The Genetics of Sickle Cell Anemia: A Literature Review

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Abstract — Sickle cell disease (SCD) is the most common form of a genetic group of hemoglobinopathies in which normal human hemoglobin (HbA) is partially or completely replaced by mutant sickle hemoglobin (HbS). The cause of HbS is a punctiform mutation with a single amino acid substitution (glutamic acid for valine), characterized by a production of erythrocytes in sickle which results in typical condition of this disease, like hemolytic anemia and vaso-occlusion. It is an autosomal recessive genetic disorder in which affected people have the genotype homozygous for HbS, which affects about 250,000 children annually, being more frequent in certain ethnic groups. Early diagnosis is needed to achieve prophylaxis and/or minimization of complications of this disease. Despite all the knowledge of this condition, the treatment is limited to crisis control and prophylaxis. Numerous advances have emerged, such as bone marrow transplantation and gene therapy, allowing infer that, in the near future, effectively cure of this disease will be achieved. This study aims to assess and collate knowledge of the literature about sickle cell anemia (SCA), and their molecular, genetic, clinical and epidemiological characters.

Index Term — Disease Autosomal, Genetics, Hemoglobinopathy, Hemoglobin, Sickle Cell Anemia

I. INTRODUCTION

SICKLE Cell Anemia (SCA) is a hemoglobinopathy wherein an abnormal chain of hemoglobin (HbS) is produced. It is an autosomal recessive hereditary anemia characterized by the presence of sickle-shaped red blood cells and by accelerated hemolysis due to the substitution of a single amino acid of the beta chain of hemoglobin. Individuals who have this character in homozygous present severe anemia

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(SCA), while those who have it in heterozygous (sickle cell trait) usually do not show symptoms. [1]

The low oxygen pressure distorts the shape of red blood cells, which suffer hemolysis, causing anemia. The sickled red blood cells (HbS) are also less flexible than normal ones (HbA), which leads to microvascular occlusion, causing in homozygotes “crisis” characterized by episodes of severe pain, bone infarcts, leg ulcers, associated with increased susceptibility to secondary infections. [1]

Sickle cell anemia, of the historical point of view, has its birthplace in Africa, where there was the habit, in many tribes, to tattoo bearers to identify the disease. Thus, it is believed that the mutant sickle cell gene is originated from black African population, the result of an evolutionary process that culminated in this hemoglobin mutation, conferring resistance to a type of malaria, since this was the cause of many deaths in that continent. In Brazil, because the country has received a large population of Africans through the slave trade (in 1500-1850), and by the beginning of the process of racial mix, there are many people with this condition, especially the afro descendant ones, and it is prevalent in states like Bahia, Rio de Janeiro and Minas Gerais. [2]

The first report of the disease occurred in the United States in autopsies of patients, in whom it was identified splenic agenesis in african american with a history similar to the chronic sickle cell anemia. Herrick, in 1910, made the first scientific report to observe the appearance of red blood cells and elongated anomalous light microscopy. [2]

Because of its high prevalence in Brazil, sickle cell disease has been considered as a public health problem and there are many studies that attempt to correlate the influence of several factors such as age, nutrition, sex and weight on the manifestation of the disease. As important as genetic variations, acquired factors are responsible for the clinical variability and prognosis of patients. The socioeconomic and educational level occupy central position, because they determine variants that directly influence the evolution of the disease, such as access to medical care, early diagnosis, adequate food and nutrition, basic sanitation, less exposure to secondary infections. [3]

Due to the relevance of this topic, it is justified the achievement of this scientific research, which aims to assess and collate knowledge in literature about sickle cell anemia, in
their molecular, genetic, clinical and epidemiological characters. This review also aims to contribute to greater knowledge about sickle cell disease in the country.

II. METHODOLOGY

The present study was conducted based on articles of source database SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Health Sciences) and DATASUS (Database System Public Health of the Ministry of Health of Brazil).

The articles taken as reference were published between the years 2001 and 2010. The survey was held between March 6 and April 30 of the year 2011. Of the 26 articles found, fifteen (15) were selected for the following inclusion criteria: scientific articles about sickle cell anemia published in the last 10 years with their approach the molecular, genetic, clinical and epidemiological studies, as well as influencing factors, and novelties in prophylaxis and treatment of disease.

From the analysis of the selected items, a revision was made to group seeking relevant information about the aspects contained in the objectives of this study.

III. DISCUSSION

Much has been discovered about the genetics of sickle cell anemia and this is clearly seen by analyzing the articles, since the from 15 studies analyzed, 12 at least mentioned aspects and molecular genetics of sickle cell anemia.

The Human Hemoglobin (Hb) is a tetramer globin polypeptide (a pair of chains "α-like" and one pair of chains "non-α") over a portion HEME for each chain, this portion consisting of a ring of protoporphyrin IX forming a complex with a single atom of ferrous ion (Fe2 +). The HEME group can connect to a single oxygen molecule, giving the Hb molecule the ability to carry up to four oxygen molecules - hence its importance in the metabolism of organisms. [4]

The production of various human hemoglobins is controlled by two groups of closely related genes. The genes of α-like globins are on the short arm of chromosome 16, between the band 13,2 and the telomere, and consist of two globin genes α (alpha) and a single copy gene ζ (zeta). The genes of non-α globin are on chromosome 11, band P15, near the end of the short arm, and consist of a single gene ε (epsilon), in the fetal globin genes G-αA and the genes G-ε(delta) and ε (beta) adult hemoglobin. [4]

It is still consensus that sickle cell anemia (SCA) is a monogenic disease caused by a single mutation in the beta globin gene, characterized by the substitution of glutamic acid by valine at position 6 (Glu→Val). This change alone causes the resulting abnormal hemoglobin, the hemoglobin S (HbS), when deoxygenated and in high concentration, provide reduced solubility with paracrystalline structure formation, leading to a sharp rise of blood viscosity. [5,11]

Characteristically, SCA presents obvious phenotypic variability and, to elucidate this phenomenon, recent research has shown that the pathogenesis of this disease is quite complex. In addition to factors themselves and the erythrocyte hemolysis, inflammation, endothelial activation and changes in vasoactive factors seem to play a role in triggering the clinical phenomenon typical of SCA, such as vaso-occlusion. [4]

The sickle gene results from a mutation punctiform causing substitution of amino acid-glutamic acid in the sixth position of the chain of β globin (β 6 Glu→Val), thereby hemoglobin S is represented by αζA β6 Glu→Val. This substitution is due to a change in the second base of the codon the encoding glutamic acid, in other words, GAG to GTG. [4,5,11]

Although all the patients with sickle cell disease presents the same genetic mutation, the relative diversity on the severity of the clinical manifestations is remarkable. Several modifying factors have been studied in order to determine why this diversity happens. The currently most important are: levels of Fetal Hemoglobin (Hb F), the coexistence of other hereditary hemoglobinopathies (eg, thalassemia) and finally, the different haplotypes of HbS. [5,11]

The association of sickle cell disease with other hereditary hemoglobinopathies is relatively frequent and leads to a variety of clinical presentations, ranging from asymptomatic to the most severe. Among its most common types include: Sickle cell disease (SCD), wherein individuals are homozygous for the gene for hemoglobin S; Sickle Cell Trait, wherein the patient has a gene that synthesizes polypeptide chains; Normal Globin (α2), and an abnormal gene (βS) with production of both hemoglobin (A and S), predominantly hemoglobin A (HbA). [6]

The latter modulators factors currently known are the haplotypes of HbS, which may be described as polymorphic sites of restriction endonuclease, located inside and around the mutant beta-chain gene. These haplotypes are commonly identified according to geographical area in which they were found (eg Benin, Senegal). [4]

The elucidation of the mechanism of action of the factors that modulate the severity of SCD will allow the introduction of individualized treatments, according to the severity of the phenotype of the patient, avoiding numerous and unnecessary interventions. [4]

Apparently, two interrelated events and triggered by polymerization of HbS appear to be responsible for the clinical manifestations of sickle cell anemia: the vaso-occlusion and the hemolytic anemia. These processes depend not only on aspects related to the erythrocyte, but also on the interaction with external factors (eg endothelial damage). [4]

The haplotypes of HbS also appear as influencers of disease severity. The mechanism by which each haplotype exerts its influence remains a mystery. Experiments prove that each have different levels of fetal hemoglobin. In America, the most common haplotypes are: Senegal, Benin and CAR. In Brazil, the most frequent haplotypes found were Bantu (77%), Benin (30%) and Senegal (3%). Patients with the Senegal haplotype usually have milder clinical forms, while those with the CAR haplotype have most severe clinical forms. Patients with Benin haplotype present forms with intermediate severity. [6]
Some authors with more holistic view formulated the hypothesis that sickle red cells act as irritants and cause inflammatory response according as they obstruct the flow, claiming that repeated episodes of localized ischemia and reperfusion can generate a state of chronic inflammatory tissue injury. These authors rely on the fact that all individuals with SCA have an identical mutation in the globin gene, but show great variation in clinical severity. These authors also relate elevated leucocyte counts and a low amount of Hb F in cases of more severe clinical, due to a greater inflammatory response. [5,6,11]

Another important aspect to be considered is the resistance to malaria that occurs in individuals with SCA. The finding of high frequency of sickle and normal alleles in certain populations led to the formulation of the concept of genetic polymorphism, where the stable frequency of the sickle cell gene in geographic regions with hyperendemic falciparum malaria results from gene deletion balanced as a result of early death of homozygous and gene selection due to heterozygote protection against death from malaria. The mechanism of this "heterozygous advantage" is not fully elucidated. However, it is believed that the sickle cell infected by Plasmodium falciparum, as a consequence of the low amount of oxygen available, will cause poor nutrition of parasites by Hb S, preventing their survival. As a result of these influences, the worldwide distribution of AF reflects the "malaria belt". [7]

Infections are the most common complications in individuals with sickle cell anemia. Countless cases of autosplenectomy phenomenon of early childhood are reported. However, even before the autosplenectomy, the phagocytic capacity mediated by opsonins and antibody production are affected as a result of persistent aggregation spleen, leading to functional asplenia, which becomes permanent in about the sixth to eighth year of life. As a consequence of asplenia, there will be an increased susceptibility to infections with encapsulated organisms such as Haemophilus influenzae type b (Hib) and pneumococcus, its occurrence is about 30 to 100 times higher than in healthy children. It was also observed in patients with sickle cell anemia a 25 times greater risk of developing salmonella infections, especially in children and adults. [8]

Several other studies have concluded that, about the gestation and the development of the fetus of a mother with the SCA, the only significant association in the literature review was the presence of bacteriuria and maternal pyelonephritis. Low birth weight has been quoted on a small number of cases. In a study conducted in India, it was found decreasing size of the femur and low birthweight among children of mothers with the sickle cell trait. Posteriorly, other studies have not confirmed these findings. [9]

The gene for hemoglobin S is a gene that occurs in high frequency across America. In Equatorial Africa, 40% of the population are carriers of this gene, and sickle cell disease reaches a prevalence of 2 to 3% of the population. The mortality of children with the disease under 5 years is about 25% to 30%, with most deaths are secondary to fatal infections, splenic sequestration or aplastic crises. [3,15]

In Brazil, it is more frequent in the southeast and northeast regions, affecting up to 0.1% to 0.3% of the dark-skinned population, tending to reach increasingly significant portion of the population due to the high degree of mixing in our country. Data of the guthrie test show that 3.500 children born with sickle cell disease in Brazil per year, and 200,000 have the sickle trait each year among newborns alive. These numbers are configured as Public Health issue. In some Brazilian states this prevalence is even higher, as in Bahia (1 in every 650 children is born with sickle cell disease, and 1 in 17, has sickle cell trait), in Rio de Janeiro (1 in every 1200 children born with sickle cell disease , and 1 in 21, has sickle cell trait) and in Minas Gerais (1 every 1,400 children born with sickle cell disease, and 1 in every 23 children has sickle trait). [3]

In the state of Piauí, in a survey conducted among the students of Pharmacy of Federal University of Piauí (UFPI), it was revealed the prevalence of 3% of sickle cell trait. Studies conducted in three quilombola communities in the region Paulistana (in Piauí), it was observed the presence of 8% of sickle cell trait. [15]

Other authors claim that the genes that control the synthesis of β globin chain in hemoglobin A and S are not sex-linked, so it is not expected difference in prevalence of the phenotype between sexes. Likewise it was not proven relationship between birth weight and Apgar score. However, in relation to nutritional microdeficiencies, few articles discuss the relevance of this factor, as an aggravating factor among children with sickle cell anemia, due to its implications on the clinical condition and the negative impact of complications on child development, and it can contribute to increase rates of morbidity and mortality in this group. [3,9, 10]

We also observed, in agreement with the available literature, that hospitalizations focus on young age groups - which reveals the large social impact of the disease and warns about the importance of improving the care of patients with SCA. Studies on sickle cell disease recognize the importance of the relationship between age and mortality. According to the international literature, there is a peak incidence of death in the age group of one to three years; bacterial infections are the main cause. The comparison between the survival curve of black patients with sickle cell disease and the curve of the black population in general shows a decrease in life expectancy of those patients 25 to 30 years. [3]

The Committee on Genetics of the American Academy of Pediatrics suggests a routine to be followed from diagnosis of neonatal hemoglobinopathies (or as early as possible) to the accompaniment of children and families affected. The strategies adopted for this screening are: selective tests of couples known to be carriers of SCA or have a sick child, or newborns from mothers with SCA detected in antenatal and universal screening of all newborns. Due to the importance of screening tests, many studies are conducted in order to verify
its effectiveness. [10]

The most effective therapeutic options currently available for the treatment of hemoglobinopathies in question are bone marrow transplantation (BMT) and hydroxyurea. Bone marrow transplantation, although to be a curative measure, it is considered high risk by presenting different degrees of complications and significant mortality. The use of Hydroxyurea in children with sickle cell anemia has reduced the clinical complications and a significant increase in life expectancy, by augmenting the levels of fetal hemoglobin, the hemoglobin concentration and the mean corpuscular volume, as well as reduced hemolysis and vaso-occlusive. [11 – 12]

Analysis of the products showed that HU has multiple effects on the erythrocyte lineage - promotes a rise in the level of HbF in 60% of treated patients, increases the rate of hemoglobin, mean corpuscular volume and reduces the number of reticulocytes. The concentration of HbF correlates with reduction of painful crises during treatment. In sickle cell anemia, the reduction in the rate of total hemoglobin associated with marked reticulocytosis characterizes the severity of hemolytic anemia – thereby, by reducing the level of reticulocytes and decreasing expression of adhesion molecules in endothelial cells, Hydroxyurea contributes to the reduction in hemolysis and in vaso-occlusive crises. [5 – 11 – 12 ]

Therefore, the hydroxyurea is considered the best option of treatment currently available for obtaining the clinical and hematologic ameliorate. However, being identified as a potentially carcinogenic drug, there are questions about the benefits and toxicities when used for long periods, which requires attention and careful investigation about the possible genotoxic actions, because it can cause irreversible changes in the genetic material, with serious consequences to the organism. [11 – 12]

A major advance in the treatment of SCA constitutes the study of a chimeric oligonucleotidio for direct correction of the mutation in allele hemoglobin S-beta. The internal sequence is complementary to the sequence of hemoglobin beta-S. The chimeric molecule is introduced into the lymphoblastoid cells (B cells) homzygous for the mutation beta-S, and after six hours had a detectable level of gene conversion of the mutant allele in the normal sequence. To measure the efficiency of correction it was used a technique of polymerase chain reaction-based analysis of "restriction fragment length polymorphisms". The efficient and accurate conversion directed by chimeric molecules may contain such a promise to a therapeutic method for the treatment of genetic diseases in a close future. [14]

Due to the unavailability of curative treatment and the high prevalence of the disease, as well as being a public health problem, a review of the bioethics issue becomes extremely necessary. The prevention of SCA is only possible by the incorporation of information about reproductive risk for heterozygous couples or for people with sickle cell anemia. [13]

In order to promote a greater focus on bioethical issue of sickle cell disease since the 1950s Brazil has records of counseling programs genético. In addition, the federal government also strives for national educational policies, such as the formation of a working group to prepare the Sickle Cell Program in 1990. The new genetics is characterized by a tension between prevention policies for prevention for diseases and promotion of fundamental rights - that is, while it aims to reduce the incidence of disease in the population, it is also committed to ethical principles such as autonomy and reproductive moral pluralism. [11 – 13]

The "combat" to SCA was a public health goal in the United States with the Institutionalization of National Prevention Act on Prevention of SCA in 1921. The big consequences of U.S. policy showed that in the absence of a cure for sickle cell anemia, the main strategy of "fighting" the disease was by eugenic measures. [11 – 13]

In a recent study on one of the major educational instruments adopted by the Ministry of Health, it is verified the centrality of reproductive care to prevention efforts in the field of sickle cell anemia. The concept of awareness refers to the expectation that people, once informed and educated about their genetic identity, are able to make right decisions in the field of reproduction. A decision would be right when it implied changing behaviors and values. The awareness is not, however, a measure free of values or expectations, but clearly an action aimed at controlling reproduction through biomedical rationality of risk. Genetic counseling is now a solid career in the health field, whose goal is, while informing about probabilities and risks, also encourage people to incorporate this information in their reproductive decisions. [11 – 13]

It is noteworthy that, traditionally, sickle cell anemia was seen as a disease exclusive to blacks or their descendants, so the margins of national health priorities. Only with the development of knowledge about the subject was recognized due to the importance of greater attention to the ethical issue of sickle cell anemia. [13]

The theme of genetic prevention brings a number of ethical challenges, in particular the impossibility of moral and legal termination of pregnancy in cases of diagnosis of sickle cell anemia in the fetus, which means there is an emphasis on pre-conception. Health policies developed aim to draw people to identify the disease and seek specialized care. But there is also an emphasis on the idea that informed people can contribute to prevent the spread of the disease. Therefore, the prevention, the risk awareness, the genetic counseling and the racial disease are discussed today in order to at least improve conditions for the people affected by the disease, while a curative measure is not discovered. [13]

IV. CONCLUSION

The findings of this study allow us to perceive the relevance of sickle cell anemia, due to its high prevalence, morbimortality and the absence of curative treatments. Thus,
the grouping of existing knowledge about this topic, as well as their detailed analysis, was necessary in order to not only reduce the incidence of SCA in the population, but mainly to promote a better quality of life and increased survival of people affected by this disease.

For the analysis of the work, we highlight the importance of understanding the genetic basis of this disease, of monitoring the possible complications associated with the desease, as well as the factors that influence their occurrence or aggravation. Moreover, conducting reviews like this enables a reassessment of discoveries, allowing, through a reflection about the genetic basis, the develop of new approaches, whether palliative or perhaps even healing.

REFERENCES

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