We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 7

Sickle Cell Disease: A Genetic Disorder of Beta-Globin

Karen Cordovil

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74778

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].

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

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].

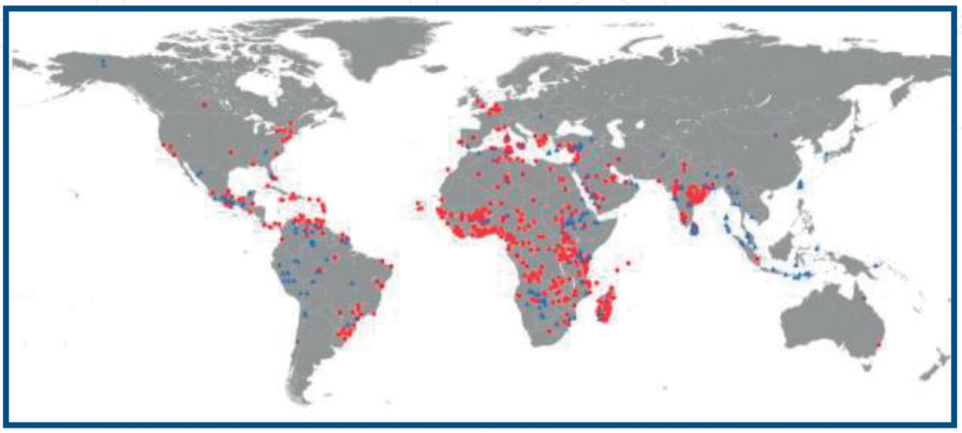


Figure 1. Distributions HbS data points. Red points indicate surveys showing the presence of HbS and blue points indicate surveys showing an absence of HbS. Source: Adaptation of Piels et al. [3].

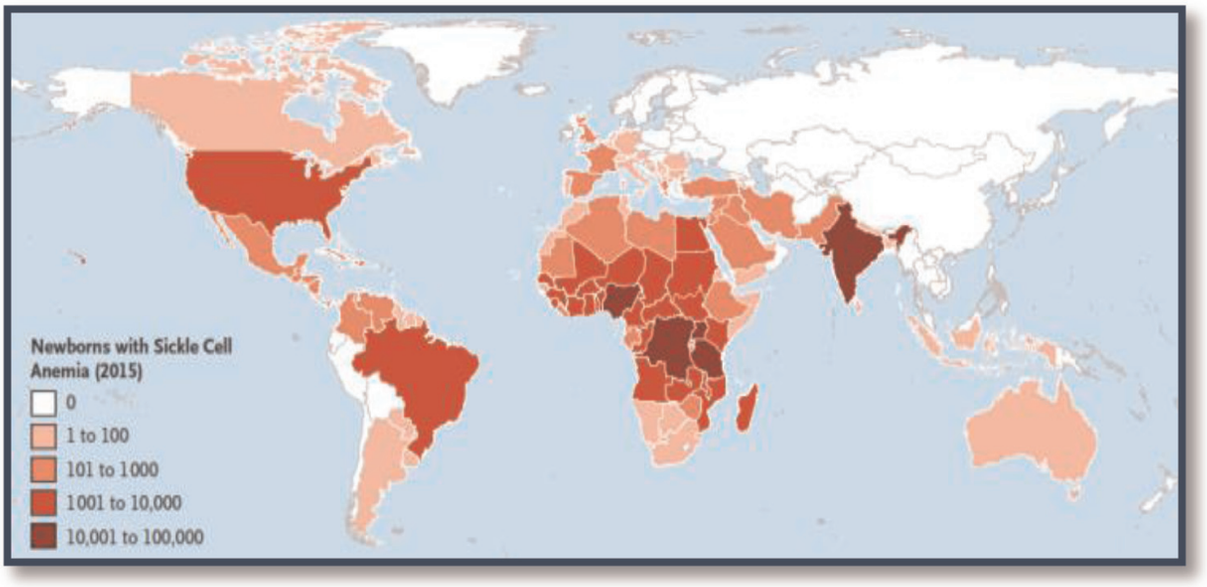


Figure 2. Numbers of Newborns with Sickle Cell Anemia (SCA) in 2015. Source: Adaptation of Piels et al., 2017.

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 ($\alpha 1\beta 1$; $\alpha 2\beta 2$), 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].

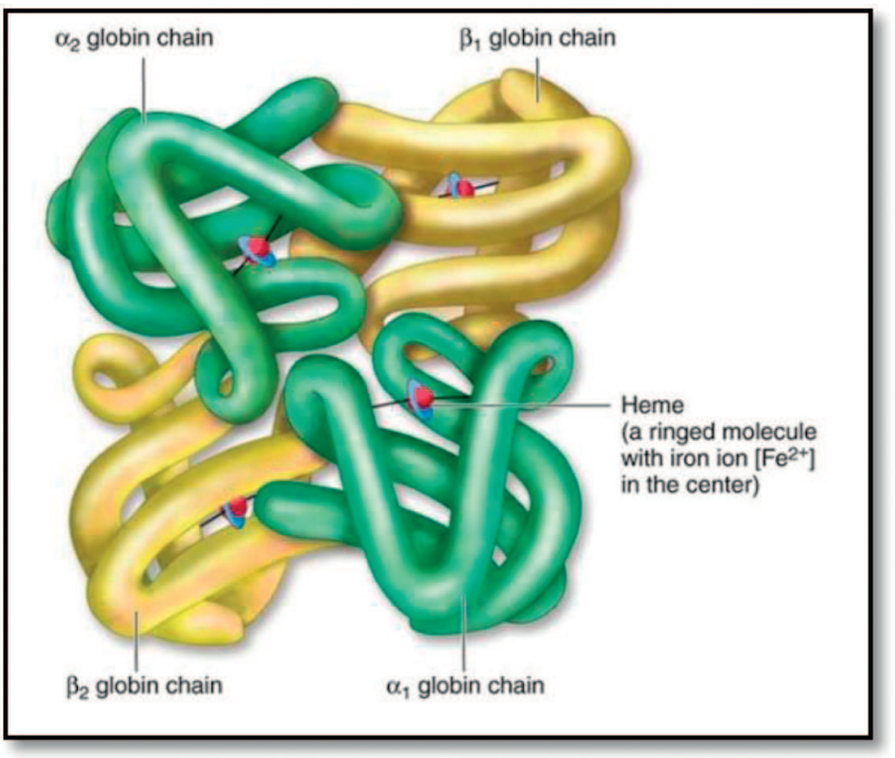


Figure 3. Structure quaternary of hemoglobin. Source: Antranik website: Available in http://antranik.org/blood-components-hemoglobin-typerh-factor-agglutination.

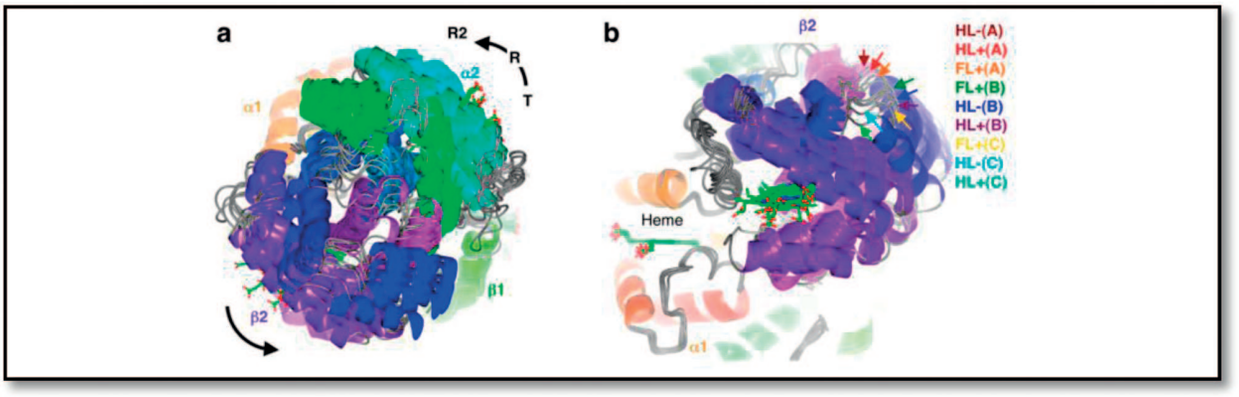


Figure 4. Presentation and comparison of nine quaternary structures of hemoglobin. In (a) diagram showing the orientation of $\alpha_2\beta_2$ dimers relative to $\alpha_1\beta_1$. In (b) the presentation of the β2 subunit with the same nine conformations represented in nine colors and at different angles. Source: Adapted from Shibayama et al. [44].

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].

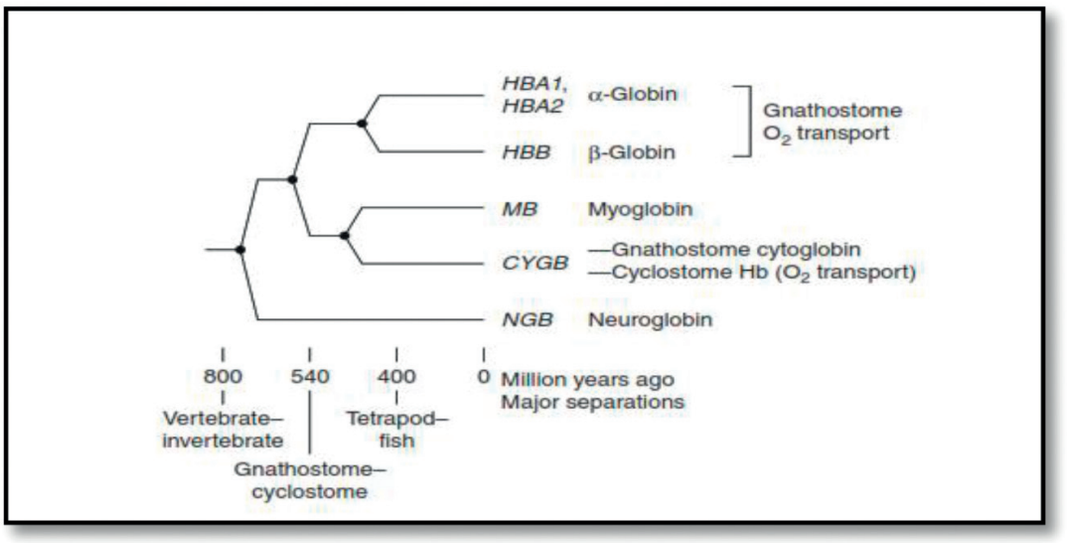


Figure 5. Phylogenetic tree model of globin genes in vertebrate animals. Source: Adapted from Hardison [58].

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,

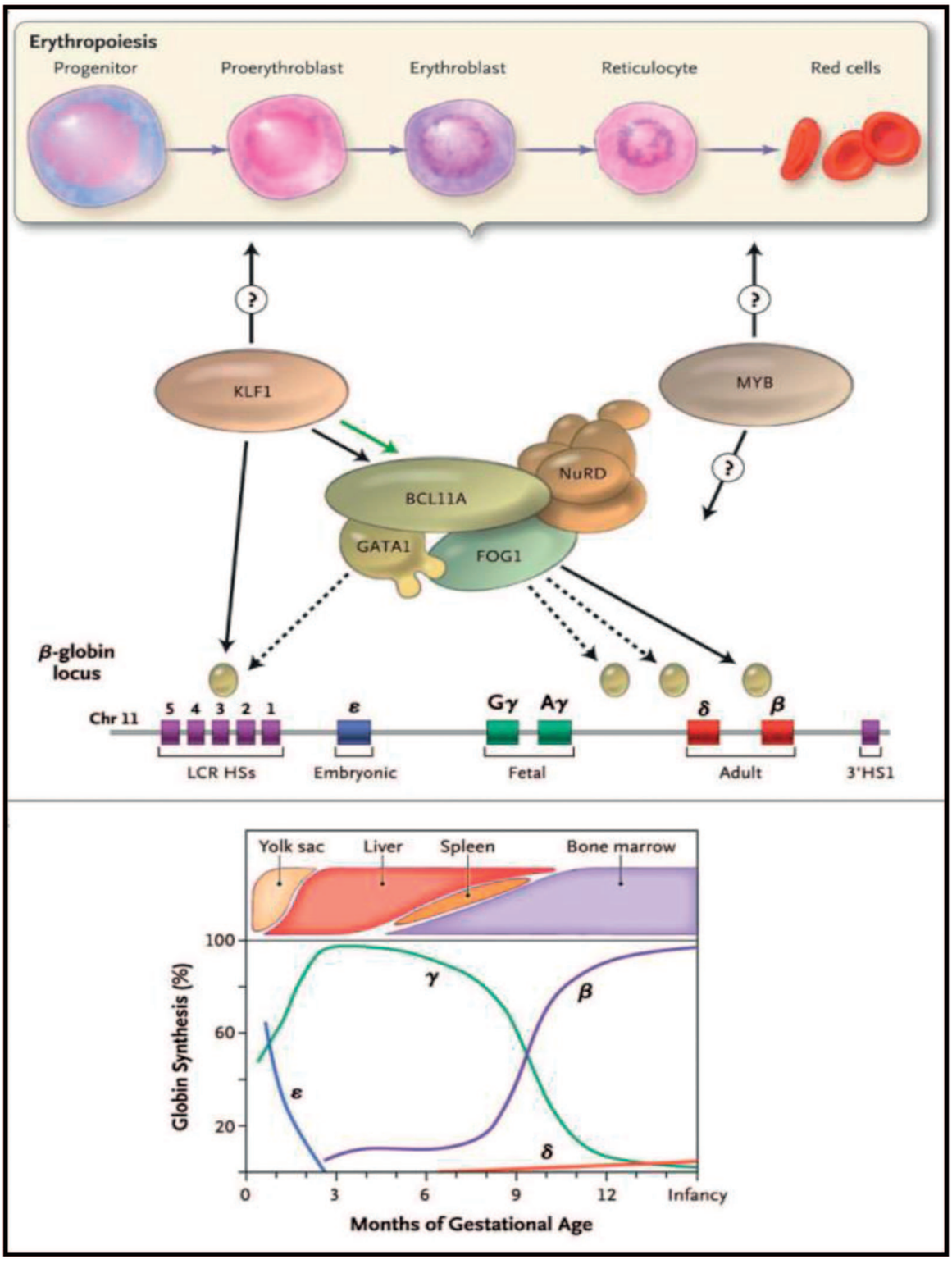


Figure 6. Representation of the red cell maturation process, molecular regulation of hemoglobin (embryonic, fetal, and adult) with focus on β globin and globin synthesis. Source: For more details, look up the Sankaran article reference of the year 2011 [68].

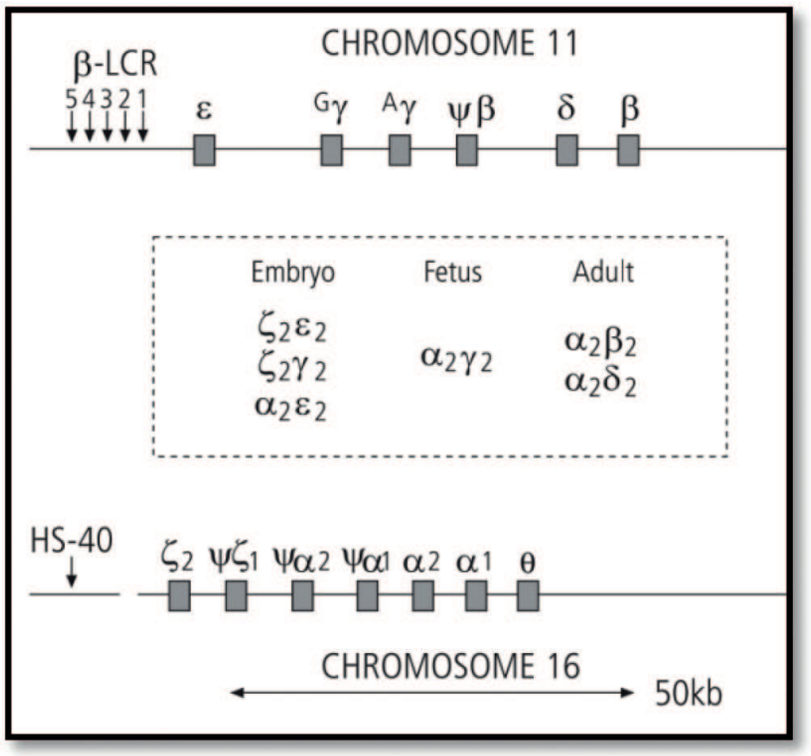


Figure 7. Variation of hemoglobin types in the embryonic, fetal, and adult period. Source: Adapted from Weatherall and Clegg [113].

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].

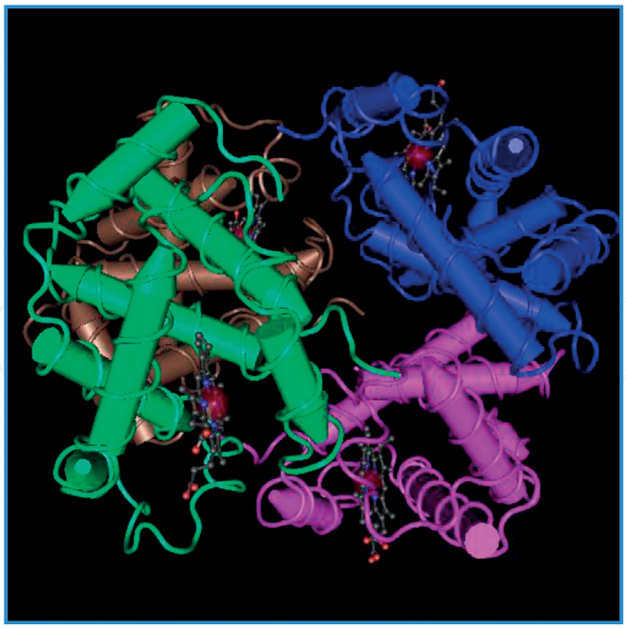


Figure 8. Crystalline structure of deoxy hemoglobin S (deoxy-Hb S). Source: For more information, see details in the study by Harrington et al., 2017.

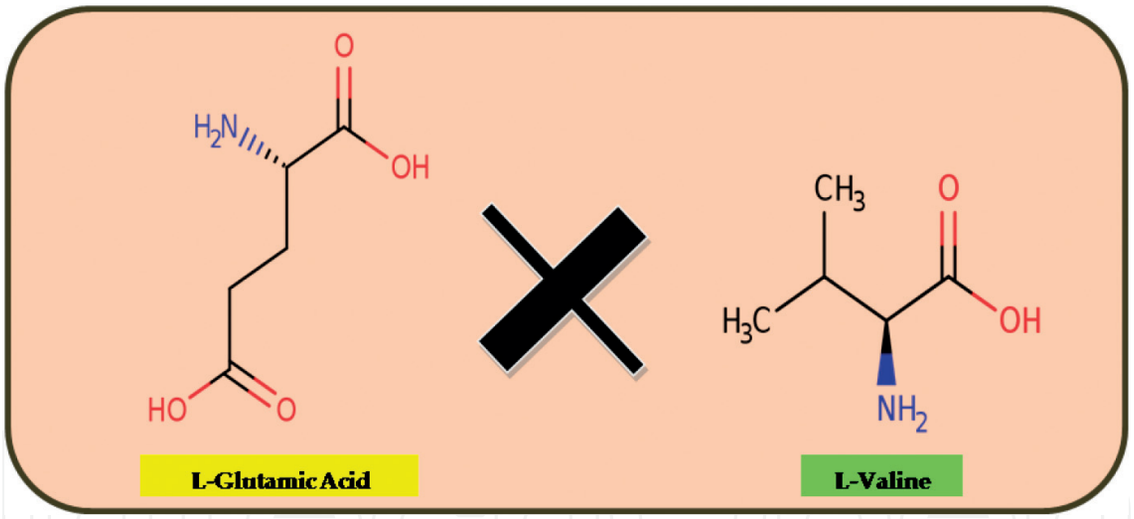


Figure 9. Representation of the mutated amino acid structures present in HbS. Glutamic acid has an acted structure and with more negative charges. Valine is an amino acid with hydrophobic characteristics that tend to have the most neutral charge. Source: Wishart et al., 2013.

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 hemoglobins (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].

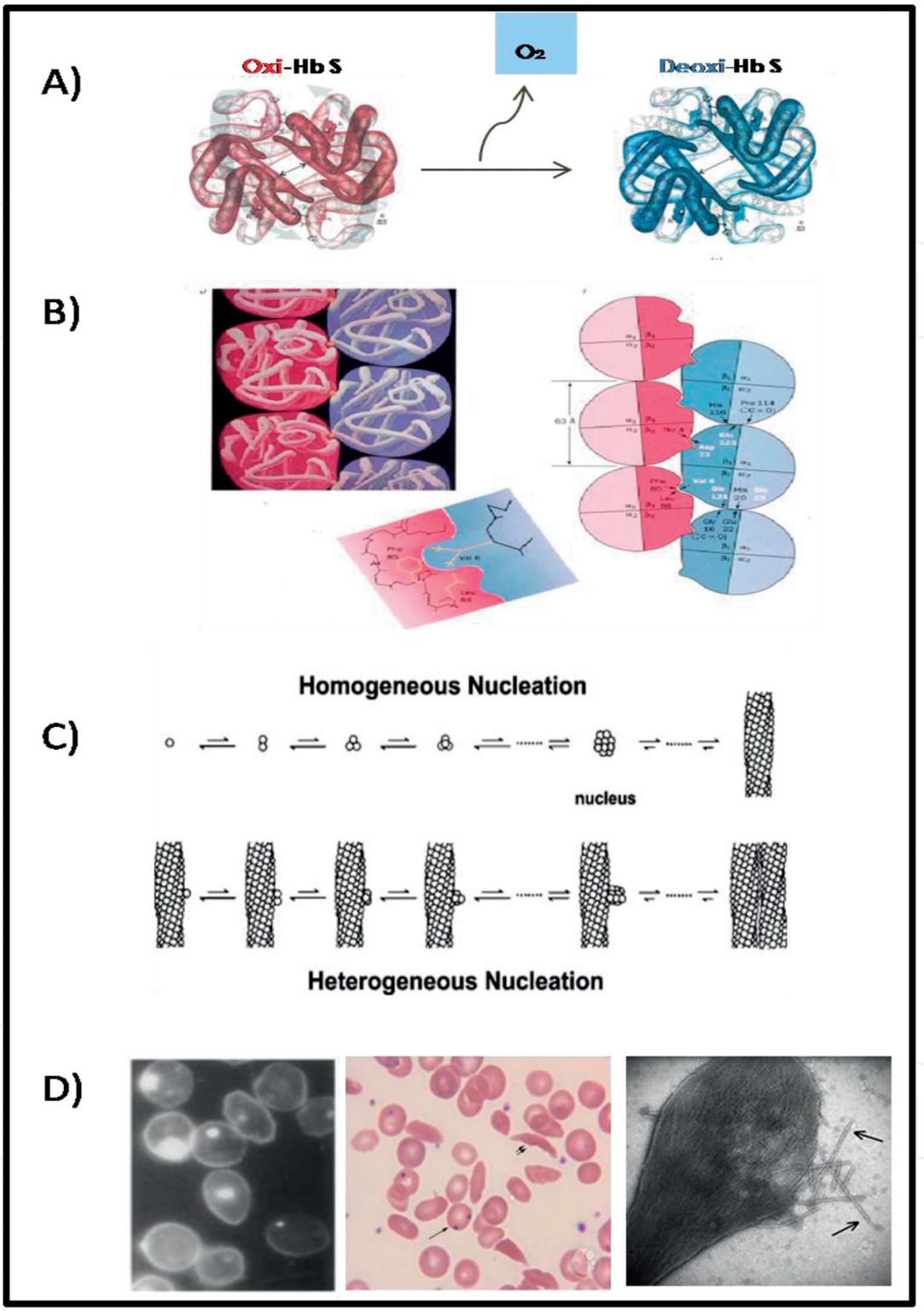


Figure 10. Summary of the pathophysiology of SCD. (A) Representation of the structural differences in the conformation of HbS when it is in oxygenated and deoxygenated form. (B) HbS polymerization process with details of the main amino acids involved in the mechanism. (C) Formation of the deoxy-HbS fibers 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



Figure 11. Microscopic finding showing structural differences observed in normal form (oxy-HbS) and sickle cell (Deoxy-HbS), responsible for the pathological aspects in individuals with SCD. Source: Site of Howard Hughes Medical Institute, 2018.

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 ($\alpha 4\beta 1$, $\alpha V\beta 3$) 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,

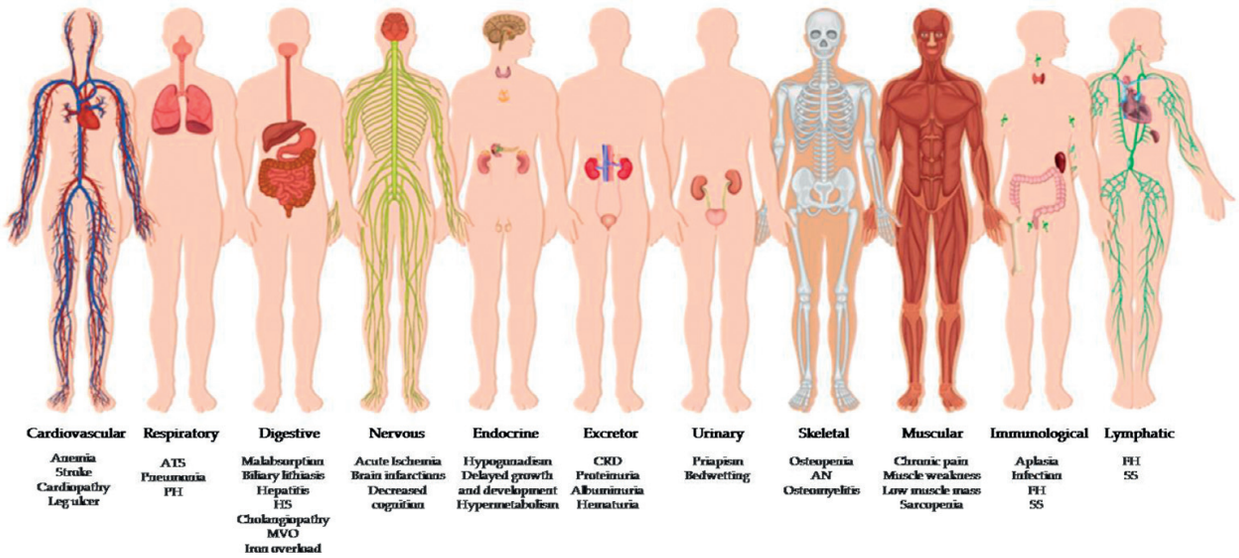


Figure 12. Major complications secondary to SCD. Source: The illustration has been adapted from the Toda Matéria website. For more details, refer to the articles Ballas et al. [78]; Saraf et al. [104]; Saraf et al., [105]; Gordbach et al., 2012; Piels et al., 2017; Di nuzzo & Fonseca [76]; Machado, 2007; Gumiero et al., 2007; Brunetta et al., 2010; Paladino, 2007; Hyacinth et al. [99]; Marques et al., 2012; Cançado, 2007; Lobo et al., 2010; Borsato et al., 2000; Saad eTraina, 2007, Marques et al., 2012; Caridade et al., 2007.

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].

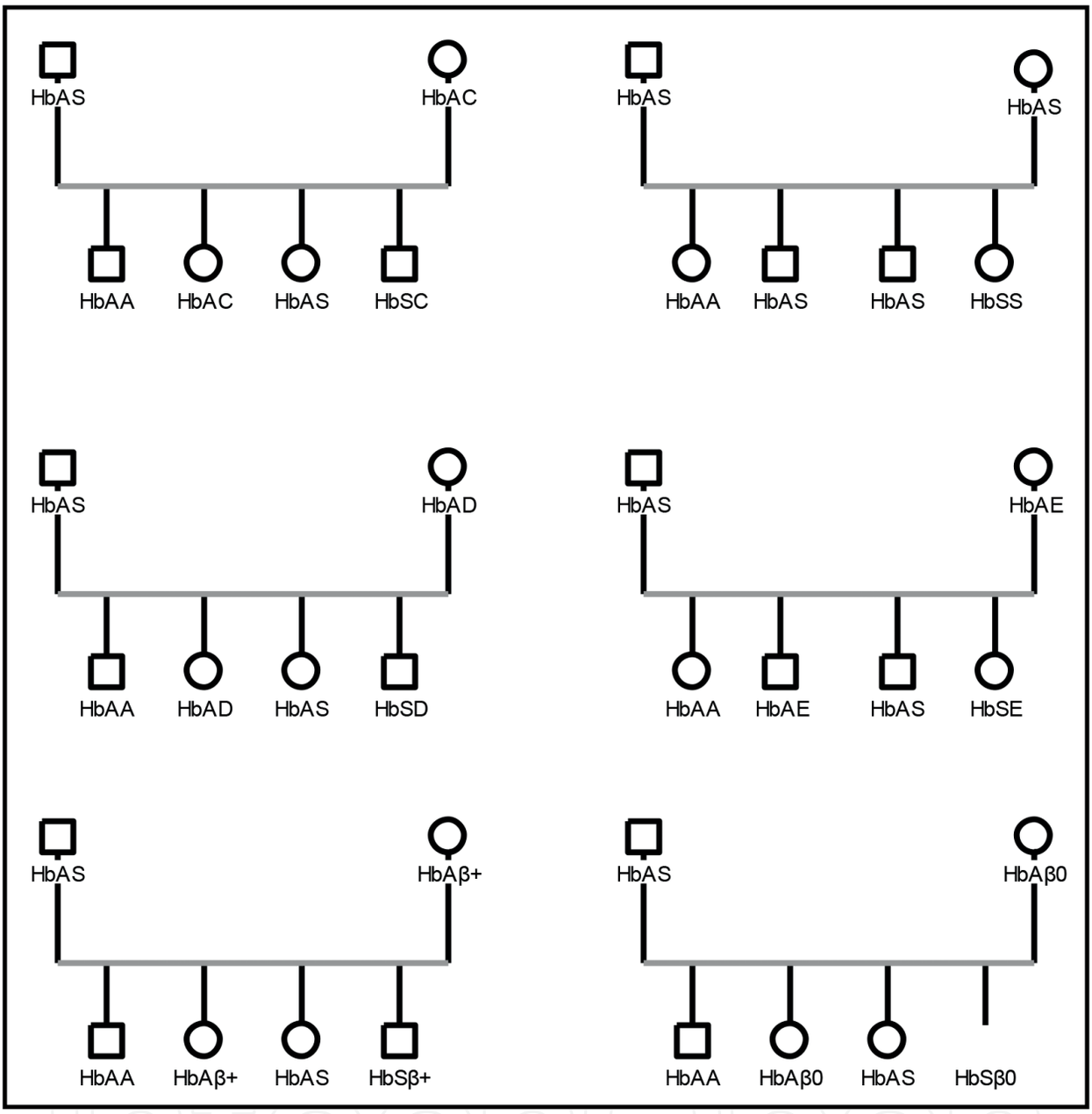


Figure 13. Genograms showing the most prevalent SCD genotypes in the world and the likelihood of homozygous or heterozygosis independent of sex when the parents have some type of hemoglobin variant that can generate SCD. The GENOPRO® software version 2016 was used to make the genograms.

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, heterozygoses 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.

Author details

Karen Cordovil

Address all correspondence to: karensouz@gmail.com

State Institute of Hematology Arthur de Siqueira Cavalcanti (HEMORIO), Rio de Janeiro, Brazil

References

[1] World Health Organization. Sickle-cell disease and other hemoglobin disorders. Media Centre. Who Technical Report Series Fact sheet; 2011. 308 p

[2] Modell B, Darlison M. Global Epidemiology of Hemoglobin Disorders and Derived Service Indicators. Public Health Reviews. 2008;**86**(6):480-487

[3] Piel FB, Patil A, Howes R, et al. Global epidemiology of Sickle haemoglobin in neonates. The Lancet. 2013a;**381**(9861):142-151

[4] Piel FB, Hay SI, Gupta S, et al. Global Burden of Sickle Cell Anaemia in Children under Five, 2010–2050. PLoS Med. 2013b;**10**(7):e1001484. DOI: 10.1371/journal.pmed.1001484

[5] Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. The New England Journal of Medicine. 2017;**376**(16):1561-1573

[6] Masiello D, Heeney M, Adewoye A, et al. Hemoglobin SE Disease. A Concise Review. 2007;**82**:643-649

[7] Utah Department of Health. Fact Sheet for Parents. Parents Guide to Sickle Cell Hemoglobin E Disease newborn screening Program. 2012. Avaliable in health.utah.gov/newbornscreening

[8] Fucharoen S, Winichagoon P. Haemoglobinopathies in Southeast Asia Indian. Journal of Medical Research. 2011;**134**(4):498-506. PMCID: PMC3237250

[9] Health Grove. Sickle Cell Disorders in Southeast Asia Statistics on Overall Impact and Specific Effect on Demographic Groups. Avaliable in http://global-disease- burden.healthgrove.com/l/74367/Sickle-Cell-Disorders-in-Southeast-Asia-East-Asia-and-Oceania

[10] Brousseau D, Panepinto J, Nimmer M, et al. The number of people with sickle-cell disease in the United States: National and state estimates. American Journal of Hematology. 2010; **85**(1):77-78

[11] Bonifacio J. Biliary lithiasis conduct in asymptomatic patients with sickle cell anemia. Federal university of Bahia. Joilton Bonifácio. Adviser: Murilo Pedreira Neves. TCC (Undergraduate - Medicine) - Federal University of Bahia, UFBA. Salvador; 2016. 27 f

[12] Rodrigues D, Fernandes K, Freitas D, et al. Clipping of the prevalence and diagnosis of sickle cell anemia. Rev Pat Toc. 2017;**4**(1):23-38

[13] Martins M, Teixeira M. Analysis of expenditures for hospital admissions for sickle cell anemia in the state of Bahia. Cad Saúde Coletiva. 2017;**25**(1):24-30

[14] Brazilin Health Website. Sickle cell disease. Coordination of the National Policy of Blood and Hemoderivatives. Ministry of Health; 2017. Available at http://portalsaude.saude.gov.br

[15] Loureiro M, Rozenfeld S. Epidemiology of sickle cell disease hospitalizations in Brazil Epidemiology of sickle cell disease hospital admissions in Brazil. Revista de saúde pública. 2005;**39**(6):943-949

[16] Brazilin Ministry of Health. Manual of Basic Ducts in Sickle Cell Disease. Department of Health Care and Specialized Attention. Brasília: Ministry of Health Ed; 2006. 56 p

[17] Wolf C. Sickle cell disease, a serious global public health problem. Revista Brasileira de Hematologia e Hemoterapia. 2010;**32**(4):280-281

[18] Lobo C, Marra VN, Silva RMG. Painful crises in sickle cell disease. Revista Brasileira de Hematologia e Hemoterapia. 2007;**29**(3):247-258

[19] Bruneira P. Splenic sequestration crisis in sickle cell disease. Revista Brasileira de Hematologia e Hemoterapia. 2007;**29**(3):259-226

[20] Karafin MS, Koch KL, Rankin AB, et al. Erythropoietic drive is the strongest predictor of hepcidin level in adults with sickle cell disease. Blood Cells Molecules and Diseases. 2015;**55**:304-307

[21] Nur E, Biemond BJ, Otten HM. Oxidative stress in sickle cell disease; pathophysiology and potential implications for disease management. American Journal of Hematology. 2011;**86**(6):484-489

[22] Ferrão T, Martins-Filho P, Aragão C. etal. Doppler velocimetry of the orbital arteries in patients with sickle cell anemia. Radiologia Brasileira. 2017;**50**(2):103-108

[23] Piel F, Patil A, Howes R, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nature communications. 2010;**1**:104

[24] Kanias T, Lanteri M, Page G, et al. Ethnicity, sex, and age are determinants of red blood cell storage and stress hemolysis. Blood Advances. 2017;**1**(15):1132-1141

[25] Gee BE. Biologic complexity in sickle cell disease: Implications for developing targeted therapeutics. The Scientific World Journal. 2013. DOI: 10.1155/2013/694146

[26] Wood D, Soriano A, Mahadevan L, et al. A biophysical marker of severity in sickle cell disease. Science Translational Medicine. 2012;**4**(123):123-126

[27] Rees D, Gibson J. Biomarkers in sickle cell disease. British Journal of Haematology. 2012; **156**(4):433-445

[28] Kato GJ, Mcgowan V, Machado RF, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with SCD. Blood. 2006;**107**(6):2279-2285

[29] Quinn C, Smith E, Arbabi S, et al. Biochemical surrogate markers of hemolysis do not correlate with directly measured erythrocyte survival in SCA. American Journal of Hematology. 2016; **91**(12):1195-1101

[30] Moreira J, Laurentino M, Machado R, et al. Pattern of hemolysis parameters and association with fetal hemoglobin in sickle cell anemia patients in steady state. Revista Brasileira de Hematologia e Hemoterapia. 2015;**37**(3):167-171

[31] Gomes LMX, Vieira MM, Reis TC, et al. Knowledge of family health program practitioners in Brazil about sickle cell disease: A descriptive, cross-sectional study. BMC Family Practice. 2011;**12**:89. DOI: 10.1186/1471/2296/12/89

[32] Lyra IM, Gonçalves MS, Braga JAP, et al. Clinical, hematological, and molecular characterization of sickle cell anemia pediatric patients from two different cities in Brazil. Cad Health Care. 2005;**21**(4):1287-1290

[33] Griffith DM. A pilot study: An examination of the quality of life of young African-American adults living with sickle cell disease (a qualitative approach). Jackson State University, ProQuest Dissertations Publishing. 2015:1011-5701 p

[34] Thompson RJ. The Interaction of Social, Behavioral, and Genetic Factors in Sickle Cell Disease. In: Hernandez LM, Blazer DG, editors. Institute of Medicine Committee on Assessing Interactions Among Social, Behavioral, and Genetic Factors in Health. Washington: National Academies Press; 2006

[35] Bakri MH, Ismail EA, Elsedfy GO, et al. Behavioral impact of sickle cell disease in young children with repeated hospitalization. Saudi Journal of Anaesthesia. 2014;**8**(4):504-509

[36] Steinberg MH, Adms JG. Hemoglobin A. Blood. 1991;**78**(9):2165-2177

[37] Hardison R. The evolution of hemoglobin. American Scientist. 1999;**87**(2):126-121

[38] Silva MM, Rogers PH, Arnoneg AA. Third Quaternary Structure of Human Hemoglobin A. at 1.7-A Resolution. Journal of Biological Chemistry. 1992;**267**(24):17248-17256

[39] Quinn NL, Boroevich KA, Lubieniecki KP, et al. Genomic organization and evolution of the Atlantic salmon hemoglobin repertoire. BMC Genomics. 2010;**11**:539

[40] Bekedam MA, van Beek-Harmsen BJ, van Mechelen W, et al. Myoglobin concentration in skeletal muscle fibers of chronic heart failure patients. Journal of Applied Physiology. 2009;**107**(4):1138-1143

[41] Kamga C, Krishnamurthy S, Shiva S. Myoglobin and Mitochondria: A relationship bound by Oxygen and Nitric Oxide. Nitric Oxide. 2012;**26**(4):251-258

[42] Kanatous SB, Mammen PPA. Regulation of myoglobin expression. Journal of Experimental Biology. 2010;**213**(16):2741-2747

[43] Rashin AA, Domagalski MJ, Zimmermann MT, et al. Factors correlating with significant differences between X-ray structures of myoglobin. Acta Crystallographica Section. 2014; **70**(2):481-491

[44] Shibayama N, Sugiyama K, Tame J, et al. Capturing the hemoglobin allosteric transition in a single crystal form. Journal of the American Chemical Society. 2014;**36**(13):5097-5105

[45] Bellelli A. Non-Allosteric Cooperativity In Hemoglobin. Current Protein & Peptide Science. 2017. DOI: 10.2174/1389203718666171030103310. PubMed PMID: 29086690

[46] Gell DA. Structure and function of haemoglobins. Blood Cells, Molecules & Diseases. 2017;**796**(17)30208-30205. pii. S1079. DOI: 10.1016/j.bcmd.2017.10.006. PubMed PMID: 29126700

[47] Rapp O, Yifrach O. Using the MWC model to describe heterotropic interactions in hemoglobin. PLoS One. 2017;**12**(8):e0182871. PMCID: PMC5549968

[48] Shibayama N, Ohki M, Tame JRH, et al. Direct observation of conformational population shifts in crystalline human hemoglobin. Journal of Biological Chemistry. 2017;**292**(44): 18258-18269

[49] Jorge SE, Bringas M, Petruk AA, et al. Understanding the molecular basis of the high oxygen affinity variant human hemoglobin Coimbra. Archives of Biochemistry and Biophysics. 2018;**1**(637):73-78

[50] Goodsell D. PDB-101: Globin Evolution. protein data bank. 2017. DOI:10.2210/rcsb_pdb/mom_2017_2

[51] Opazo J, Hoffmann F, Storz J, et al. Genomic evidence for independent origins of -like globin genes in monotremes and therian mammals. Proceedings of the National Academy of Sciences. 2008;**105**(5):1590-1595

[52] Hardison R. Hemoglobins from bacteria to man: Evolution of different patterns of gene expression. The Journal of Experimental Biology. 1998;**201**:1099-1117

[53] Nagatomo S, Nagai Y, Aki Y, et al. An Origin of Cooperative Oxygen Binding of Human Adult Hemoglobin. Eberini I, ed. PLoS ONE. 2015;**10**(8)

[54] Collins J-A, Rudenski A, Gibson J, et al. Relating oxygen partial pressure, saturation and content: The haemoglobin– oxygen dissociation curve. Breathe. 2015;**11**:194-201

[55] Riley RL, Lilienthal JL, Proemmel DD, et al. The relationships of oxygen, carbon dioxide, and hemoglobin in the blood of man: Oxyhemoglobin dissociation under various physiological conditions. Journal of Clinical Investigation. 1946;**25**(1):139-144

[56] Mills D, Ward L, Jones C, et al. Oxygen requirements of the earliest animals. Proceedings of the National Academy of Sciences. 2014;**111**(11):4168-4172

[57] Zhang S, Wang X, Wang H, et al. Sufficient oxygen for animal respiration 1,400 million years ago. Proceedings of the National Academy of Sciences. 2016;**113**(7):1731-1736

[58] Hardison RC. Evolution of hemoglobin and its genes. Cold Spring Harb Perspect Med. 2012;**2**(12):a011627

[59] Lane N, Martin W, Raven J, et al. Energy, genes and evolution: Introduction to an evolutionary synthesis. Biological Sciences. 2013;**368**(1622):2012-2053

[60] Fernandez-Jaramillo A, Duarte-Galvan C, Contreras-Medina L, et al. Instrumentation in developing chlorophyll fluorescence biosensing: A review. Sensors (Switzerland). 2012

[61] Chatterjee A, Kundu S. Revisiting the chlorophyll biosynthesis pathway using genome scale metabolic model of Oryza sativa japonica. Scientific Reports. 2015;**5**:14975

[62] Choi J, Mahadik B, Harley B. Engineering the hematopoietic stem cell niche: Frontiers in biomaterial science. Biotechnology Journal. 2015;**10**(10):1529-1545

[63] Lim W, Inoue-Yokoo T, Tan K, et al. Hematopoietic cell differentiation from embryonic and induced pluripotent stem cells. Stem Cell Research & Therapy. 2013;**4**(3):71

[64] Manning LR, Russell JE, Padovan JC, et al. Human embryonic, fetal, and adult hemoglobins have different subunit interface strengths. Correlation with lifespan in the red cell. Protein Science. 2007;**16**(8):1641-1658. DOI: 10.1110/ps.072891007

[65] Nandakumar S, Ulirsch J, Sankaran V. Advances in understanding erythropoiesis: Evolving perspectives. British Journal of Haematology. 2016;**173**(2):206-218

[66] Koolman J, Roehm KH. Hemoglobin: Tissue and Organ. In: Koolman, Color Atlas of Biochemistry, 2Ed. 2005

[67] Hoffbrand AV, Moss PAH. Genetics disorder of hemoglobin. In: Hematology fundaments. 6 ed. Porto Alegre: Artmed editors; 2013. 88-90 p

[68] Sankaran V. Targeted therapeutic strategies for fetal hemoglobin induction. ASH Education Program Book. 2011;**1**:459-465

[69] Thom C, Dickson C, Gell D, et al. Hemoglobin variants: Biochemical properties and clinical correlates. Cold Spring Harbor Perspectives in Medicine. 2013;**3**(3):a011858

[70] Daniel Y, Turner C, Haynes R, et al. Quantification of hemoglobin A2 by tandem mass spectrometry. Clinical Chemistry. 2007;**53**(8):1448-1454

[71] Perrine S. Fetal globin induction can it cure thalassemia? Hematology. 2005:38-44

[72] Hoots W. The registry and surveillance in hemoglobinopathies. Improving the lives of individuals with hemoglobinopathies. American Journal of Preventive Medicine. 2010 Apr;**38**(4 Suppl):S510-1

[73] Metcalf B, Chuang C, Dufu K, et al. Discovery of GBT440, an orally bioavailable r-state stabilizer of sickle cell hemoglobin. ACS Medicinal Chemistry Letters. 2017 Jan 23;**8**(3): 321-326

[74] Carter T, Von Fricken M, Romain J, et al. Detection of sickle cell hemoglobin in Haiti by genotyping and hemoglobin solubility tests. The American Journal of Tropical Medicine and Hygiene. 2014;**91**(2):406-411

[75] Chang J, Ye L, KanY. Correction of the sickle cell mutation in embryonic stem cells. Proceedings of the National Academy of Sciences of the USA. 2006;**103**(4):1036-1040. [Epub 2006 Jan 11]

[76] Di Nuzzo DVP, Fonseca SF. Anemia falciforme e infecções. Journal of Pediatrics. 2004;**80** (5):347-354

[77] Li X, Dao M, Lykotrafitis G, et al. Biomechanics and biorheology of red blood cells in sickle cell anemia. Journal of Biomechanics. 2017 Jan 4;**50**:34-41

[78] Ballas S, Kesen M, Goldberg M, et al. Beyond the definitions of the phenotypic complications of sickle cell disease. Scientific World Journal. 2012;**2012**:949535

[79] Steinberg M, Sebastiani P. Genetic modifiers of sickle cell disease. American Journal of Hematology. 2012;**87**(8):795-803

[80] Zago MA, Pinto ACS. Phytopathology of sickle cell disease: From genetic mutation to insufficiency of multiple organs. Revista Brasileira De Hematologia E Hemoterapia. 2007;**29**(3):207-214

[81] Neto GCG, Pitombeira MS. Moleculars aspects of sickle cell anemia. Jornal Brasileiro de Patologia e Medicina Laboratorial. 2003;**39**(1):51-53

[82] Erythrocyte NPC. Environmental interferons in sickle cell anemia. Revista Brasileira De Hematologia E Hemoterapia. 2000;**22**(1):05-022

[83] Eaton W, Bunn H. Treating sickle cell disease by targeting HbS polymerization. Blood. 2017;**129**(20):2719-2726

[84] Habara A, Minireview SM. Genetic basis of heterogeneity and severity in sickle cell disease. Experimental Biology and Medicine. 2016;**241**(7):689-696

[85] Frenette P, Atweh G. Sickle cell disease: Old discoveries, new concepts, and future promise. Journal of Clinical Investigation. 2007;**117**(4):850-858

[86] Rogers SC, Ross JGC, d'Avignon A, et al. Sickle hemoglobin disturbs normal coupling among erythrocyte o2 content, glycolysis, and antioxidant capacity. Blood. 2013;**121**(9):28

[87] Sonveaux P, Lobysheva II, Feron O, et al. Transport and peripheral bioactivities of nitrogen oxides carried by red blood cell hemoglobin. Physiology. 2007;**22**:97-112

[88] Galkin O, Pan W, Filobelo L, et al. Two-step mechanism of homogeneous nucleation of sickle cell hemoglobin polymers. Biophysical Journal. 2007;**93**(3):902-913

[89] Iqbal Z, Li M, Mckendry R, et al. Investigation of sickle-cell haemoglobin polymerisation under electrochemical control. Chemphyschem. 2013;**14**(10):2143-2148

[90] Rotter M, Yosmanovich D, Briehl RW, et al. Nucleation of sickle hemoglobin mixed with hemoglobin A. Biophysical Journal. 2011;**101**(11):2790-2797

[91] Uzunova V, Pan W, Galkin O, Vekilov PG. Free heme and the polymerization of sickle cell hemoglobin. Biophysical Journal. 2010;**99**(6):1976-1985

[92] Godwin M, Baysinger M. Understanding antisickling agents and the sickling process. Nursing Clinics of North America. 1983 Mar;**18**(1):207-14. PubMed PMID: 6550864

[93] Soderblom EJ,Thompson JW,Schwartz EA, et al. Proteomic analysis of erk1/2-mediated human sickle red blood cell membrane protein phosphorylation. Clinical Proteomics. 2013;**10**:1

[94] Gorbach A, Ackerman H, Liu WM, et al. Infrared imaging of nitric oxide-mediated blood flow in human sickle cell disease. Microvascular Research. 2012;**84**(3):262-269

[95] Ikuta T, Adekile AD, Gutsaeva DR, et al. The proinflammatory cytokine GM-CSF downregulates fetal hemoglobin expression by attenuating the cAMP-dependent pathway in sickle cell disease. Blood Cells, Molecules & Diseases. 2011;**47**(4):235-242

[96] Zennadi R, Moeller B, Whalen E, et al. Epinephrine-induced activation of LW-mediated sickle cell adhesion and vaso-occlusion in vivo. Blood. 2005;**110**(7):2708-2717

[97] Desai AA, Patel AR, Ahmad H, et al. Mechanistic insights and characterization of sickle cell disease-associated cardiomyopathy. Circ Cardiovasc Imaging. 2014;**7**(3):430-437

[98] Hyacinth HI, Adekeye OA, Yilgwan CS. Malnutrition in sickle cell anemia: Implications for infection, growth, and maturation. Journal of Social, Behavioral, and Health Sciences. 2013;**7**(1)

[99] Akohoue SA, Shankar S, Milne GL, et al. Energy expenditure, inflammation, and oxidative stress in steady-state adolescents with SCA. Pediatric Research. 2007;**61**:233-238

[100] Veríssimo MPA. Growth and development in sickle cell disease. Revista Brasileira De Hematologia E Hemoterapia. 2007;**29**(3):271-274

[101] Borel MJ, Buchowski MS, Turner EA, et al. Alterations in basal nutrient metabolism increase resting energy expenditure in sickle cell disease. American Journal of Physiology. 1998;**274**:357-364

[102] Cury D. Ocular lesions in patients with scd in Bahia. Revista Brasileira de Oftalmologia. 2010;**69**(4):259-263

[103] Saraf S, Zhang X, Shah B, et al. Genetic variants and cell-free hemoglobin processing in sickle cell nephropathy. Haematologica. 2015;**100**(10):1275-1284

[104] Saraf S, Molokie R, Nouraie M, et al. Differences in the clinical and genotypic presentation of sickle cell disease around the world. Paediatric Respiratory Reviews. 2014;**15**(1):4-12

[105] Minniti C, Taylor J, Hildesheim M, et al. Laboratory and echocardiography markers in sickle cell patients with leg ulcers. American Journal of Hematology. 2011;**86**(8):705-708

[106] Oliveira PA, Fernandes CV, Hencklain FGH, et al. Negative pressure therapy for complex wounds in patients with sickle-cell disease. Ost W Man. 2010;**56**(8):62-67

[107] Connor JL, Minniti CP, Tisdale JF, et al. SCA and comorbid leg ulcer treated with curative peripheral blood stem cell transplantation. Int J L Extr W. 2017;**16**(1):56-59

[108] Cox SE, Makani J, Fulford AJ, et al. Nutritional status, hospitalization and mortality among patients with sca in tanzania. Haematologica. 2011;**96**(7):948-953

[109] Potoka K, Gladwin M. Vasculopathy and pulmonary hypertension in sickle cell disease. American Journal of Physics. 2015;**308**(4):314-324

[110] Adewoyin A. Management of sickle cell disease: A review for physician education in Nigeria (Sub-Saharan Africa). Anemia. 2015;**7**(9):14-98

[111] Patel J, Patel B, Serjeant GR. The bone pain crisis of sickle cell disease and malaria: Observations from Gujarat, India. Indian Journal of Community Medicine. 2017;**42**(3): 167-169

[112] Weatherall DJ, Clegg JB. Public health reviews inherited haemoglobin disorders: An increasing global health problem. Public Health Reviews. 2001;**79**:704-712

[113] Lawrence J, Valentine W. Abnormal Hemoglobins: Clinical disorders resulting from various combinations. California Medicine. 1955;**82**(1):1-5

[114] Kikuchi BA. Nursing assistance in sickle cell disease in primary care services. Revista Brasileira De Hematologia E Hemoterapia. 2007;**29**(3):331-338

[115] Naik R, Haywood C. Sickle cell trait diagnosis: Clinical and social implications American Society of Hematology. Education Program. 2015;**1**:160-167

[116] Goldsmith J, Bonham V, Joiner C, et al. Framing the research agenda for sickle cell trait. American Journal of Hematology. 2012;**87**(3):340-346

[117] Kreuels B, Ehrhardt S, Kreuzberg C, et al. Sickle cell trait and stunting in children below two years of age in an area of high malaria transmission. Malaria Journal. 2009;**8**:16

[118] Mikobi T, Lukusa TP, Aloni M, et al. Clinical phenotypes and the biological parameters of Congolese patients suffering from sickle cell anemia. Journal of Clinical Laboratory Analysis. 2017;**31**(6):e22140

[119] Mikobi TM, Lukusa TP, Aloni MN, et al. Correlation between the lactate dehydrogenase levels with laboratory variables in the clinical severity of sickle cell anemia in congolese patients. PLoS ONE. 2015;**10**(5):e0123568

[120] Du E, Diez-Silva M, Kato G, et al. Kinetics of sickle cell biorheology and implications for painful vasoocclusive crisis. Proceedings of the National Academy of Sciences of the USA. 2015;**112**(5):1422-1427

[121] Alapan Y, Kim C, Adhikari A, et al. Sickle cell disease biochip: A functional red blood cell adhesion assay for monitoring sickle cell disease. Journal of Laboratory and Clinical Medicine. 2016;**173**(8):74-91

[122] Steinberg MH. Predicting clinical severity in sickle cell anaemia. British Journal of Haematology. 2005;**129**(4):465-481. PubMed PMID: 15877729

[123] Brasililian Ministry of Health . Manual of Basic Ducts in Sickle Cell Disease. Secretaria to Health and Specialized Attention. Brasília, Editor of the Ministry Of Health; 2006. 56 p

[124] Bruneira P. Skeletal kidney crisis in SCD. Revista Brasileira De Hematologia E Hemoterapia. 2007;**29**(3):259-261

[125] Mikobi TM, Lukusa TP, Aloni MN, et al. Clinical phenotypes and the biological parameters of Congolese patients suffering from SCA. Journal of clinical laboratory analysis. 2017;(6):31

[126] Araujo PIC. Self Care In Sickle Cell Disease. Revista Brasileira De Hematologia E Hemoterapia. 2007;**29**(3):239-246

[127] Reid M, Badaloo A, Forrester T, et al. In vivo rates of erythrocyte glutathione synthesis in adults with sickle cell disease. American Journal of Physiology-Endocrinology and Metabolism. 2006;**291**:E73-E79

[128] Krishnan S, Setty Y, Betal G, et al. Increased levels of the inflammatory biomarker c-reactive protein at baseline are associated with childhood sickle cell vasocclusive crises. British Journal of Haematology. 2010;**148**(5):797-804

[129] Jacob E, Miaskowski C, Savedra M, et al. Changes in sleep, food intake, and activity levels during acute painful episodes in children with SCD. Journal of Pediatric Nursing. 2006;**21**(1):23-34

[130] Pells JJ, Presnell KE, Edwards CL, et al. Moderate chronic pain, weight and dietary intake in african-american adult patients with SCD. Journal of the National Medical Association. 2005;**97**(12):1622-1629

IntechOpen

IntechOpen

IntechOpen

IntechOpen