, Smith-Whitley K. Epidemiology of bloodstream infections in children with sickle cell disease. Pediatr Infect Dis J. 2013 May;32(5):560–3.

20. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. Br J Haematol. 2014 Jul;166(2):165–76.

21. Emond AM, Collis R, Darvill D, Higgs DR, Maude GH, Serjeant GR. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. J Pediatr. 1985 Aug;107(2):201–6.

22. Norris WE. Acute hepatic sequestration in sickle cell disease. J Natl Med Assoc. 2004 Sep;96(9):1235–9.

23. Gardner K, Suddle A, Kane P, O'Grady J, Heaton N, Bomford A, et al. How we treat sickle hepatopathy and liver transplantation in adults. Blood. 2014 Apr 10;123(15):2302–7.

24. Quinn CT, Lee NJ, Shull EP, Ahmad N, Rogers ZR, Buchanan GR. Prediction of adverse outcomes in children with sickle cell anemia: a study of the Dallas Newborn Cohort. Blood. 2008 Jan 15;111(2):544–8.

25. Chou ST, Fasano RM. Management of Patients with Sickle Cell Disease Using Transfusion Therapy: Guidelines and Complications. Hematol Oncol Clin North Am. 2016 Jun;30(3):591–608.

26. Ballas SK. Current issues in sickle cell pain and its management. Hematol Am Soc Hematol Educ Program. 2007;97–105.

27. Robieux IC, Kellner JD, Coppes MJ, Shaw D, Brown E, Good C, et al. Analgesia in children with sickle cell crisis: comparison of intermittent opioids vs. continuous intravenous infusion of morphine and placebo-controlled study of oxygen inhalation. Pediatr Hematol Oncol. 1992 Dec;9(4):317–26.

28. Simon E, Long B, Koyfman A. Emergency Medicine Management of Sickle Cell Disease Complications: An Evidence-Based Update. J Emerg Med. 2016 Oct;51(4):370–81.

29. Gardner RV. Sickle Cell Disease: Advances in Treatment. Ochsner J. 2018;18(4):377–89.

30. Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood. 2010 Mar 25;115(12):2354–63.

31. Brandow AM, Panepinto JA. Hydroxyurea use in sickle cell disease: the battle with low prescription rates, poor patient compliance and fears of toxicities. Expert Rev Hematol. 2010 Jun;3(3):255–60.

32. Evidence-based management of sickle cell disease: expert panel report, 2014. National Heart, Lung, and Blood Institute www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Published September 2014. Accessed October18, 2018. In.