

# Sickle Cell Anemia: Genetic Factors, Prevalence and Control

Shahid Raza<sup>1</sup>, Muhammad Waseem Shoaib<sup>2</sup>, Saima Jabeen<sup>2</sup> and Hira Mubeen<sup>1</sup>

<sup>1</sup>University of South Asia, Lahore, Pakistan

<sup>2</sup>District Head Quarter (DHQ), Faisalabad, Pakistan

**Abstract-** Sickle cell anemia is a genetic disorder resulting in irregularly regulating red blood cells also called as sickled cells leading to serious conditions like stroke, acute chest syndrome, pulmonary hypertension, organ damage, blindness and skin ulcers. Several mutations in HBB gene can cause sickle cell disease. Persons with sickle cell anemia can inherit infected genes from both parents. Despite a variable disease severity, individuals affected require regular health care from childhood all the way to adult age. This review, highlights the increased susceptibility to infections, the genetic factors and preventive measures to overcome various complications and challenges for sickle cell anemia.

**Index Terms-** stroke, sickled cells, mutations, hypertension

## I. INTRODUCTION

Sickle cell anemia is a genetic disease associated with episodes of acute illness and progressive organ damage leading to erythrocyte rigidity. People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle shape.

The sickle cell mutation reflects a single change in the amino acid building blocks of the oxygen-transport protein, hemoglobin. This protein has two subunits and gives red color to cells. The alpha subunit is normal in people with sickle cell disease. The beta subunit has the amino acid valine at position 6 instead of the glutamic acid that is normally present. Sickled cells cannot squeeze through the narrow blood vessels and stack up to block blood flow. This blockage prevents oxygen from being transferred to tissue and organs which is known as ischemia. The loss of oxygen can result in tissue damage. The lifespan of sickle RBCs 10-20 days as compared to the 120-day lifespan of normal RBCs which results in chronic anemia in SCD patients [1]. This chronic hemolysis leads to the generation of many other toxic molecules.

In 1949, Dr. Pauling and colleagues were the first to indicate that sickle cell disease occurs as a result of an abnormality in the hemoglobin molecule [2]. This was the first time a genetic disease was linked to a mutation of a specific protein. The sickle cell mutation occurs when a single base change in the DNA, is the fundamental genetic material that determines the arrangement of the amino acid building blocks in all proteins. It is now a known fact that SCD is an inherited disease which is passed down from parents to children. SCD is a serious disorder in which the body makes sickle-shaped red blood cells. They move easily through blood vessels. Red blood cells contain a protein

called hemoglobin. Hemoglobin binds oxygen in the lungs and transport to the rest of the body. Sickle cells are stiff and sticky and tend to block blood flow in the blood vessels, which can cause pain and organ damage.

## II. GENETICS OF SICKLE CELL DISEASE

Mutations in the HBB gene cause sickle cell disease. Hemoglobin consists of four protein subunits, typically, two subunits called alpha-globin and two subunits called beta-globin. The HBB gene provides instructions for making beta-globin. Different mutations are caused due to various forms of beta globin in the HBB gene. One particular HBB gene mutation produces an abnormal version of beta-globin known as hemoglobin S (HbS). Other mutations in the HBB gene lead to additional abnormal versions of beta-globin such as hemoglobin C (HbC) and hemoglobin E (HbE). In people with sickle cell disease, at least one of the beta-globin subunits in hemoglobin is replaced with hemoglobin S. In sickle cell anemia, hemoglobin S replaces both beta-globin subunits in hemoglobin. In other types of sickle cell disease, just one beta-globin subunit in hemoglobin is replaced with hemoglobin S. Abnormal versions of beta-globin can distort red blood cells into a sickle shape. The sickle-shaped red blood cells die prematurely, which can lead to anemia.

## III. SYMPTOMS

Symptoms of sickle cell disorder include Hand-foot syndrome, anemia symptoms such as fatigue and paleness, unpredictable episodes of pain, chronic inflammation, eye problems, jaundice, delayed growth in children, infections and sometimes stroke. Patients with SCD are also susceptible to diseases such as osteomyelitis and the spleen and kidneys of SCD patients are particularly susceptible to ischemic damage. The underlying abnormality is a single nucleotide substitution (GTG for GAG) in the gene for  $\beta$ -globin on chromosome 11, resulting in the replacement of a glutamic acid residue with valine on the surface of the protein (termed HbS)[3]. In normal adult HbA, two chains of  $\alpha$ -globin and two of  $\beta$ -globin form a tetramer, stabilized by specific intra molecular points of contact, but without interactions between individual tetramers within the RBC [4]. When the molecule binds or releases oxygen, it undergoes a conformational change. In HbS, deoxygenation exposes the abnormal valine residue on the surface of the molecule, which then forms hydrophobic interactions with adjacent chains. The resulting polymers align into bundles, causing distortion of the RBC into a crescent or sickle shape and

reducing flexibility and deformability, which impairs passage of the cells through narrow blood vessels [5]. Sickling can be precipitated by environmental factors such as hypoxia, low pH, cold, and dehydration of the RBC, as well as adhesion molecules and cytokines associated with infections.

A number of other mechanisms for increased susceptibility to infection in SCD have been explored. Major infections occur in early infancy when the spleen is still partially functional and some increased risk persists despite modern prophylactic measures, suggesting additional immune deficits are present [6]. Patients also seem predisposed to other infections, including *Escherichia coli* urinary tract infection, *Mycoplasma pneumoniae* respiratory infections, and dental infections caused by anaerobes. The complement system involves a large number of plasma proteins that are cleaved sequentially by protease enzymes to generate active fragments. The cascade can be activated either via the classical pathway, following binding of IgM or IgG to surface antigens, or the alternative pathway, in which C3b interacts directly with the pathogen cell surface, then recruiting further downstream components [7].

#### IV. GENETIC FACTORS

Despite sharing the same underlying genetic mutation, the range of severity in the phenotype of SCD is striking, with some patients disabled by frequent crises and long-term complications while others live virtually normal lives. Individuals are also differently predisposed to particular pathological manifestations of the disease. This suggests that the phenotype is multigenic, variation in alleles at multiple loci may modify outcome [8]. Polymorphisms in a number of genes involved in the immune response have been suggested as contributing to increased susceptibility to infection in SCD. Particular HLAII subtypes have been shown to be predisposing or protecting factors for infectious complications, while certain polymorphisms of the FcR receptor (involved in clearing encapsulated bacteria), mannose-binding lectin, insulin-like growth factor 1 receptor (IGF1-R; involved in B and T cell recruitment and differentiation), and genes of the transforming growth factor  $\beta$  (TGF $\beta$ )/bone morphogenetic protein (BMP) pathway have been associated with an increased risk of bacteremia [9-10]. These studies also highlight the need for caution in making generalizations about immune function in SCD, for example complement activation or neutrophil action, based on experiments using small numbers of subjects in localized geographical areas. Observed differences may increase individual risk, but may not be a universal feature [11]. Large samples across multiple racial groups would be needed to distinguish effects due to SCD per se from those caused by other unlinked and variable alleles.

#### V. PREVENTION

As illustrated, infection can lead to a range of complications in SCD, and these are not readily reversed simply by treating the infection. For this reason, prevention is the key strategy in management. Interventions in the last 20 years have dramatically reduced mortality, especially in children, and the

recommendations continue to evolve. Simple general measures are important in reducing the risk of infection, though the aim is to ensure as normal a lifestyle as possible. Meticulous attention to hygiene, particularly hand-washing, is vital, and to protect against Salmonella, patients are advised to cook food thoroughly, particularly chicken and eggs, keep items refrigerated, and avoid contamination [12]. Nutritional supplementation with zinc has been reported to reduce infection risk, improve growth rates in SCD children, and possibly improve skeletal and sexual maturation as well as having psychological benefits [13]. Early identification of infections is another key area, enabling prompt initiation of treatment to reduce complications. Parents are encouraged to monitor their children closely at home and seek advice if they have a fever or respiratory symptoms, while maintaining good hydration. There should be a low threshold for the use of antibiotics in ill children with SCD, particularly in the presence of chest signs or symptoms, which may herald ACS. A fever of more than 38.5 °C is an indication for the empirical use of broad-spectrum antibiotics such as a third-generation cephalosporin, with a macrolide added in potential ACS. Relevant specimens (blood, urine, sputum, etc.) should be taken for culture and antibiotics later modified or stopped depending on the results [14].

#### VI. GENETIC COUNSELING

Sickle cell disease is inherited in an [autosomal recessive](#) manner. If one parent is a [carrier](#) of the *HBB* Hb S pathogenic variant and the other is a carrier of any of the *HBB* pathogenic variants (e.g., Hb S, Hb C,  $\beta$ -thalassemia), each child has a 25% chance of being [affected](#), a 50% chance of being [unaffected](#) and a carrier, and a 25% chance of being unaffected and not a carrier. Carrier detection for common forms of sickle cell disease is most commonly accomplished by HPLC. Prenatal diagnosis for pregnancies at increased risk for sickle cell disease is possible by [molecular genetic testing](#) if the *HBB* pathogenic variants have been identified in the parents.

#### VII. INFECTION

Individuals with sickle cell disease develop splenic dysfunction as early as age three months; thus, young children with sickle cell disease are at high risk for septicemia and meningitis with pneumococci and other encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Historically, the single most common cause of death in children with sickle cell disease was *Streptococcus pneumoniae* sepsis, with the risk of death being highest in the first three years of life. Notably, the role of [newborn screening](#), education, and access to healthcare cannot be overstated. Despite not altering infection rates, these measures do lower morbidity and mortality [15]. With the further addition of vaccination programs and prophylactic penicillin the incidence of these infections has decreased significantly [16]. Individuals with sickle cell disease are also at increased risk for other infections such as osteomyelitis caused by *Staphylococcus aureus* or other organisms such as *Salmonella* species. Infectious agents implicated in acute chest syndrome include *Mycoplasma*

*pneumoniae*, *Chlamydia pneumoniae*, and *Streptococcus pneumoniae*, as well as viruses. Parvovirus remains an important cause of aplastic crisis. Indwelling central venous catheters confer a high risk of bacteremia in individuals with SCD.

### VIII. PREVALENCE

The Hb S [allele](#) is common in persons of African, Mediterranean, Middle Eastern, and Indian ancestry and in persons from the Caribbean and parts of Central and South America but can be found in individuals of any ethnic background. Among African Americans, the prevalence of sickle cell trait (Hb AS) is about 10%, resulting in the birth of approximately 1100 infants with sickle cell disease (Hb SS) annually in the US. Approximately one in every 300-500 African Americans born in the US has sickle cell disease; more than 100,000 individuals are estimated to have homozygous sickle cell disease [17].

The prevalence of *HBB* alleles associated with sickle cell disease is even higher in other parts of the world. In many regions of Africa, the prevalence of the Hb S pathogenic variant (Glu6Val) is as high as 25%-35%, with an estimated 15 million Africans [affected](#) by sickle cell disease and 200-300,000 affected births per year worldwide [18-19]. Sickle cell disease accounts for as many as 16% of deaths of children younger than age five years in Western Africa [20-21].

### IX. DISCUSSION

The sickle cell disease includes a group of genetic alterations characterized by the predominance of the S hemoglobin, which causes red blood cells to have the shape of a sickle. Sickle cells have a specific cascade of gene expression in response to the constant hemolysis. There is a dramatic upregulation of pro-inflammatory genes, but an anti inflammatory pathway that is induced upon sickle cell crises. Sickled red blood cells cannot pass through the capillaries.

Tissue that does not receive a normal blood flow eventually becomes damaged.

Normal red blood cells contain hemoglobin A. They are soft and round and can squeeze through tiny blood vessels. Normally, red blood cells live for about 120 days before new ones replace them. The lifespan of sickle cells is at least six times shorter than that of normal RBCs. The main clinical manifestations of sickle cell anemia are a chronic anemia caused by the destruction of red blood cells. Despite a variable disease severity, individuals affected require regular health care from childhood all the way to adult age.

### X. CONCLUSION

Sickle cell anemia is a world-wide disease, especially present in countries with blacks and mixed populations, where the SS sickle cell form is very common. Most individuals can be expected to live well into adulthood, enjoying an improved quality of life including the ability to choose a variety of education, career, and family-planning options for themselves.

According to studies, it is the need of time to prevent, diagnose and systematically follow up children with sickle cell anemia. Hence, it is concluded that, SCD can be controlled with better implementation of preventive measures.

### REFERENCES

- [1] Ohnishi ST, Ohnishi T, Ogunmola GB.(2000) Sickle cell anemia: a potential nutritional approach for a molecular disease. *Nutrition*. 16: 330-338.
- [2] Steensma, D. P., Kyle, R. A., & Shampo, M. A. (2010). Walter clement noel-first patient described with sickle cell disease. *PMC*, 85(10), 74-75.
- [3] Stuart, M.J. and Nigel, R.L. Sickle-cell disease. *Lancet*. 2004; 364: 1343-1360.
- [4] Madigan, C. and Malik, P. Pathophysiology and therapy for haemoglobinopathies. Part I: sickle cell disease. *Exp Rev Mol Biol*. 2006; 8: 1-23.
- [5] Tamouza, R., Neonato, M.G., Busson, M., Marzais, F., Giro, R., Labie, D. et al. Infectious complications in sickle cell disease are influenced by HLA class II alleles. *Hum Immunol*. 2002; 63: 194-199.
- [6] Janeway, C. and Travers, P. *Immunology. The immune system in health and disease*. 3rd ed. Churchill Livingstone, London; 1997.
- [7] Adewoye, A., Nolan, V., Ma, Q., Baldwin, C., Wyszynski, D.F., Farrell, J.J. et al. Association of polymorphisms of IGF1R and genes in the TGFβ/BMP pathway with bacteremia in sickle cell anemia. *Clin Infect Dis*. 2006; 43: 593-598.
- [8] Wong, W.Y., Overturf, G.D., and Powars, D.R. Infection caused by *Streptococcus pneumoniae* in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis and vaccination. *Clin Infect Dis*. 1992; 14: 1124-1136.
- [9] Atkins, B.L., Price, E.H., Tillyer, L., Novelli, V., and Evans, J. Salmonella osteomyelitis in sickle cell disease children in the East End of London. *J Infect*. 1997; 34: 133-138.
- [10] Prasad, A.S., Beck, F.W., Kaplan, J., Chandrasekar, P.H., Ortega, J., Fitzgerald, J.T. et al. Effect of zinc supplementation on incidence of infections and hospital admissions in sickle cell disease. *Am J Hematol*. 1999; 61: 194-202.
- [11] Zemel, B.S., Kawxhak, D.A., Fund, E.B., Ohene-Frempong, K., and Stallings, V.A. Effect of zinc supplementation on growth and body composition in children with sickle cell disease. *Am J Clin Nutr*. 2002; 75: 300-307.
- [12] Powars D, Overturf G, Weiss J, Lee S, Chan L. Pneumococcal septicemia in children with sickle cell anemia. Changing trend of survival. *JAMA*. 1981;245:1839-42.
- [13] Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. *Pediatrics*. 1988;81:749-55.
- [14] Adamkiewicz TV, Sarnaik S, Buchanan GR, Iyer RV, Miller ST, Pegelow CH, Rogers ZR, Vichinsky E, Elliott J, Facklam RR, O'Brien KL, Schwartz B, Van Beneden CA, Cannon MJ, Eckman JR, Keyserling H, Sullivan K, Wong WY, Wang WC. Invasive pneumococcal infections in children with sickle cell disease in the era of penicillin prophylaxis, antibiotic resistance, and 23-valent pneumococcal polysaccharide vaccination. *J Pediatr*. 2003;143:438-44.
- [15] Chulamokha L, Scholand SJ, Riggio JM, Ballas SK, Horn D, DeSimone JA. Bloodstream infections in hospitalized adults with sickle cell disease: a retrospective analysis. *Am J Hematol*. 2006;81:723-8.
- [16] Zarrouk V, Habibi A, Zahar JR, Roudot-Thoraval F, Bachir D, Brun-Buisson C, Legrand P, Godeau B, Galacteros F, Lesprit P. Bloodstream infection in adults with sickle cell disease: association with venous catheters, *Staphylococcus aureus*, and bone-joint infections. *Medicine (Baltimore)* 2006;85:43-8.
- [17] Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. 2010;38 (4) Suppl:S512-21.
- [18] WHO Regional Committee for Africa. 56th Annual Session Final Report. 2006.
- [19] Aliyu ZY, Kato GJ, Taylor J, Babadoko A, Mamman AI, Gordeuk VR, Gladwin MT. Sickle cell disease and pulmonary hypertension in Africa: a

global perspective and review of epidemiology, pathophysiology, and management. Am J Hematol. 2008;83:63–70.

[20] Mousa SA, Qari MH. Diagnosis and management of sickle cell disorders. Methods Mol Biol. 2010;663: 291–307.

[21] Neville KA, Panepinto JA. Pharmacotherapy of sickle cell disease. 18th Expert Committee on the Selection and Use of Essential Medicines. 2011;10-16-14.

#### AUTHORS

**First Author** – Shahid Raza, University of South Asia, Lahore, Pakistan

**Second Author** – Muhammad Waseem Shoaib, District Head Quarter (DHQ), Faisalabad, Pakistan

**Third Author** – Saima Jabeen, District Head Quarter (DHQ), Faisalabad, Pakistan

**Fourth Author** – Hira Mubeen, University of South Asia, Lahore, Pakistan, Email: hira\_sh@hotmail.com