Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/19805
DOI URL: http://dx.doi.org/10.21474/IJAR01/19805

RESEARCH ARTICLE

HOSPITALIZATION TRENDS AND MORBIDITIES IN SICKLE CELL ANEMIA: A CENTRAL INDIA PERSPECTIVE

Dr. Piyush Mutyalwar[1], Dr. Bhalchandra Falke[2] and Dr. Avinash Tekade[1]

1. Department of Physiology, Government Medical College, Chandrapur.
2. Department of Pediatrics, Government Medical College, Chandrapur.

Manuscript Info

Manuscript History
Received: 31 August 2024
Final Accepted: 30 September 2024
Published: October 2024

Key words:-
Sickle Cell Disease (SCD), Vaso-Occlusive Crisis (VOC), Morbidity profile, Pediatric Hospitalization, Painful crisis, Hemolytic Crisis, Acute Febrile Illness, Splenic Sequestration, Acute Chest Syndrome (ACS), Severe Anemia, Presenting Symptoms, Hospital-Based Study

Abstract

Background and Objective: Sickle cell anemia is a common genetic disorder characterized by recurrent crisis, complications, and significant morbidity, particularly in children. This study aimed to investigate the pattern, type, and frequency of crisis, systemic complications, and morbidity profile in hospitalized children with sickle cell disease (SCD) at Government Medical College and Hospital, Chandrapur.

Methods: A prospective study was conducted over a year, from November 2023 to October 2024, involving 133 hospitalized children aged 0-12 years diagnosed with SCD, including both previously and newly diagnosed cases through Hemoglobin Electrophoresis. The study collected data on hospitalization frequency, crisis types, systemic complications, and morbidity. Children were evaluated for symptoms, clinical findings, and laboratory parameters related to sickle cell crisis and organ failure.

Results: The most common presenting symptom was pain, observed in 53.94% of the children, with bone pain, abdominal pain, and joint pain being the predominant types. Fever seen in 45.18% and pallor in 26.75% were the next most frequent symptoms, followed by jaundice in 21.05% and respiratory complaints such as cough in 13.60% and breathlessness in 11.40% patients. The majority of hospitalizations were due to vaso-occlusive crisis as seen in 53.94%, followed by severe anemia in 35.52% and acute febrile illness in 43% of patients. Systemic complications included hepatomegaly (65.78%), splenomegaly (45.61%), and respiratory distress (8.33%). Acute chest syndrome (3.55%), hemolytic crisis (14.9%), and splenic sequestration crisis (5.70%) were also notable findings.

Conclusion: In children with sickle cell anemia, VOC, febrile illnesses, and severe anemia are the leading causes of morbidity and hospitalization. Bone and abdominal pain were common symptoms, frequently associated with fever. The study highlights the need for community-based screening, parental counseling, and antenatal interventions to reduce the burden of sickle cell disease in tribal populations.

Corresponding Author:- Dr. Piyush Mutyalwar
Address:- 7, Vidarbha Housing Board Colony, Ramnagar, Chandrapur-442401, Maharashtra, India.

……..

Introduction:-

Sickle cell disease is most common inherited disorder of Hemoglobin which cannot be cured but its variation and variable manifestations can be effectively treated and often prevented.' Though stem cell or bone marrow transplants are the cure for SCD they are not done often because of significant risk invoved. Sickle-cell anemia (also known as sickle-cell disorder or sickle-cell disease) is genetic condition due to a hemoglobin disorder - inheritance of mutant hemoglobin genes from both parents. Such hemoglobinopathies, mainly thalassaemias and sickle-cell anaemia, are globally widespread. About 7% of the world's population carries genes responsible for hemoglobinopathies.

Each year about 300 000 to 500 000 infants are born with major hemoglobin disorders including more than 200 000 cases of sickle-cell anemia in Africa. Sickle cell syndromes are more frequent and constitute 70% of affected births worldwide.[1]

SCD, as a genetic condition, is widespread among the tribal population in India where about 1 in 86 births among Scheduled Tribes have SCD. Hemoglobinopathies are more widely prevalent among the tribal population than the non-tribal communities in India. The disease has a higher prevalence in States like Madhya Pradesh, Gujarat, Maharashtra, Rajasthan, Chhattisgarh, Bihar, Jharkhand, West Bengal, Odisha, Tamil Nadu, Telangana, Karnataka, Assam, Andhra Pradesh, Uttarakhand, Uttar Pradesh, and Kerala.[2]

Sickle cell anemia is a disease that is responsible for considerable amount of morbidity and mortality in children in Central India and Vidarbha and particularly in area near Wardha.[3] The overall prevalence of SCD was 2.9%. in Wardha district[4] which is adjacent to Chandrapur.

Nearly 4% (approximately 2,000) were identified as sickle cell trait carriers; while 181 individuals were diagnosed with sickle cell disease in initial phase of the survey successfully screened 59,828 individuals by GMCH Nagpur.[5]

Various studies have been performed for knowing the incidence of Sickle cell disease in various communities but no study has been performed for knowing the incidence in this district.[5, 8]

In most countries where sickle-cell anemia is a major public health concern, its management has remained inadequate, the basic facilities to manage the patients are usually absent, systematic screening is not a common practice and the diagnosis is usually made when a patient presents with a severe complication. Simple, cheap and very cost-effective procedures such as the use of penicillin to prevent infections are not widely available in many countries.[2]

In India National programme to improve care of all Sickle Cell Disease patients for their better future and to lower the prevalence of the disease through multi faceted coordinated approach towards screening and awareness strategies was started in 2016. There vision is to eliminate sickle cell disease as public health problem in India before 2047.[6]

According to ICMR there are around 12000 Sickle Cell Disease patients in Vidharbha region and over 3000 Sickle Cell Disease patients in Chandrapur alone who require optimum management and there may be many more who are undiagnosed. Estimated numbers of sickle cell carriers in Vidharbha is aprox. 4,00,000 and there is a lack of diagnostic and management facilities in most of these places.[7]

The complex nature of disease with its variability in clinical features from region to region along with various risk factors for hospitalization needed to be thoroughly investigated and this study tried to analyze clinical spectrum of diseases in our area where many patients are brought in OPD and hospitalized for broad clinical features.

Aims and Objectives:-

-To study the pattern, type and frequency of crisis in sickle cell anemia children in hospitalized children
-To study systemic complications of Sickle cell anemia
-To study morbidity profile of children with sickle cell disease

Materials and Methods:-

The present study was carried out in Department of Pediatrics of Govt. Medical College and Hospital, Chandrapur from November 23 to October 24

Selection of Cases

The cases of Sickle cell disease admitted to pediatric ward between 0- 12yrs in 1yr duration were included in this prospective study.

Sample Size

Comprised of children with Sickle cell disease (including diagnosed and newly diagnosed children by Hemoglobin Electrophoresis) hospitalized in pediatric wards in Govt. Medical College and Hospital during study period.

Sampling Method

A consecutive 133 hospitalized children satisfying the selection criteria were recruited.

Inclusion Criteria

1. Patients of Sickle cell disease and sickle thalassemia admitted to pediatric ward, GMC Chandrapur from November 23 to October 24.
2. Patients of either sex male/female.
3. Age group 0-12 years.
4. Children those were willing to participate in study.

Exclusion Criteria

1. Children who did not consent to participate in study
2. Patient attending Out Patient Department only.
3. Patient above 12 yrs of age.
4. Patients of Sickle cell trait.

Method:-

Children with Sickle cell disease, already diagnosed and diagnosed during study period by Hemoglobin Electrophoresis and HPLC were involved in the study. Their frequency of admission, duration of hospitalization, number of blood transfusion, general and physical examination was carried out and growth was assessed. The hemoglobin and hematocrit along with battery of investigations (given below) to detect crisis and organ failure were carried out during study period were noted and these were our main outcome variables.

The data of every admission was entered in pre designed proforma. Data included complete details i.e. age, sex, caste, consanguinity and residence along with various risk factors.

Throughout the study patients with SS pattern on electrophoresis or HPLC were called as ‘disease’.

Sickling was done by using freshly prepared 2% sodium metabisulphite solution followed by sealing the assembly and observing for early sickling after 30 min and late after 24 hours.

Hemoglobin electrophoresis was done on cellulose acetate test strip with Tris phosphate buffer at a pH of 8.4.

Following investigations were done for all patients at the first visit and in between whenever required:

- Blood Group
- Complete Haemogram (Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, absolute platelet count) by Mythic 18 Fully automated 18-parameters Haematology analyser manufactured by Orphee, Switzerland. Reticulocyte count
- Sickling (early and late)
- Hemoglobin Electrophoresis by Hemoglobin electrophoresis 606 manufactured by Systronics, India.
- HPLC by D-10 Hemoglobin Testing system by D-10 BIORAD.

Following investigations were carried out as and when required:

Liver function tests
- Kidney function tests
- Serum electrolytes
- Urine routine and microscopy and culture sensitivity (Nephrotic Syndrome and Urinary tract infection)
- Pulse oxymetry (In distress)
- X-Ray Chest (Acute Chest Syndrome, Pneumonia)
- Ultrasound examination of abdomen
- Widal and Blood Culture (If infection is suspected)
- Cerebrospinal fluid biochemical examination, microscopy and culture sensitivity (Meningo encephalitis, Febrile Convulsions).
- Stool routine and microscopy (Acute gastroenteritis).
- Ophthalmology Consultation (Raised intra-cranial tension, neurological signs, micro hemorrhages in retina).
- Surgery consultation (severe form of sequestration crisis, acute cholecystitis, mesenteric ischemia).
- Orthopedic consultation (if surgical intervention is needed in cases such a osteomyelitis)
- Electro Encephalogram (in case of suspected central nervous system involvement, convulsions)-Computed tomography scan (in case of convulsions or neurodeficit).

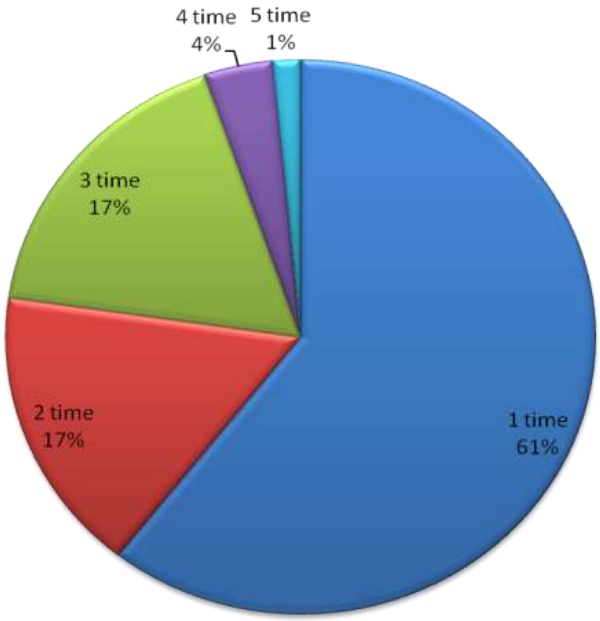
Ethical consideration

Ethical clearance for conducting the study was obtained from the Institutional Ethics Committee. Information obtained during the study is confidential. Written informed consent in the local language was obtained from the parents or guardians of each enrolled patient who were willing to get enrolled in the study after explaining to them the nature of the study

Observations and Results:-

Total 133 cases were enrolled in study which required hospitalization in 1 year.

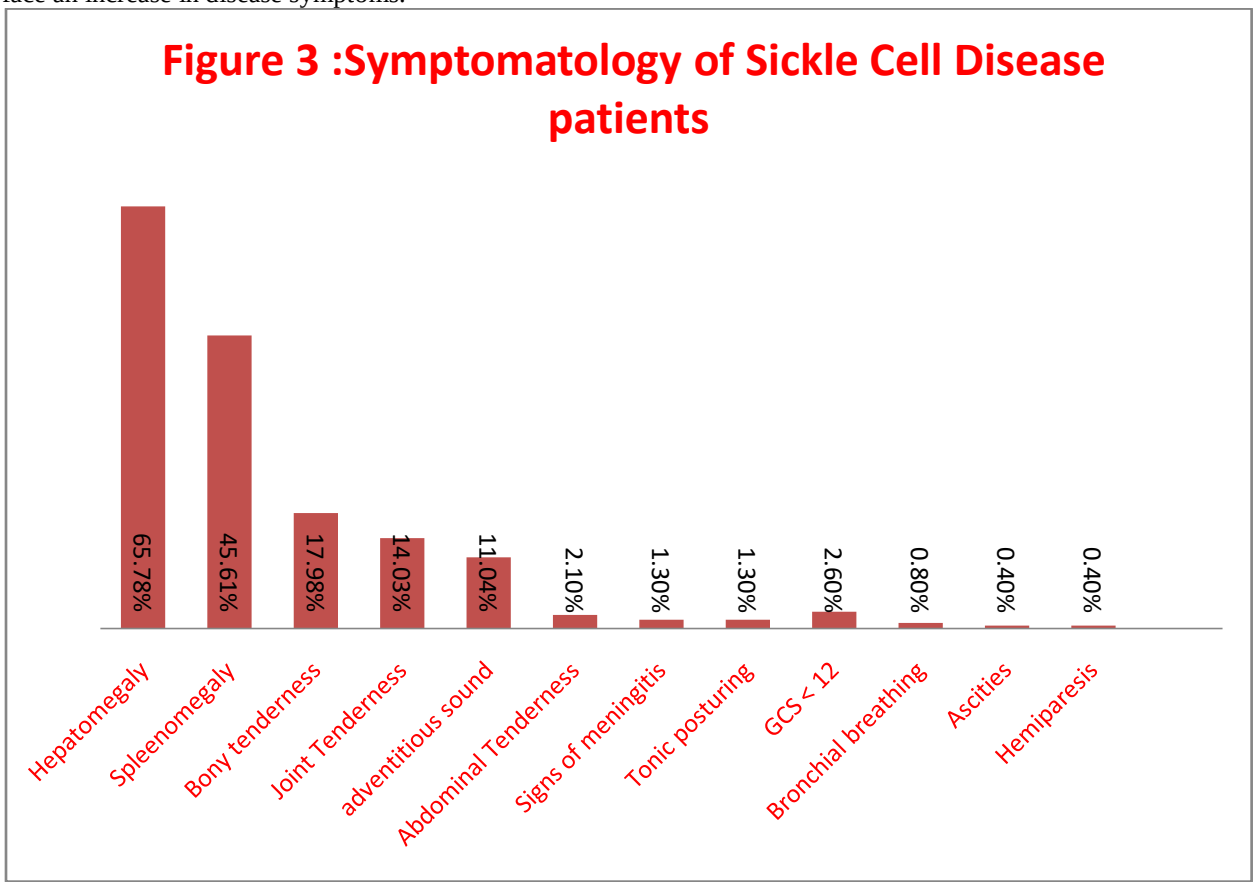
Fig 1 : Number of Hospitalisation



According to Figure 1, 180 patients 60.15% (n=80) were admitted for 1 time during study period while 0.75% (n=1) patient required 6 times admission in hospital during study period. Thus 133 patients required around 228 admissions in 1 year.

Fig : 2 Age of patient needing Hospitalisation

Fig 2 shows the age distribution for hospitalizations among sickle cell patients across different age groups. Here's a breakdown of what it indicates: The age group **6-9 years (37.20%)** within this age range have largest percentage of hospitalization suggesting that children with sickle cell disease may experience more frequent or severe health issues that require hospitalization around this period. This age group might be more vulnerable to complications or might face an increase in disease symptoms.



According to Figure 3 Pain was most important complaint for admission. Overall 123 patients had the chief complaint of pain. Amongst that Bone pain was seen as complaint in 40(17.5%), Pain abdomen in 37(16.22%), joint pain in 19 (8.33%), pain digits in 16(7%), Chest Pain in 11(3.9%) and Backache in 9(3.5%) patients. After pain the patient requiring hospitalization with Sickle Cell anemia was fever in 103 patients (45.15%) followed by paleness in 85 (37.28%) patients. Out of 85 children who presented with pallor 61 (26.75%) patients had progressive pallor and 24 (10.52%) patients had sudden onset pallor.

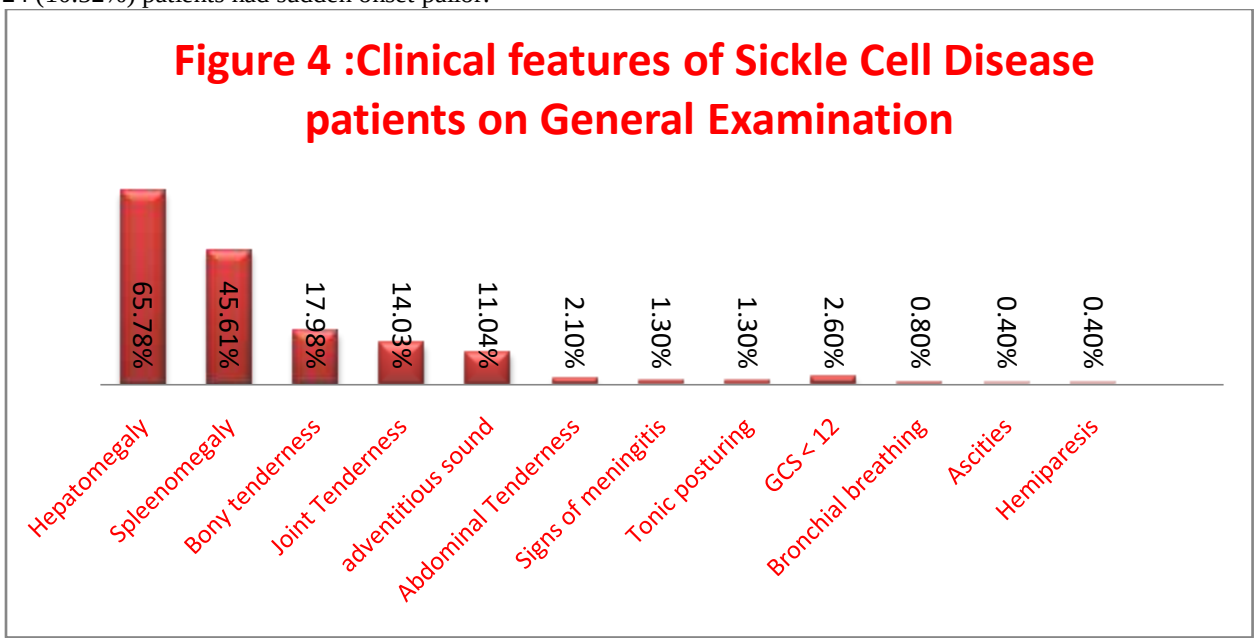


Figure 4 suggest on general examination most of the patients with disease were admitted with tachycardia in 184(80.70%), pallor in 119(52.19%), fever in 99(43.42%), hemolytic facies in 49(21.49%), icterus 34 (14.91%), tachypnoea 31(13.59%). Joint swelling/tenderness in 21(9.2%) and respiratory distress in 19 (8.33%) were other common signs. All the signs of infection like fever, tachycardia, lymphadenoapthy, tachypnoea, icterus, and joint swelling tenderness were significantly more in patients with sickle cell disease.

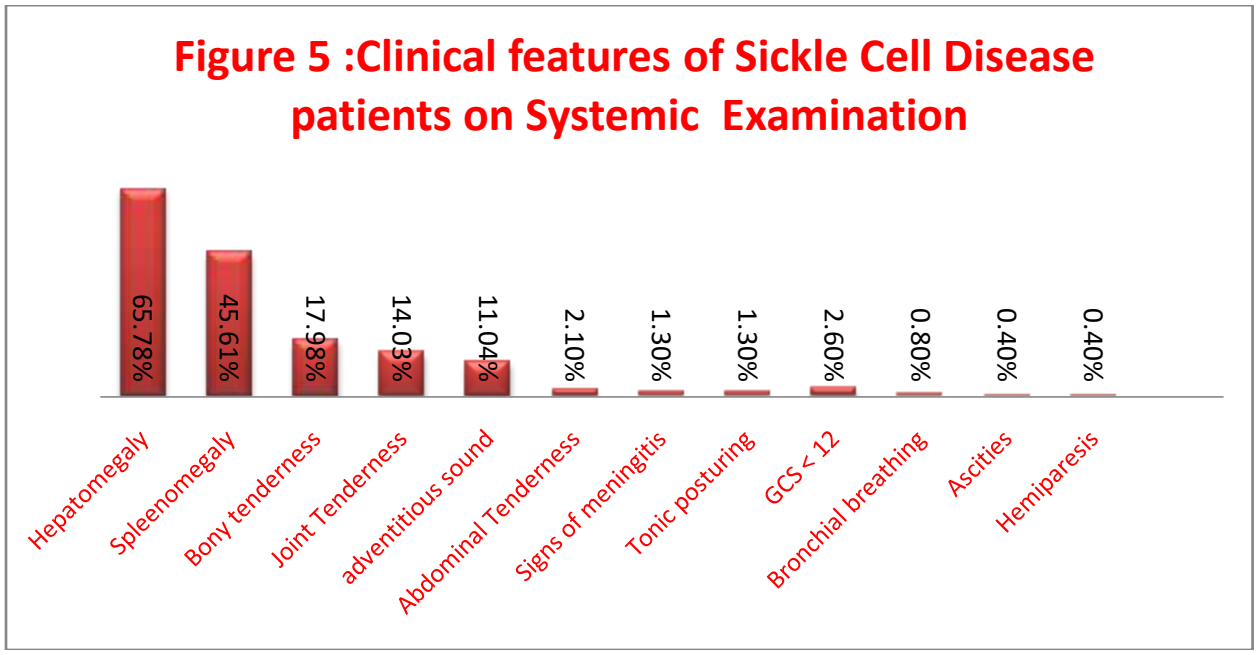


Fig 5 suggest Hepatomegaly was most common finding on systemic examination seen in 150(52.08%) followed by splenomegaly in 94 patients. Hemiparesis was seen in 1 patient. Bony tenderness was seen in 17.98% while joint tenderness was seen in 14.03% of the cases.

Discussion:-

Table 1:- Morbidity Profile of patients hospitalized with SCD.

CRISIS/CAUSE	Our Study	Singh et al[8]	El-Ghany et al[9]	Jain D et al[10]	N. Madhavi et al[13]	Kamble M et al[3]	Patel KG et al[14]
VOC*	53.94%	36.75%	64.09%	31%	60%	23.3%	39%
AFI*	43%	34.42%	24.5%	31%	40%		36.06%
ACS*	3.55%	1.8%	18.1%	3.3%	8%		1%
Splenic sequestration	5.70%	9.77%		4%		6%	
Hemolytic Crisis	14.9%	1.8%	12.8%			23%	
Severe anemia	35.52%	39.06%		30%			39.34%
Aplastic crisis	3%	22%					
Stroke	0.4%	1.4%		0.6%			

*VOC- Vasoocclusive Crisis, AFI- Acute febrile Illness, ACS- Acute Chest Syndrome

Male 75 (56.33%) to Female (43.67%) ratio was 1.29:1. This finding was consistent with Singh A et al[8], Abd El-Ghany et al[9,] Jain D[10], Tayade NB[11], Parekh A et al[12], N. Madhavi [13] and Patel KG[14]. Less Female preponderance is due to Nitric Oxide bioavailability and Nitric oxide responsiveness is greater in women than in men with sickle cell disease and determines adhesion molecule expression. Endothelium-dependent blood flows are largely non-NO mediated in male patients. These results provide a possible mechanism for reported sex differences in sickle cell disease morbidity and mortality.[15]

Vaso-Occlusive Crisis

A vaso-occlusive crisis (VOC), also known as a sickle cell crisis, is a painful complication of sickle cell disease that occurs when sickled red blood cells (RBCs) get stuck in blood vessels and block blood flow.

In the homozygous form of sickle cell disease, inciting triggers (eg, hypoxia, dehydration, exposure to cold or weather changes, stress) cause hemoglobin polymerization, resulting in the sickling and increased rigidity of erythrocytes.[19] The subsequent deoxygenation of erythrocytes, the sickling, and now damaged red blood cells attach to the endothelial wall, forming a mass comprised of leukocytes and platelets with adhesion molecules P and E selectins. The formation of these heterocellular aggregates physically causes small vessel occlusion and resultant local hypoxia. This process triggers a vicious cycle of increased HbS formation and releases inflammatory mediators and free radicals, contributing to reperfusion injury. Hemoglobin also binds to nitric oxide (NO), a potent vasodilator, and releases oxygen.

Other pathological events include increased neutrophil adhesiveness, nitric oxide binding, platelet activation, and hypercoagulability. Further microvascular occlusion occurs due to activated neutrophils. Inflammatory mediators (eg, plasma cytokines) lead to a proinflammatory state, causing further complications of vaso-occlusion. Experts postulate that the intestinal micro biome may be a potential trigger for the vaso-occlusive crisis.[20] While some triggers (eg, cold temperature, dehydration, low humidity, stress) for pain are identifiable, most episodes do not have an identifiable cause.[21]

Vaso Occlusive crisis was most common diagnosis at the time of admission along with most common cause of morbidity in patients with SCD. 53.94% of the patients in our study shown VOC. Morbidity pattern of all previous studies performed in this region showed similar figures of admission for VOC. Kamble M et al[3] had 23.3%, Jain D et al[10] had 31%, Singh et al[8] had 36.75% and Patel KG et al[14] had 39%. While study performed in Vishakapatnam by N Madhavi et al had 60% and Saudi Arab by El-Ghany et al[9] had 64.09%. Only study in India which demonstrated high figures was by N. Madhavi et al[13] and it might be due to their inclusion criteria of study which was patients admitted in PICU and not in wards.

In the first year of life one of the cardinal features is the 'hand-foot syndrome' due to vaso-occlusion of post-capillary vasculature resulting in tissue edema and pain of the extremities . Infants display their pain nonverbally with irritability and apparent 'regression' tendencies such as inability to weight bear, walk or crawl. In older children and adults, vaso-occlusive pain can affect any part of the body[17].

Acute Febrile Illness

Fever is a significant condition in children with SCD, often indicating serious underlying conditions requiring medical attention.[22] SCD children face an increased risk of invasive infection, morbidity, and mortality due to splenic dysfunction.[23] Children with severe chronic pulmonary disease are more susceptible to fatal infections due to dysfunctional antibodies and febrile conditions. Despite penicillin prophylaxis and pneumococcal conjugate vaccines reducing gram-positive pneumococcus infections, antibiotic-resistant genes and bacterial strains have increased the risk of infection, making them more vulnerable.[24]

Fever remained next major cause of admission in this study with 45.18% patients having it. This figures remains nearly consistent with all other studies, Singh A et al[8] with 34.42%, El-Ghany et al[9] with 24.5% Jain D[10] et al with 31%, and N. Madhavi[13] with 40% of patients. Various infections which caused fever in our study was LRTI in 16 patients, PUO in 15 cases and Viral fever 12 cases. Staphylococcus aureus was isolated in 5 cases, Streptococcus pneumonia in 4 and E Coli in 3 cases.

Pallor due to severe anemia

Paleness was third most criteria for admission in this study with 26.75 %(n=61) which was much less than previous study. Tayade et al shown 97.75% and , N. Madhavi[13] which shown 70%. This decrease in figure may me due to grading variation from person to person. In this study we have admitted patients with moderate pallor which means Conjunctival pallor and/or of tongue + palmer pallor plus severe pallor which is moderate pallor plus pallor of palmer creases.[18] Other common presentations were yellowish discoloration of eyes in 48 (21.05%) , cough in 31(13.59%) and breathlessness in 26(11.4%). The clinical manifestations of sickle cell disease are notoriously variable. The African patients exhibit a more severe phenotype compared with those from India or eastern province of Saudi Arabia and difference is attributed to genetic factors.

Hemolytic crisis

A hemolytic crisis is a condition where a large number of red blood cells are destroyed in a short period of time, faster than the body can produce new ones. It can lead to anemia, jaundice, and reticulocytosis.

The pathophysiology of a hemolytic crisis includes:

Hemoglobin release:

The hemoglobin, which is the part of red blood cells that carries oxygen, is released into the bloodstream. This can lead to kidney damage. Red blood cell destruction: Red blood cells can be destroyed by mechanical trauma, complement fixation, infectious agents, or membrane alterations. Macrophage destruction: Macrophages in the spleen and liver remove and destroy red blood cells that have membrane alterations. Chain of reactions: the destruction of red blood cells causes a chain of reactions that can lead to further complications. Some symptoms of hemolytic anemia include: Confusion, Increased pain, Extreme fatigue, and increased shortness of breath.Our study showed 14.9% patients of Hemolytic crisis. Singh et al showed 1.8%, El Ghany 12.8% and Kamble et al 23% patients in there study.

Hyperhemolysis syndrome (HHS) :

This is rare phenomenon of Hemolytic crisis .This is a complication of repeated blood transfusions in sickle cell disease patients. Here, hemolysis occurs in both native and donor erythrocytes. Hyperhemolysis syndrome is found within many hemoglobinopathies, although its existence in sickle cell disease is foremost. Many theories have been forwarded to explain hyperhemolysis. One belief is that erythrocytes in sickle cell disease are damaged and stressed to the extent of increased surface phosphatidyl serine. This marks then for accelerated destruction by macrophages. This accounts for the increased LDH, increased bilirubin, decreased reticulocyte count, and an unchanged Hgb A / Hbg S ratio as both the donor and the native erythrocytes are destroyed[28.] No patient was seen with HHS in our study.

Splenic Sequestration Crisis

Acute splenic sequestration crisis is generally defined as acute splenic enlargement concurrent with a fall in the hemoglobin of more than 20% from the baseline in the face of a normal or increased reticulocyte count. Within the spleen, the blood, which is directed to the red pulp flows slowly in a concentrated state as it becomes exposed to the reticuloendothelial cells of the immune system.[25]

This situation promotes a deoxygenated state within the RBC that leads to polymerization and aggregate formation of deoxygenated beta-globin. These RBCs, now sickled, are unable to pass through the small endothelial slits of the venous sinuses and rejoin the intravascular system. Typically these events self-resolve or lead to isolated areas of congestion and fibrosis, which, over time, contribute to the auto infarction of the spleen. However, in some cases, the obstruction may spread, causing the spleen to rapidly fill with RBCs which cannot flow out. A large percentage of the body's blood volume may become acutely trapped within the spleen, leading to a sequestration crisis.[26, 27]

Splenic sequestration crisis was seen in 5.7 % patients in our study which was consistent within the range of previous studies with Jain et al showing 4% and Singh et al showing 9.77%.

Acute Chest Syndrome

Acute chest syndrome is a dangerous complication of sickle cell disease characterized by a new radio density on chest imaging accompanied by respiratory symptoms and possibly fever.[29]

ACS is a form of acute lung injury in SCD. The development of ACS represents a vicious cycle of lung infarction, inflammation, and atelectasis leading to ventilation–perfusion mismatch, hypoxemia, and acute increases in pulmonary artery and right ventricular pressures. At the cellular level, in the presence of low alveolar oxygen tension, abnormal rheology of the sickled red blood cells (sRBCs) facilitates adhesion to each other, leukocytes, and the vascular endothelium, resulting in vaso-occlusion and tissue hypoxia. These interactions also cause the release of inflammatory cytokines which promote acute and chronic inflammation in the airways by virtue of being in close proximity with the vasculature.[30, 31]

3.55% of the patients in our study had Acute chest syndrome. Findings are consistent with Singh et al 1.8%, Jain et al 3.3%, Madhavi et al 8% and Patel et al 1 %. El Ghany et al shown figures of 18.1 %. This figures are high as compared to other studies performed in Saudi Arabia [32].

Aplastic Crisis

Aplasia in sickle crisis presents with sudden pallor and weakness confirmed by rapidly dropping hemoglobin levels accompanied by reticulocytopenia. The usual trigger for aplastic crisis is parvovirus B19, which directly suppresses the bone marrow, affecting RBC production, but other viral infections can also cause it.[33] Findings in our study was 3% and was very less compared to Singh et al 22 %.

Limitation

Limitation of our study is that we did not compare HbF levels in each patient with severity of painful crisis. This study was a hospital based study and hence, does not represent the true rate of events for SCD children in the general population. The study only included patients with Sickle cell patients who needed hospitalization. Lastly, the study did not consider outpatient burdens who do not visit hospitals.

Conclusion:-

Comparing various studies in other parts of India, It was found that in our study morbidity events were common in male patients in 5-12 years of age groups. In hospitalized children with sickle cell anemia, acute painful crisis was the most the common morbidity event followed by severe anemia and acute febrile events. Bone and abdominal involvement was common and mostly associated with fever, with simultaneous bilateral multiple joint involvement along with persistence of splenomegaly. It was also observed that vaso-occlusive crisis is the commonest manifestation in pediatric age group Parental counseling and antenatal screening are essential to prevent occurrence of the disease in families with an already affected child. Multipronged community awareness approach is needed. Mass screening of marriageable youth for SCD and premarital counseling should be done in the tribal population.

References:-

1. WHO resolution on Sickle Cell Disease (WHA59.20) and Thalassemia (EB118.R1), 29 May 2006. (http://www.who. int/ genomics/WHO-TIF_genetics_final.pdf)
2. https://tribal.nic.in
3. Kamble M, Chaturvedi P.Epidemiology of Sickle Cell Disease in rural hospital of Central India.Indian Pediatr 2000; 37(4): 391-6
4. Deshmukh, Pradeep & Garg, Bishan & Garg, Neelam & Prajapati, N.C. & Bharambe, M S. (2006). Prevalence of sickle cell disorders in rural Wardha. Indian Journal of Community Medicine. 31. 10.4103/0970-0218.54928.
5. https://timesofindia.indiatimes.com/city/nagpur/nearly-4-of-nagpur-found-to-be-carriers-of-sickle-cell/articleshow/111096163.cms
6. https://sickle.nhm.gov.in/sickle2.0/home/about
7. https://icmr-crmch.org/aboutus.php
8. Singh A, Bokade C, Tirpude B, et al. (May 14, 2023) Clinical Profiles of Children With Sickle Cell Anaemia Presenting With Acute Clinical Events: A Single-Center Study. Cureus 15(5): e39008. DOI 10.7759/cureus.39008Abd
9. El-Ghany et al : Analysis of Causes of Hospitalization Among Children with Sickle Cell Disease in a Group of Private Hospitals in Jeddah, Saudi Arabia: Journal of Blood Medicine 2021:12 733–740
10. Jain D, Bagul AS, Shah M, Sarathi V. Morbidity pattern in hospitalized under five children with sickle cell disease. Indian J Med Res 2013;138:317-21.
11. Tayade NB, Pande SS, Deotale MK. Clinical profile of sickle cell disease patients attending pediatric department of a tertiary care hospital and Sickle-Thal center: Across-sectional study. Iraqi J Hematol 2022;11:98-102.
12. Parekh A et al. Int J Contemp Pediatr. 2016 Aug;3(3):965-970
13. N. Madhavi : A STUDY OF CLINICAL AND HEMATOLOGICAL PROFILE IN CHILDREN AFFECTED WITH SICKLE CELL DISEASE IN TERTIARY LEVEL HOSPITAL: Int J Acad Med Pharm 2024; 6 (1); 85-90
14. Patel KG, Chaudhari C, Sharma D.A study of clinical and hematological profile of children with sickle cell disease in a tertiary care hospital,Valsad, India. Int J Contemp Pediatr 2017;4:1317-21
15. Gladwin M. T., Schechter A. N., Ognibene F. P., Coles W. A., Reiter C. D., Schenke W. H., et al.. (2003). Divergent nitric oxide bioavailability in men and women with sickle cell disease. B Circulation 107, 271–278.
16. K Swarnkar, A Kale, B Lakhkar. Clinico-Epidemiological And Hematological Profile Of Sickle Cell Anemia With Special Reference To Penicillin Prophylaxis In A Rural Hospital Of Central India. The Internet Journal of Epidemiology. 2010 Volume 9 Number 2
17. Watson R.J., Burko H., Megas H., Robinson M. The hand-foot syndrome in sickle-cell disease in young children. Pediatrics. 1963;31:975–982.
18. Regina D et al. Correlation of pallor with hemoglobin levels and clinical profile of anemia in primary and middle school children of rural Telangana. Int J Contemp Pediatr. 2016 Aug;3(3):872-877
19. 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
20. 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
21. Porter M. Rapid Fire: Sickle Cell Disease. Emerg Med Clin North Am. 2018 Aug;36(3):567-576
22. Fever among children with sickle-cell disease: findings from the General Pediatric Ward of the Owendo Pediatric Hospital in Libreville, Gabon. Koko J, Gahouma D, Ategbo S, et al. Open J Pediatr. 2014;4:262–268.
23. Incidence and predictors of bacterial infection in febrile children with sickle cell disease. Morrissey BJ, Bycroft TP, Almossawi O, Wilkey OB, Daniels JG. Hemoglobin. 2015;39:316–319
24. Practice variation in emergency department management of children with sickle cell disease who present with fever. Eisenbrown K, Ellison AM, Nimmer M, Badaki-Makun O, Brousseau DC. Pediatr Emerg Care. 2018;34:574–577
25. Khatib R, Rabah R, Sarnaik SA. The spleen in the sickling disorders: an update. Pediatr Radiol. 2009 Jan;39(1):17-22
26. 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

27. El Hoss S, Cochet S, Marin M, Lapouméroulie C, Dussiot M, Bouazza N, Elie C, de Montalembert M, Arnaud C, Guitton C, Pellegrino B, Odièvre MH, Moati F, Le Van Kim C, Aronovicz YC, El Nemer W, Brousse V. Insights into determinants of spleen injury in sickle cell anemia. Blood Adv. 2019 Aug 13;3(15):2328-2336
28. Trivedi K, Abbas A, Kazmi R, Shaaban H, Miller R. Hyperhemolytic Crisis Following Transfusion in Sickle Cell Disease With Acute Hepatic Crisis: A Case Report. Cureus. 2022 Aug;14(8):e27844. [
29. Koehl JL, Koyfman A, Hayes BD, Long B. High risk and low prevalence diseases: Acute chest syndrome in sickle cell disease. Am J Emerg Med. 2022 Aug;58:235-244
30. Mekontso Dessap A, et al.. Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. Am J Respir Crit Care Med 2008; 177:646–653
31. Platt OS. Sickle cell anemia as an inflammatory disease. J Clin Invest 2000; 106:337–338
32. Ibrahim A. Al-Dabbous, ACUTE CHEST SYNDROME IN SICKLE CELL DISEASE IN SAUDI ARAB CHILDREN IN THE EASTERN PROVINCE Annals o f Saudi Medicine, Vol 22, Nos 3-4, 2002
33. Beck CE, Trottier ED, Kirby-Allen M, Pastore Y. Acute complications in children with sickle cell disease: Prevention and management. Paediatr Child Health. 2022 Mar;27(1):50-62.