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Sickle Cell Disease: A Genetic Disorder of Beta-Globin

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Abstract

Sickle cell disease (SCD) is a structural and monogenetic genetic disorder due to a mutation that occurs in the globin β-chain, resulting in the formation of hemoglobin S (Hb S), a protein composed of two normal, and two β-type mutant chains. Estimates indicate that the prevalence among live births is 4.4% in the world. The difficulty in circulating the sickle cell, its interaction with endothelial cells, leukocytes, platelets, endothelial dysfunction, and the abnormal expression of adhesion molecules permeate the beginning of the blood vessel occlusion process as well as pathophysiological aspects of SCD. Among the secondary complications are the stroke, pulmonary hypertension, leg ulcer, renal disorders, and all complications associated with vascular dysfunction. Clinical and biochemical markers of disease severity can be used to predict risk, prevent complications, and increase the expectation and quality of life of the SCD population. The entire scenario generated by Hb S has implications for the health and social inclusion of patients, so the treatment of the person with SCD needs an approach focused on the prevention of these complications in an individualized way.

Keywords: sickle cell disease (SCD), hemoglobin, genetic disturber, nucleation, molecular interaction

1. Introduction

According to global estimates, approximately 5% of the population has some type of hemoglobin variant, and more than 300,000 babies are born each year with hemoglobinopathies, with sickle cell disease (SCD) being the most prevalent type [1–2]. It is estimated that the prevalence of live births with the disease is 4.4% in the world, where rates remain high on the main continents of Africa, Southeast Asia, and the Americas [2].
In 2013, perform a first evidence analysis focusing on sickle hemoglobin using a 2010 dataset combined with demographic data and modern geostatistical modeling techniques that explain spatial heterogeneities and precision measurements of global statistics about sickle cell disease neonates (Figure 1) [3]. In 2010, the births of infants with sickle cell anemia (SCA-Hb SS) accounted for 2.4% of the world’s most severe cases of the disease [3]. However, worrying estimates indicate that the number of newborns with SCA will increase from approximately 305,000 in 2010 to 404,000 in 2050 [4, 5].

The African continent, which has 3.6 million new cases of sickle cell trait (HbAS) and 238,000 SCA, remains the largest cradle of SCD genetic inheritance [3]. Nigeria, and the Democratic Republic of Congo would urgently need to plan policies for prevention and management of SCA, so that implementations carried out in 2015 could save many lives by 2050 (Figure 2) [4, 5].

In Southeast Asia where a hemoglobin variant Hb E is more prevalent, a heterozygosity with Hb S has increased mainly due to immigration and interracial relationships [6–8]. Nevertheless, according to data between the years 1990 and 2013, an annual mortality rate SCD HbSE per 100,000 inhabitants decreased by 63.9%, keeping them in the media of 2.8% per year [9]. It is estimated that the prevalence of live births with the SCD is 1.1% in the American continent [2]. In the United States, it is estimated that 113,000 hospitalizations are in the occurrence of the disease and the cost of hospitalization for SCD reaches 488 million dollars per year [10].

In Brazil, the estimated incidence of SCD is 1 case per 2700 live births: Bahia, Rio de Janeiro, and Minas Gerais being the main states with the highest prevalence [11–13]. According to data from the Ministry of Health of Brazil, child and perinatal care lethality rates can reach 80% and between 20% and 50%, respectively, of uncared children who cannot reach 5 years of life [14]. Among the adults followed in the high prevalence states, such as Bahia and Rio de Janeiro, the median age of death due to SCD is still low, 26.5 years and 31.5 years, respectively [15]. Nevertheless, in the last 13 years, the Brazilian government implemented several public health policies focused on the detection of new cases by neonatal screening and on improving the quality of treatment provided to these patients, implying an increase in life expectancy, with individuals reaching the fourth, fifth, and up to the sixth decade of life [16–19].

Figure 1. Distributions HbS data points. Red points indicate surveys showing the presence of HbS and blue points indicate surveys showing an absence of HbS. Source: Adaptation of Piels et al. [3].
The pathological presentment of SCD begins with the process of formation of Hb S polymers triggers dehydration and increased cell stiffness, giving rise to the vaso-occlusion event [20, 21]. This phenomenon leads to the appearance of several pathophysiological events such as tissue ischemia, anemia, inflammation, and hemolysis [20–24].

Hemolysis consists of the early destruction of the erythrocytes by membrane rupture, being a common event in the pathophysiological process of SCD [25–27]. During hemolysis, vasodilation, transcriptional activation of endothelin and vascular adhesion molecule are reduced, whereas nitric oxide is exposed directly to free Hb S, causing its degradation [28, 29]. Chronic hemolysis in SCD causes vascular imbalance, reflecting directly on hemoglobin concentration, reticulocyte count, bilirubin levels, lactic dehydrogenase (LDH), and nitric oxide bioavailability [28, 30, 31]. The reduction of the supply of oxygen to the tissues and organs causes the appearance of several complications secondary to disease [5].

Nevertheless, genetic, age, gender, hematological, and environmental factors afford to interfere on the characteristics of SCD and also impact on the quality and life expectancy of patients, mainly reducing their social insertion [32–35].

2. The hemoglobin: origins and function

Hemoglobin is one of the most abundant proteins in animals, performing important functions such as oxygen transport, started when hemoglobin binds to oxygen that arrives from the airways in the lungs and is taken to organs and tissues that need it to maintain life through red blood cells [36–38]. The genomic structure of genes encoding hemoglobin subunits, characterized by three exons and two introns, are highly similar among vertebrate animal strains [39].
Despite this, the function of some proteins belonging to the contemporary hemoglobin family in vertebrates is to store oxygen in tissues such as myoglobin, a protein formed by a globin chain, gives the red color to the muscular tissues and has structural and genomes similar to globins that form hemoglobin [37, 40–43].

Composed of four polypeptide subunits, two alpha chains and two beta chains (α1β1; α2β2), respectively, each of the four globin groups has a porphyrin ring (Heme group) containing the iron element in its constitution (Figure 3) [38, 44].

Hemoglobin is considered an allosteric molecule because it regulates its functionality very well, especially in situations of change in the environment where it is present, in the increase or decrease of the concentration of a certain ligand [45, 46]. A classic example of this can be highlighted in how oxygen binds cooperatively in the heme cluster [47, 48].

Previously, researchers admitted that the base of hemoglobin allosterism was based on the Monod Wyman-Changeux (MWC) two-state allosteric model, which corresponded to oxyhemoglobin (bound) and deoxyhemoglobin (unlinked) forms [44, 46, 49]. It is currently believed that hemoglobin can adopt several allosteric conformations in dynamic equilibrium, also implying different functionalities (Figure 4) [44, 48].

Over time hemoglobin has been consistently an object of scientific research given its relevance to biology [50–52]. One of the most important aspects is related to the study of its origin and its relation with oxygen, a very reactive metal, but necessary for mammalian metabolism [53–55].

![Figure 3. Structure quaternary of hemoglobin. Source: Antranik website. Available in http://antranik.org/blood-components-hemoglobin-typeh-factor-agglutination.](image-url)
From the evolutionary point of view, about 4 billion years ago, the gaseous layer that enveloped the Earth was composed only of nitrogen, methane, water effluvia, and ammonia [37]. Probably many organisms that emerged in the early days used these gases for their own subsistence [56]. It is believed that iron and magnesium were involved in many of these actions in the metabolism of these extremely primitive organisms [57, 58].

In order to increase the efficiency of life-generating energy systems, somehow still not so enlightened and despite being toxic, oxygen has been incorporated by organisms [37, 50]. It is believed that initially this large protein complex that now bears oxygen-dependent organisms, organs, and tissues was very primitive, probably composed only of a metal that was able to bind and carry oxygen [37].

In the process of evolution, at one point, it was necessary that this structure is wrapped within a porphyrin ring and then embedded in enovelled protein [52]. During evolution, this ring-shaped structure has accompanied generations of organisms of animal origin (Heme group) and plant (Clorofila group) [37, 59].

The Heme group not only binds to globin molecules to form hemoglobin but can bind other molecules with a certain function to give rise to oxygenases proteins, cytochromes, and even fungal ligninases [37]. Chlorophyll, the green-coloured substance in plants, is basically an organic molecule characterized by a porphyrin ring that contains magnesium, and its function is to absorb electromagnetic energy through sunlight, which will be used in photosynthesis [58, 60, 61].

Studies to identify the origin of hemoglobin compare their respective coding genes with several parent organisms in order to detect the changes that have been made throughout evolutionary history and time [37]. But the change identified in hemoglobins was more in the form of how they are genetically regulated than in their structural basis from which they were strongly conserved [58]. In general, studies indicate that hemoglobin appeared about 500 million years ago (Figure 5), prior to the time that eukaryotic cells diverged from eubacterial cells [37].
3. Pathophysiology of Hb S: a mutation, an amino acid, a disease

Multipotent hematopoietic stem cells have the potential to be targeted to a number of special differentiation pathways that originate several blood cell lines in mammals [62–64]. One of the pathways, erythropoiesis, is responsible for the production of red blood cells, discoid and anucleated cells that carry oxygen (O2) and carbon dioxide (CO2) through an intracellular metalloprotein called hemoglobin throughout the body [39, 65].

As seen previously, hemoglobin is a heterotetramer composed of two α-globin and β-globin subunits linked by a non-covalent bond [2, 39]. Each globin subunit has a heme group containing the bivalent iron ion [64, 66].

Different globin genes are activated or deactivated both in embryonic, fetal and adult life in order to meet different oxygen demands and facilitate the placental transfer of oxygen from the mother to the embryo (Figures 6 and 7) [64, 66, 67].

In humans, throughout embryonic life to adulthood, various types of hemoglobin can be expressed and this process is regulated in a complex manner, involving several molecular mediators in order to stimulate hemoglobin production (Figure 6) [2, 66, 68]. The globin genes α and β, arranged on chromosomes 16 and 11, respectively, control the production of globins through the expression of the subunits from the α globin locus: ζ (embryonic) and α-globin (adult) genes; and locus β globin: ε (embryonic), γG and γA (fetal), and δ and β-globin (adult) (Figure 7) [64, 66].

However, due to spontaneous mutations, variant hemoglobins may arise and be structurally different [68, 69]. These mutations can, for example, trigger a change in the amino acid sequence,
Figure 6. Representation of the red cell maturation process, molecular regulation of hemoglobin (embryonic, fetal, and adult) with focus on β globin and globin synthesis. Source: For more details, look up the Sankaran article reference of the year 2011 [68].
leading to the decrease or suppression of the production of a globin chain, as observed in β Thalassemia [70, 71]. Such genetic changes often lead to the onset of diseases, which are called hemoglobinopathies [2, 8, 72].

A mutation in the gene of the sixth codon of exon 1 in the DNA of chromosome 11, which synthesizes the β globin, leads to the replaced adenine nitrogen base (from the GAG codon) by thymine (GTG), resulting in the substitution of glutamic acid for valine in position 6 of the N-terminal end in the Beta (β) chain of globin [73–76]. The pathophysiology of sickle cell disease (SCD), a monogenetic disorder that gives rise to the formation of hemoglobin S (Hb S), a protein composed of two normal α-chains and two mutant chains of the β-type (α2A β2S) (Figure 8).

Three levels direct the scientific knowledge related to the pathophysiological changes present in SCD: molecular and cellular, tissue and organism [77–80]. At the molecular level, the exchange of amino acids with different isoelectric points, glutamic acid (IP = 5.97) per valine (IP = 2.77), causes an imbalance because of the loss of negative charges of Hb S in relation to Hb A (Figure 9) [81, 82]. These changes in the physical structure of hemoglobin will imply impairments in its functionality, mainly related to oxygen loading [83–85].

In certain periods or situations where hypoxia occurs (absence or decrease of oxygen tension in the body), oxygenated mutant hemoglobin (oxy-HbS) loses oxygen, adopting deoxygenated conformation (deoxy-Hb S) [81, 86, 87].

Figure 7. Variation of hemoglobin types in the embryonic, fetal, and adult period. Source: Adapted from Weatherall and Clegg [113].

Figure 8. Sickle cell disease (SCD).
In its own structure, the formation of hydrogen bonds between the amino acids valine of position n1 of the globin beta S (normal position) and the mutant valine of the same globin begins [82, 83, 84]. Hydrogen bridges promote intermolecular approximations and contacts between the amino acids of hemoglobin (GLU121 → GLY16, ASP73 → THR4, etc.) that favor the formation of Hb S polymers [84, 85]. However, it is through the hydrophobic interactions between valine (βVAL6) and the hydrophobic concavity formed mainly by leucine (βLEU88) and phenylalanine (βFEN85) that the formation of Hb S polymers occurs [81, 83, 88].
Figure 10. Summary of the pathophysiology of SCD. (A) Representation of the structural differences in the conformation of HbS when it is in oxygenated and deoxygenated form. (B) HbS polymerization process with details of the main amino acids involved in the mechanism. (C) Formation of the deoxy-HbS fibers through the phenomenon of homogeneous and heterogeneous nucleation. (D) Microscopic findings of sickle cell. Left cells of the blood with the formation of Heinz bodies (fluorescence method). In the center, smear blade containing scythe-shaped cells. On the right is a lysed sickle cell showing several deoxy-HbS fibers. Source: See details at Howard Hughes Medical Institute, 2018; Galkin et al. [88]; Rooter, 2005; Liu et al., 1996.
Polymerization in SCD is a process triggered by a phenomenon known as nucleation in which a number of molecules come together within an embryo of the new phase that resembles a first transition phase similar to a gas-solid transformation [88, 89]. The nucleation progressively progresses through the initial fiber growth and its branching, due to the secondary nucleation of new fibers on top of the existing ones, as if it were a double nucleation [77, 88, 90, 91].

Polymerization of HbS is a primary event in the pathophysiology of SCD, generally favored by several factors such as insufficient oxygen saturation, loss of potassium and water, reductions in blood pH, increased the concentration of 2, 3-diphosphoglycerate [81, 82, 86]. In the formation of HbS fibers, they are capable of generating 14 members of T-shaped conformation fibers when hemoglobin is in the deoxygenated state [87, 88]. Among these aligned fibers hydrophobic contacts occur, which are initiated between the valine of the HbS molecule and alanine, phenylalanine and leucine of adjacent Hb S molecules [88]. In the case of a high degree of polymerization, the deoxy-HbS presents a behavior characteristic of a polymer gel [88, 90].

After polymerization progresses through enveloped fibers, which will alter the structure of the red cell, mainly through the formation of more elongated fibers and mechanisms of precipitation in the cell wall with the formation of Heinz bodies, triggering the appearance of sickle-shaped red blood cells, rather than discoid and malleable (Figure 10) [81, 82, 87].

The affinity of oxygen for hemoglobin, Hb S concentration, dehydration, the minimum concentration of gelation, acidosis and elevated temperature are determinant events, which directly influence the falcization process [92].

Sickle cells have a rigid, adherent and fragile structure, which compromises their circulation in the bloodstream [86, 87]. Cell damage and deformation of erythrocytes occur as a result of polymerization of deoxy-HbS and high concentrations of unpolymerized oxy-HbS, as well as influenced by cellular levels of HbF, water content, pH, temperature and mechanical stresses that will result in membrane injury [84].

The difficulty of circulating the sickle cell, its interaction with endothelial cells, leukocytes, platelets, endothelial dysfunction and the abnormal expression of adhesion molecules permeate the beginning of the process of occlusion of the blood vessels, generating tissue hypoxia, hemolysis, increased oxidative stress and other pro-inflammatory phenomena [80, 87, 91, 93].

4. Clinical consequences of the presence of Hb S

SCD is a chronic hemolytic anemia characterized by clinical events involving recurrent vaso-occlusion, and its main clinical manifestations are anemia, pain, and multiple organ failures [18, 80, 87]. To understand the clinical aspects of SCD, we must go a bit further into the pathophysiological and molecular aspects of this genetic disorder.

As we saw earlier, the presence of a genetic alteration in the nitrogen base in the gene that encodes the β globin production triggers the formation of HbS, modifies the structure of the erythrocytes (Figure 11), and implies a series of pathophysiological complications for individuals
with SCD. Many of the following events do not occur in isolation and are directly involved in the pathogenesis of SCD.

The sickle cell has many difficulties in permeating the blood vessels. Due to the speed of the bloodstream, many end up clinging to each other thus harming the passage. Sickle cell occlusion mechanism is started. Spleen cells are pounded, violently pushed, lysed, and intravascular hemolysis causes the red blood cells to release a series of biocomponents, mainly hemoglobin and arginase that will interact with nitric oxide (NO) produced in the endothelium, reducing its bioavailability and arginine and its main precursor [84, 94, 95].

The vessel occlusion plus constant hemolysis initiates tissue hypoxia. At the same time, early oxidation of NO increases oxidative stress implying endothelial dysfunction, with imbalances in the mechanisms of vessel dilatation and constriction [84, 85].

At a time when local occlusion ends, and blood perfusion returns, more free radicals are produced, and they further increase lesions to the endothelium, which becomes more adherent, especially to red blood cells and leukocytes, making the vascular wall again exposed to a new occlusion [84, 95, 96].

Among the main adhesion pathways that progress the sickle cell and endothelial cell interactions are the soluble adhesion proteins (thrombospondin, fibrinogen, fibronectin, and von Willebrand factor), integrins (α4β1, αVβ3) and their membrane-bound receptors and sulfated glycolipids), immunoglobulins VCAM-1 and ICAM-4, endothelial selectin, as well as leukocyte activation by epinephrine through β-AR stimulation [85, 96].

Recurrent hemolysis eventually becomes chronic, and the inflammatory state is established. Thus, the organism needs to increase the production of red blood cells by the bone marrow,
resulting in high cardiovascular work, with increased cardiac output in order to facilitate the rapid delivery of blood with a higher content of oxygen to the organs, avoiding hypoxia and tissue death [97]. More precisely, a compensatory mechanism is established that increases heart rate, leading to increased myocardial energy demand with the effect between myocardial energy requirements and total body [98, 99, 100].

The hypermetabolism present in these patients has an impact on body composition and has been related to increased energy expenditure, increased protein turnover, increased oxidative stress, higher reticulocyte levels, and reduced body mass [97, 99, 101, 102].

Progressive degeneration of the organs results from infarctions in the affected areas, leading to several secondary complications that directly compromise patients’ lives and survival [18, 80, 103].

Patients with SCD are more likely to have episodes of vascular accident, pulmonary hypertension, proteinuria and chronic kidney disease, all complications associated with vascular dysfunction caused by the disease [78, 94, 104, 105].

Vasodilation is reduced in patients with SCD and may have other consequences, such as the appearance of leg ulcers [94, 106, 107]. These lower limb ulcer lesions represent 8 to 10% of the cases and have a higher incidence in people with SCA males and in the age group between 10 and 50 years [99, 107, 108, 109].

Ulcerations may appear after trauma, insect bites, excessive dryness of the skin or spontaneously generally in the ankle or malleolar region (middle or lateral portion), where there are less subcutaneous tissue and blood flow as a consequence of tissue hypoxia, endothelial dysfunction, and vaso-occlusion [107, 108, 110].
Infections in these patients are also a major cause of concern both in childhood and in adulthood [76, 78, 111, 112]. In general, this and other complications (Figure 12) bring many misfortunes to individuals with SCD and basically compromise the quality of life of these patients. Despite all the consequences of HbS formation, the degree of severity of the disease depends on numerous factors, and the first one is the genotype.

SCD can be subdivided into distinct genotypes, six of which are more frequent in the world, SCA (Hb SS), heterozygotes (Hb SC, Hb SE, Hb SD), sickle thalassemia (Hb Sβ+ and Hb Sβ0),
and sickle cell trait (Hb AS) [8, 84, 104, 113, 114]. Individuals with Hb SS genotypes, heterozygotes and associations with thalassemia are generally symptomatic, and at each gestation, there is a 25% chance that the child will be born with SCD from parents carrying some S gene or other variant hemoglobin (Figure 13) [84, 104, 115]. In general, the HbAS genotype is considered to be asymptomatic in that it hardly develops any clinical picture, but it represents a type of hemoglobinopathy, since the recessive gene is likely to be inherited for the next generation [115–118].

Other indicators of disease severity are bilirubin, PCV, erythropoiesis rate, leukocytes, LDH, fetal hemoglobin, creatinine, proteinuria, reticulocytes, HSV, phenotypes, days of hospitalization per year, severe vaso-occlusive crisis per year, number of transfusions per year, hip disease, leg ulcer, hepatobiliary complications, neurological events, renal disorders and body mass index [84, 119–123].

5. Treatment of SCD: general aspects

Treatment, in general, is differentiated by pathophysiological changes during life and will also depend on the type of genotype, which is accompanied by a hematologist. The use of folic acid supplements is included in order to contain hemolysis and to accelerate the production of red blood cells.

Also used are: (A) antibiotics, especially in children under 5 years, since generalized infections can lead to death within a few hours due to splenic sequestration; (B) analgesics, codeine, morphine, and anti-inflammatories in the presence of acute or chronic pain crises; venous hydration in the vessel occlusion; (C) transfusion or blood exchange; (D) periodic and special immunizations; and (E) treatment of the sequelae or chronic consequences caused by the disease [18, 124, 125].

The use of hydroxyurea medication over the years as a treatment that greatly increased the quality of life of patients. However, not all individuals are eligible or adapted to their use [77, 126]. Alternative treatments, transplantation, and gene therapy are welcome measures for clinical treatment; however, some of these are still under discussion and require technical and scientific clarification for their implementation.

Clinical and biochemical markers of disease severity should be used to predict risk, prevent complications, and increase the expectation and quality of life of the population with SCD [77, 87, 127]. Often patients with SCD report the development of vaso-occlusive symptoms after emotional/psychological stress, temperature changes, and physical exertion [95]. Therefore, patients undergoing treatment and their caregivers are encouraged to practice self-care, with measures that can prevent acute events, improve prognosis, and allow a better quality of life [128].

In general, people with SCD due to chronic hemolysis and inflammatory state have higher energy expenditure to develop daily activities and tendency to anorexia [109, 129, 130]. Pain crises generate a decrease in food consumption, which has a direct impact on caloric and nutrient intake. Probably, the pain crises associated with the constant hospitalizations contribute to the
lower food consumption that consequently compromises the nutritional status [127, 129, 130]. Thus, this population calls for nutritional monitoring for the intervention of the problems related to food and nutrition. In general, it is important the presence of a multi-professional team, centered in the assistance and matrix support to the hematologist doctor and the patients assisted with SCD.

6. Conclusion

Scientific research and technical work around the world have been done to better understand the pathophysiological and clinical aspects of SCD. It is a severe hemolytic disease that causes great morbidity and mortality, especially in underdeveloped countries. The entire scenario generated by HbS has implications for the health and social inclusion of patients, so the treatment of the person with SCD needs an approach focused on the prevention of these complications in an individualized way.

Acknowledgements

The author thanks the invitation to write the chapter and to Kristina Kardum for the noble assistance.

Conflict of interest

The author does not present conflicts of interest.

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