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SICKLE CELL ANAEMIA: A Dismissed Constant DISEASE OF Expanding Worldwide Wellbeing

Adrita Das
Heredity Lifesciences Pvt Ltd

Sweta Yadav
Heredity Lifesciences Pvt Ltd

Saptarshi Bhattacharyya
Heredity Lifesciences Pvt Ltd

Arpita Patnaik
Heredity Lifesciences Pvt Ltd

Sushree swagatika subhadarsini
Heredity Lifesciences Pvt Ltd

Dr. Gopal Krishna Purohit
Heredity Lifesciences Pvt Ltd

Dr. llalli Smruti Sahu
SCB Medical College, Cuttack

Abstract: -Sickle cell disease (SCD) is usually caused due to the alteration of the beta-globin subunit in the primary adult haemoglobin (HbA). When both the beta-globin subunits get mutated, i.e., in the heterozygous condition, the HbS polymerizes upon deoxygenation, resulting in the erythrocytes acquiring sickle or crescent shape, known as sickling. During the initial process, the acquired erythrocytes often sway between the circular and sickle shapes when oxygen pressure is lower. However, the situation becomes critical if the change becomes irreversible resulting in permanent sickling of the erythrocytes, worsening the threat of hemolysis and vascular damage. The most common form of the disease is sickle cell anemia, where the patient is susceptible to hemolysis. Every year, thousands of cases are being reported, the majority being from Sub-Saharan Africa. Despite the genetic similarity at the site of mutation, not all patients get equally affected. If the sickle cell disease is left untreated for long, it causes neurological complications, pulmonary hypertension, cardiac disease, renal complications etc. Various methods have been developed for the treatment of the disease. This review briefly discusses sickle cell disease, its pathophysiological aspects, its causes, effects and treatment.

Keywords:- *Sickle Cell Anemia, Pathophysiology, Hemolysis, Thalassemia, Mutation.*

I. INTRODUCTION

Sickle cell anemia is a genetic disease where the erythrocytes present in the blood change their shape from a usual biconcave disk to a crescent or sickle shape by a process known as sickling. Repeating sickling in the erythrocytes can lead to intravascular hemolysis resulting in anemia.[1] This disease was more prevalent in Africa and a few Mediterranean countries among a few ethnic groups such as African-Americans, Hispanic-Americans, and people of Indian, Middle East; Asian, and Mediterranean descent, but was later found to affect people worldwide[2][5]. It is an autosomal recessive disease that results due to defective hemoglobin, where the beta globins in the primary hemoglobin HbA get mutated. [3] It is a non-conservative missense mutation where the sixth amino acid of beta-globin chain hydrophilic Glutamic acid is replaced by hydrophobic Valine. The mutation in both the beta-globin chains leads to sickle cell disease which is the root cause of conditions like Hyposthenuria, hematuria, isosthenuria, expansion of medullary cavities in the skull, extramedullary hematopoiesis, hepatomegaly etc. Also, the accumulation of the sickle cells in the capillaries, termed as Vasco-occlusion, leads to dactylitis, avascular necrosis, and splenic sequestration [2]. Pulmonary complications of sickle cell anemia (HbSS) such as airway hyperresponsiveness, acute chest syndrome, chronic sickle cell disease, pulmonary arterial hypertension, and sleep-related breathing disorders, are common causes of morbidity; however, only a few large pulmonary function test (PFT) studies have been reported in this population. The sickle cell Hb is less soluble in blood than the normal Hb due to a lack of oxygen. Even the advanced treatments including the early usage of prophylactic antibiotics, cautious transfusions, operation of hydroxylurea in preferred patients, remained unsuccessful in decreasing the mortality rate of the patients [4]. The variant of sickle cell disease, called sickle thalassemia, is less severe despite the serious conditions.

Significant researches claim that the use of allogeneic stem cell transplantation is a therapy for Sickle cell disease. There is growing evidence that favors the statement that stem cell therapy and gene editing are the potential in curing the disease. However, most of the patients residing in resource-limited countries are deprived of these facilities which provide drug therapies that are safe, effectual and economical [8]. Other treatment methods can be the best supportive care, direct blood transfection, pain medications and use of hydroxycarbamide in certain circumstances which reduces the severity of the disease and are also found to be clinically effective [7].

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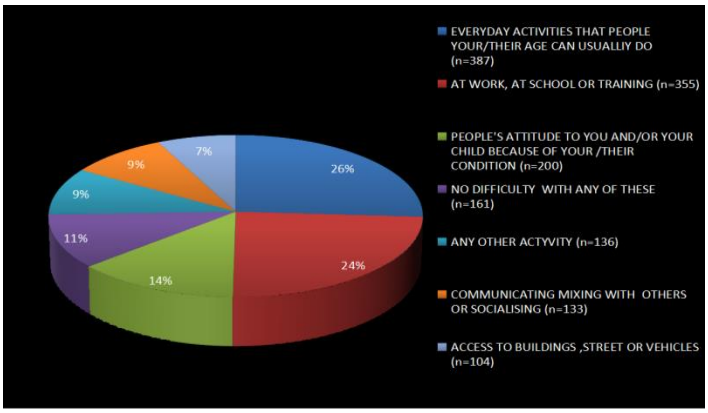

Fig: 1 Patient-reported experience measure in sickle cell disease.

II. PATHOPHYSIOLOGY

Sickle cell sickness is one of the obsessive side effects of sickle cell infection and is described by the presence of sickle cell hemoglobin (HbS). HbS is brought about by a transformation in the βglobin quality, where the seventeenth nucleotide changes from thymine to adenine and the sixth amino acid in the globin chain becomes valine rather than glutamic acid.

This transformation frames a hydrophobic environment in the deoxygenated HbS tetramer, bringing about restriction between the β1 and β2 chains of the two hemoglobin atoms. This crystallization makes a polymer center that fills red platelets, obliterates their shape and adaptability, and elevates cell parchedness because of cell stress. At the point when there isn't sufficient oxygen in the vascular framework, sickle hemoglobin turns out to be moderately insoluble, expanding the arrangement of polymers in the blood, consequently expanding its general thickness. This forms a gel-like hemoglobin known as a tidbit. The proportion of each kind of state relies upon:

- The presence of oxygen: the more oxygen present, the higher the proportion of the fluid state.
- Sickle cell hemoglobin fixation: The higher the HbS, the more superiority of the gel like state.
- Other Hemoglobin: Normal grown-up and fetal hemoglobin advance liquid status.

After some time, cell membranes are forever destroyed leaving cells in a long-lasting sickle shape.

One of the pathophysiological cycles of sickle cell sickness is hemolytic iron deficiency, additionally brought about by HbS polymerization. Hemolysis has for quite some time been believed to be answerable for anemia and cholangiolithiasis, yet it has now been shown that it likewise adds to the improvement of cutting-edge vascular sickness. As patients with sickle cell infection age, they are at expanded danger for endothelial brokenness, fundamental and pneumonic blood vessel hypertension, and vascular infection described by proliferative changes in the body and smooth muscle layer of veins.

Patients with low hemoglobin levels and significant degrees of hemolysis comprise the patient subtype at higher danger of creating vascular sickness than patients with high hemoglobin levels and appear to be inclined to indications like intense agony and intense chest condition. A few complexities can happen in a kid before the conclusion, like weakness, sickle cell infection, and harm to different organs. These difficulties can make sickle cell sickness due to expanded blood consistency and blockage of veins. Anemia can result from hemolysis of red platelets, which contain sickle cell hemoglobin in the spleen. Thus, this can prompt a more limited life expectancy of red platelets and the improvement of hemolytic paleness. Patients with sickle cell hemoglobin can create multiorgan harm throughout a significant period. It can influence a patient's heart, cerebrum, eyes, lungs, skeleton, spleen, kidneys, penis, and skin. HbS polymerization likewise happens in reticulocytes, representing around 20% of the red platelets in SCA patients. HbS polymers induce different irregularities at the cell level and contribute essentially to the generally speaking pathophysiology of SCD

A. Impacts of SCA

Neurological difficulties In MRI-based examinations by Elizabeth et al. Up to 20% of kids with sickle cell illness have a quiet stroke. Pneumonic hypertension in an examination performed by Elizabeth et al. 20% of members had a marginally raised assessed pneumonic vein pressure, characterized as an aspiratory supply route systolic tension more prominent than 35 mm Hg. Coronary illness in the equivalent tested by Elizabeth et al. Left coronary illness happens in around 13% of grown-ups with sickle cell infection and is caused basically by diastolic disorder; Systolic disorder can likewise happen, and valvular coronary illness is available in around 2% of patients. Renal difficulties in a similar analysis, 30% of grown-ups created constant kidney disappointment, which was the main source of death. Impacts of SCA on the Nervous System Sickle cell sickness has no truly immediate impact on the sensory system since sickle cells are available in the blood, not nerve cells. The greatest impact of SCA on the sensory system is that it harms the cerebrum. An ischemic stroke happens when a vein in the cerebrum becomes obstructed, leaving that piece of the mind without oxygen. Blood clumps are bound to frame since red platelets are sickle-molded. A blood coagulation that structures in a cerebrum corridor can prompt a stroke. Indications of a stroke remember deadness for the appendages, loss of awareness, or trouble talking. Indications are not restricted to this and may incorporate different confusions. Assuming an individual encounter these manifestations, they should look for sure fire clinical consideration on the grounds that a stroke can be deadly. Strokes can happen all the time, and SCA patients should consistently play it safe.

Therapy (previous name)	**Mechanism**	**Advantages**	**Limitations**
Phase III study			
Hydroxycarbamide	Increases expression of HbF	Reducing the frequency of acute attacks of pain, acute chest syndrome, and blood transfusions in infants and adults	Disproportionate perceptions of carcinogenicity, teratogenicity and reduced fertility
Phase II study			
Crizanlizumab (SelG1)	P-selectin inhibitor	Reduced the incidence of acute complications by 45–63%	Monthly intravenous infusions required
Phase I study			
Pomalidomide	Increases expression of HbF	Well tolerated; increases HbF and total Hb levels; anti-inflammatory effects	Limited data
Preclinical study			
Genome editing	Programmable nucleases	Methods consist of zinc-finger nucleases, transcription activator-like impact or nucleases and CRISPR–Cas9	Unknown long-time period risks; capacitytreatment or sickness amelioration, relyingon themethod

Table 1: Therapies related to SCA [11]

	THERAPEUTIC APPROACH	SPECIFIC EXAMPLES
To reduce infective complications	Improve vaccination against *N Streptococcus pneumonia*	7-valent and 13 –valent conjugated vaccines
To reduce tissue hypoxia	Treatment of sleep apnea, blood exchange	Overnight oxygen, continuous positive airways pressure, pegylated haemoglobin

Table 2: Treatment options for SCA [9]

	Hydroxyurea	**L-Glutamine**	**Crizanlizumab**	**Voxelotor**
Age (years)	≥2	≥5	≥16	≥12
Genotypes	HbSS, HbSβ^0 thalassemia	All genotypes (only studied in HbSS, HbSβ^0 thalassemia)	All genotypes	All genotypes
Mechanism of action	Multiple, but primarily by increasing HbF production	Uncertain, howeveridea to lessen NAD redox capacity, possible lower in molecular adhesion,	Anti P-selectin inhibitor (decreases adhesion of WBCs and RBCs to endothelium)	Decreases HbS polymerization by growing Hb–oxygen affinity
Route of administration	Oral (capsules/tablets)	Oral (powder)	Intravenous	Oral (tablets)

Table 3: Drug therapies management for SCA [8]

B. SCA Infection: Indian Perspective Vs Global Perspective

The following figures depict a comparative study between the SCA infection in India based on different states and countries outside India; for example, USA (state wise) and different countries of Africa.

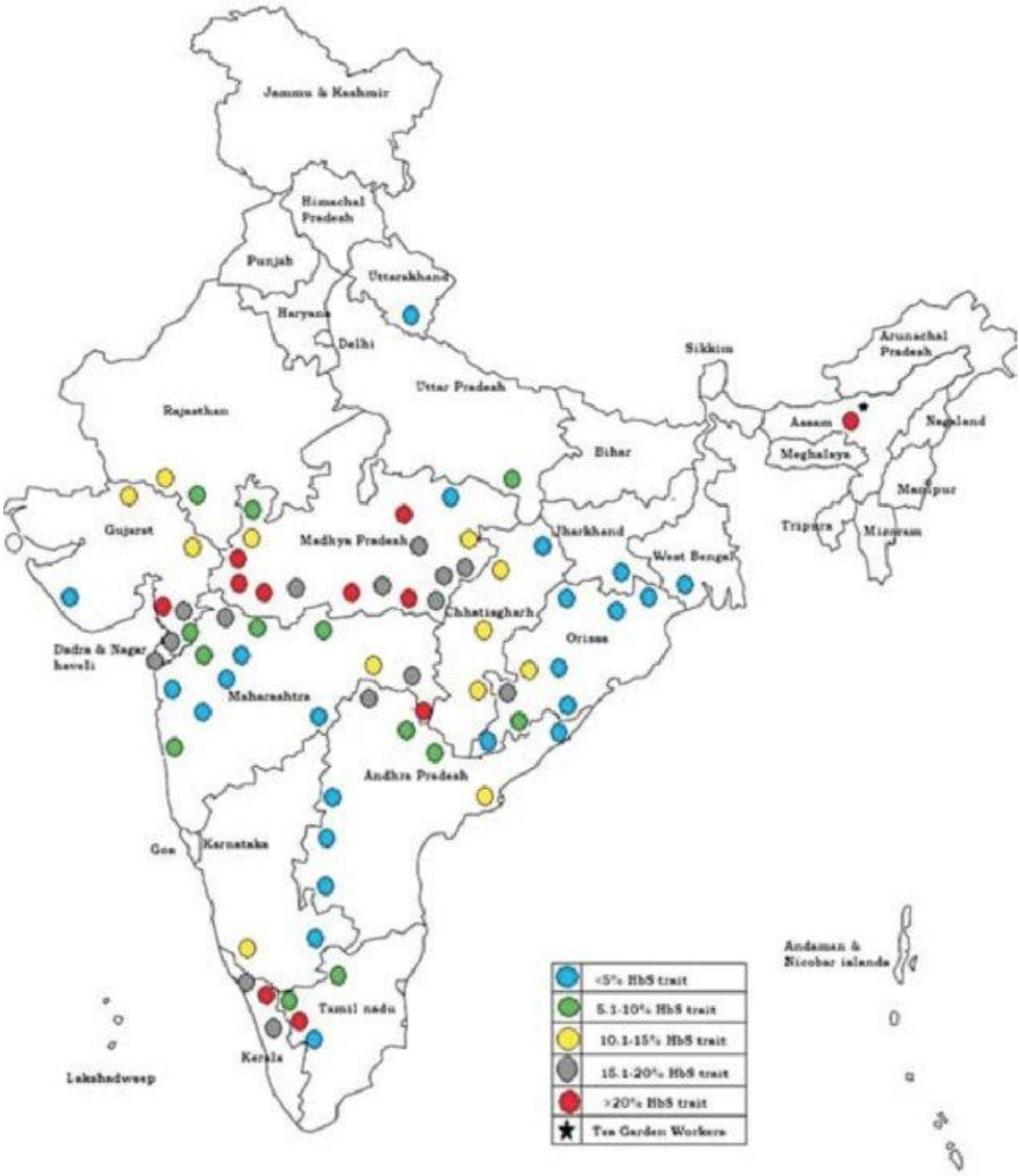

Fig 2: This picture represents new born with SCA in India, (**a**) in the state wise birth and, (**b**) in the district wise births, in 2020. [11]

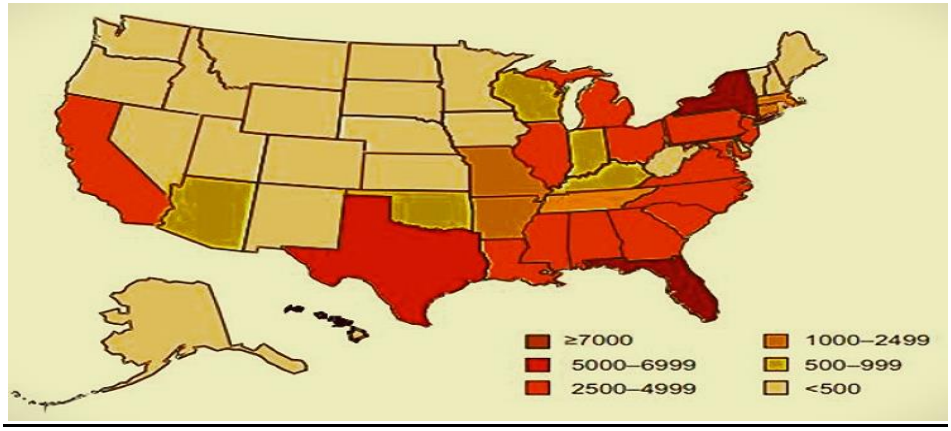

Fig 3 : State wise distribution of SCA infected patients in The USA. [12]

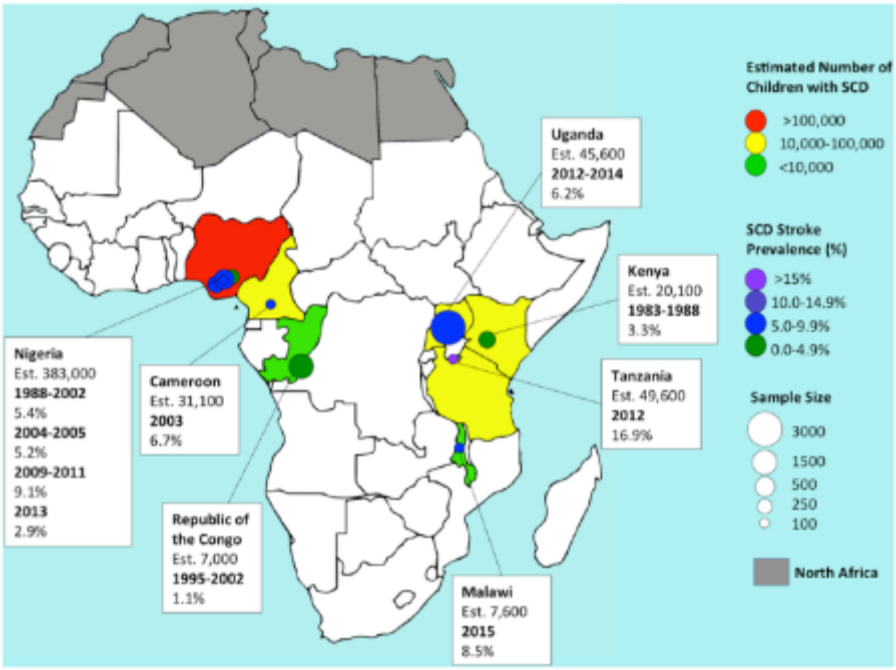

Fig 4: Country wise distribution of SCA infected patients in the African subcontinent. [13]

III. CONCLUSION AND FUTURE PROSPECTS

It is easier to detect Sickle cell disease due to the availability of Hemoglobin during blood sampling. A better understanding of the evolution of the disease allows better prophylaxis, inspection and therapy. The studies related to the pathophysiological aspect of the disease had led to predict useful ways for its treatment.[2] Hence, intensive research are being done to develop methods to predict the severity of the sickle cell anemia disease at a tender age or even prenatally. It would be invaluable as potentially dangerous treatments like hematopoietic stem cell transplant and drug manipulation of HbF levels become common.[6]

The development of the treatment is disproportionately slower in comparison to the progress of understanding of the disease, which can be witnessed from the evidence in the past few years. It is expected that in the coming years, there will be a significant increase in the development of the therapeutic aspects of the disease due to the combined advances in the fields of genetics and genomics, increased number of clinical trials and increased awareness of the disease by the funding bodies. [9]

The ongoing clinical research trials should ensure that they also include patients coming from low-income and middle-income countries, where the load of the disease is higher. This would ensure that the potentially effective and disease-modifying drugs and therapies are easily accessible to such patients. [8]

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