Bibliographic investigation of hemoglobin S from 1976 to 2007

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ABSTRACT

Purpose: To search the literature for epidemiological aspects of hemoglobin S. **Methods**: This study was a bibliographic investigation from 1976 to 2007 using Medline and Lilacs databases. A manual search was also conducted. **Results**: Among the 21 articles selected, 7 of them (33.3%) were published between 1976 and 2000, 10 of them (47.7%) were published between 2001 and 2004, and 4 of them (19.0%) were published between 2005 and 2007. Three of those articles that described the pathophysiology and clinical presentation were published by nurses. One of the publications, using Roy's adaptation model, described the nursing process to clients with falciform anemia. Eleven publications (52.0%) were worldwide epidemiological studies. Seven publications (34.0%) described the diagnosis, neonatal screening, and programs for the management of falciform anemia in Brazil. **Conclusion**: There is a need for further research in the topic by health care professionals, especially by nurses regarding preventive measures, and the management and rehabilitation of patients with falciform anemia.
Keywords: Anemia , sickle cell anemia; Sickle cell trait; Neonatal screening.

RESUMO

Objetivo: Buscar na literatura aspectos epidemiológicos explorados sobre a hemoglobina S. **Métodos:** Trata-se de um levantamento bibliográfico nas bases de dados Medline e Lilacs. Também foi feita uma busca não eletrônica, em publicações de 1976 a 2007. **Resultados:** Os resultados mostraram que, dos 21 artigos selecionados, 7 (33,3%) foram publicados entre 1976 e 2000, 10 (47,7%) entre 2001 e 2004 e 4 (19%) entre 2005 e 2007. Com relação aos descritores, três referências (14%), são da área da enfermagem, descrevem o quadro clínico e a fisiopatologia, sendo que uma delas sistematiza a assistência à clientela com anemia falciforme à luz do referencial de adaptação de Roy; 11 (52%) destacaram estudos epidemiológicos e a distribuição mundial; e sete (34%) contemplaram diagnóstico médico, triagem neonatal e programas voltados à população falcêmica no Brasil. **Conclusão:** Os resultados apontam a necessidade de investigação nessa área pelos profissionais de saúde, principalmente os da área da enfermagem, em relação aos cuidados de prevenção, promoção e reabilitação dos pacientes falcêmicos.
Descritores: Anemia falciforme; Traço falciforme; Triagem neonatal

RESUMEN

Objetivo: Buscar en la literatura aspectos epidemiológicos explorados sobre la hemoglobina S. **Métodos:** Se trata de un levantamiento bibliográfico en las bases de datos Medline y Lilacs. También se hizo una búsqueda no electrónica, en publicaciones de 1976 a 2007. **Resultados:** Los resultados mostraron que, de los 21 artículos seleccionados, 7 (33,3%) fueron publicados entre 1976 y 2000, 10 (47,7%) entre 2001 y 2004 y 4 (19%) entre 2005 y 2007. Con relación a los descriptores, tres referencias (14%) son del área de enfermería, describen el cuadro clínico y la fisiopatología, siendo que una de ellas sistematiza la asistencia a la clientela con anemia falciforme bajo el marco teórico de adaptación de Roy; 11 (52%) destacaron estudios epidemiológicos y la distribución mundial; y siete (34%) contemplaron el diagnóstico médico, la clasificación neonatal y los programas dirigidos a la población con anemia falciforme, en Brasil. **Conclusión:** Los resultados apuntan la necesidad de realizar investigaciones en esa área por profesionales de la salud, principalmente los del área de enfermería, en relación a los cuidados de prevención, promoción y rehabilitación de los pacientes con anemia falciforme.
Descriptores: Anemia falciforme; Trazo falciforme; Clasificación neonatal.

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INTRODUCTION

Hemoglobinopathies, also known as hemoglobin hereditary diseases, are included among the most frequent genetic diseases in the human population and show significant morbidity worldwide. This fact has contributed to the early implementation of community programs of investigation and control of such diseases, especially in more developed countries in the Northern hemisphere[1].

The cause of this hemoglobin change is that valine replaces glutamic acid at position 6 of the â polypeptide chain, resulting in physico-chemical change of the hemoglobin molecule, producing hemoglobin S[2].

As a result, there is a change in the morphology of erythrocytes. A normal erythrocyte is characterized as a flexible, bi-concave disc-shaped cell that enables efficient exchange of gases and water permeability, with a mean life span of 120 days. In contrast, sickle-cell erythrocytes are gathered in sickle-shaped structures, induced by the polymerization of deoxy-Hb S molecules, thus greatly reducing their mean life span to between 7 and 25 days[3].

In addition to decreasing its mean life, this causes obstruction of capillaries, known as vaso-occlusions. This phenomenon occurs in the whole organism, causing pain and, throughout the years, ischemic lesions in all organs that comprise the group of clinical manifestations observed in these individuals[4].

A study developed in the *Ambulatório de Hemoglobino-patias* (Hemoglobinopathy Outpatient Clinic) with nine patients (eight women and one man), in 2003, revealed low oxygenation and its effects, in the physiological mode (compromised physical development, sexual retardation, hemolytic jaundice, respiratory changes). In the psychosocial field, the self-concept showed a reduction in self-esteem; changes of occupation predominated when performing one's role and, in the interdependence, the mother stood out as the significant other. Vaso-occlusion was the stimulus that caused physiological changes; in addition, the affected physiological function was found to change other adaptive modes[4].

As regards the role of nursing professionals in the political context of sickle cell diseases, a study performed in primary health care services, in the city of São Paulo, aimed to view the disease according to its cultural, social and health care aspects, in addition to describing nursing care, with the purpose of minimizing the impacts of morbidity and mortality on the affected population[5].

Another study, focusing on the role of nurses in sickle cell anemia, was performed in the blood center of the city of Ribeirão Preto, SP, between 1991 and 1998, aiming to provide basic knowledge to those with sickle cell anemia, enabling them to live better with the episodes triggered by this chronic disease throughout the years. Moreover, this study focused on the promotion of information about the disease and educational actions for health professionals, especially nurses[6].

Considering the high frequency of heterozygotes in the population, this study aimed to search for epidemiological aspects of hemoglobin S that have been analyzed in the literature. Thus, a contribution to health care for individuals with sickle cell anemia is expected to be achieved.

METHODS

This study was a bibliographical survey, a method that consists in surveying relevant literature in databases (in this case, MEDLINE and LILACS), by means of a non-electronic search, to be the basis of investigation of the proposed study. A total of 21 studies, published between 1976 and 2007, in English and in Portuguese, were selected. For this search, the following descriptors were used: "*traço falciforme*" (sickle cell trait), "*triagem neonatal*" (neonatal screening) and "sickle cell anemia". Inclusion criteria adopted to select publications were as follows: articles that discuss epidemiological aspects that focus on sickle cell trait and anemia; screening with distribution in the population; existing programs. Exclusion criteria were as follows: articles that focus on clinical aspects of complications, treatment and prognosis of the disease, indexed in their entirety in the SciELO and BIREME databases. Once identified, publications were analyzed and data recorded in forms, designed for this purpose, according to the proposed objectives. After this analysis, data were organized and ideas interpreted, leading to the writing of the study.

RESULTS

Of all the 24 references selected(1-24), 7 (33.3%) were published between 1976 and 2000, 10 (47.7%) between 2001 and 2004, and 4 (19%) between 2005 and 2007.

As regards the concept and definition of normal hemoglobin and hemoglobin S (genetic classification of sickle cell diseases); 3 (14.3%) are from the nursing area and describe the clinical picture and physiopathology, one of which systematizes health care provided to individuals with sickle cell anemia in view of Roy's adaptation framework; 11 (52.4%) emphasize epidemiological studies and their worldwide distribution; and seven (34%) deal with the medical diagnosis, neonatal screening and programs aimed at the Brazilian population.

Normal hemoglobin is the respiratory protein present inside erythrocytes of mammals, which has the main function of carrying oxygen throughout the organism. Its structure is a spheroid, globular protein, formed by four sub-units, comprised of two pairs of globin polypeptide chains, one of which is known as alpha-type and the other, non alpha-type (beta, delta, gamma and epsilon). Its structure is chemically bonded to a prosthetic iron nucleus, ferroprotoporphyrin IX, which shows the property of receiving, bonding to and/or releasing oxygen in tissues. Each globin polypeptide chain is comprised of a sequence of amino acids, alpha chains having 141 amino acids and non-alpha

chains, 146. Combinations between several chains of proteins originate different hemoglobins, present in erythrocytes from the embryonic stage (intra-uterine) to the adult stage and produced throughout the distinct phases of human development[7].

Changes in globin genes determine hereditary defects in hemoglobin synthesis. As each normal individual has only one pair of â genes, a defect in one of these genes causes changes in approximately half of the adult hemoglobins. This genetic condition is known as heterozygote[8].

Hemoglobin hereditary defects are classified as follows: structural changes of hemoglobins (genetic condition in which a hemoglobin appears with an abnormal structure of the globin chain – Hb S, Hb C, Hb D, Hb E); defects in the rhythm of synthesis or thalassemias (hereditary condition where there is an imbalance in the synthesis of one or more globin chains, designated according to the type of chain whose synthesis has been harmed); hereditary persistence of fetal hemoglobin (a frequently asymptomatic hereditary condition where the synthesis of substantial amounts of Hb F persists in adulthood). The present study focuses on structural changes, which are more frequent and produce important clinical manifestations, of which Hb S and Hb C are more relevant[8].

In Brazil, sickle cell trait is a prevalent genetic characteristic, especially due to the number of black people in the population and the miscegenation process[9-10].

Heterozygosis for hemoglobin S consists in a relatively common situation, although clinically benign, once the majority of individuals do not show adverse clinical effects[11]. Clinical complications are extremely rare, due to a concentration of Hb S below 50%, which causes erythrocytes to be resistant to the sickle cell process[8].

Individuals with sickle cell trait have a life expectancy equal to that of the rest of the population and show normal hemogram hematological values and hematimetric indices[12]. They should be referred to genetic counseling, once they may have children with severe sickle cell disease[6].

"Sickle cell disease" is a term used to determine a group of genetic changes characterized by the predominance of Hb S, with sickle cell disease, the homozygous form of Hb S (Hb SS), being the most severe[13].

In sickle cell anemia, there is a mutation in the genes that regulate the synthesis of amino acids (sequence) of globin polypeptide chain, changing its structure. The cause of this hemoglobin change is the replacement of glutamic acid for valine at position 6 of the â polypeptide chain. This fact results in the change of erythrocyte morphology, with erythrocytes shaped like sickles being formed[2]. The change to a "sickle" shape reduces the mean life of an erythrocyte, causing it to be less flexible producing capillary obstructions, a phenomenon known as vaso-occlusion, followed by pain and ischemic lesions, which occur in the whole organism throughout the years[4].

The presence of an abnormal hemoglobin – hemoglobin S – shaped like a half-moon or sickle, as found in sickle cell anemia, thus named because this is the shape in which erythrocytes appear[14].

The occurrence of vaso-occlusions, especially in small vases, is the predominant physiopathological event in the origin of the majority of signs and symptoms present in the clinical picture of patients with sickle cell anemia. These include painful crises, hemolytic crises, lower limb ulcers, acute chest syndrome, splenic sequestration crisis, priapism, femoral head aseptic necrosis, retinopathy, chronic renal insufficiency, self-splenectomy and cerebrovascular accident, among other things[7].

Such clinical manifestations do not appear during the first six months of life; individuals remain asymptomatic due to high levels of fetal hemoglobin[15].

There are many factors participating in the pathogenesis of sickle cell anemia symptoms. The following are among these factors: percentage of hemoglobin S and F, oxygen tension, types of sickle cells, pH, blood viscosity, mechanical fragility of sickle cells and extravascular hemolysis[16,24].

Sickle cell disease has a hereditary nature and affects a significant number of individuals in several parts of the world[23]. It originated in Center-West African countries, India and East Asia, between around 100,000 and 50,000 B.C., between the Paleolithic and Mesolithic periods[5].

The first description in the medical literature was made by Herrick, in 1910, based on a clinical case of sickle cell anemia[7].

The disease was brought to the Americas by forced immigration of slaves. In addition to Africa and the Americas, it is currently found throughout Europe and in extensive regions of Asia.

Haplotypes are specific of certain populations or ethnic groups. Although the final product is the synthesis of Hb S, there are at least three population groups in Africa with different chromosome segments, characterized by specific sequential arrangement of nitrogen bases. These three groups, distributed in distinct geographic regions, were named Senegal, Benin and Bantu. In addition to these three groups, two other small ethnic groups have been described as they have different haplotypes than those already described, one of which belongs to individuals from Southeastern Cameroon, another belonging to a tribe known as Eton people or Bushmen, characterizing the Cameroon haplotype. However, the theory of multicentric origin of the Hb S gene began to have considerable credibility when it identified another haplotype, distinct from the four previous ones, among populations from Eastern Saudi Arabia and tribal groups from India. This Hb S haplotype, known as Arab-Indian, is notably present in populations of Eastern Saudi Arabia, Bahrain, Kuwait and Oman[3].

The six main haplotypes have been reported in different regions of the world and are related to countries or areas of the African continent or close to it, being linked to specific population

groups. They are named after their places of origin: Benin, Center African Republic, Senegal, Cameroon, Saudi Arabia and India. Such haplotypes can be useful in the study of the origin and evolution of the human race. The genetic variability involved in the mutation enabled a better understanding of the disease's clinical heterogeneity, in addition to its importance for anthropological studies[7].

In Brazil, historical data on the slave trade from Western Africa, on the Atlantic coast, where the Senegal haplotype predominates, show that these slaves were taken to Northern Brazil, whereas slaves coming from Center-West Africa, where the Benin haplotype is more frequent, were taken to Northeastern Brazil (states of Bahia, Pernambuco and Maranhão). However, by analyzing DNA polymorphisms in the hemoglobin's â gene complex in 30 patients with sickle cell anemia in the population of the city of Belém, capital of the state of Pará, only 3% were found to have the Senegal haplotype; 30%, the Benin haplotype; and 67%, the Bantu haplotype. Regional differences in the origin of African slaves were changed by the domestic slave traffic and, subsequently, by migratory movements, as observed by the prevalence of 1.14% of sickle cell traits in the state of Rio Grande do Sul, in Southern Brazil[17-18].

In Brazil, sickle cell anemia is the most prevalent hereditary disease, affecting between 0.1% and 0.3% of the black population and with a tendency to affect significantly higher numbers of individuals in the population, due to the high level of miscegenation[16].

This disease is heterogeneously distributed, being more frequent where the proportion of black ancestors is higher; in addition, it is predominant among black and mixed individuals, although it can occur in white individuals as well. Estimates based on prevalence point to two million individuals with the Hb S gene and more than 8,000 affected with the homozygous form (Hb SS). It is estimated that between 700 and 1,000 children with sickle cell diseases are born every year[10].

A more recent study estimates that, in Brazil, there are about 4 million individuals with the sickle cell trait and nearly 30,000 affected by severe forms of the disease, including sickle cell anemia (Hb SS), Hb SC disease and the interaction between beta thalassemia and Hb S[1].

The expansion of Hb S occurred in the Pre-Neolithic period, between 10,000 and 2,000 B.C., marked by miscegenation among different peoples of the Saharan region. In this period, Sahara was comprised of fertile lands and agriculture was developed to supply the local populations. In the Neolithic period (from 5,000 to 3,000 B.C.), there was a parasite transmission caused by *Plasmodium falciparum*, which originated in the region corresponding to modern day Ethiopia. Malaria spread among four main centers (centers of civilization in the Nile river valley, Mesopotamia, India and Southern China) and, in the specific case of Hb S, malaria spread from the Nile river valley to the Mediterranean coast. It is believed that, with the development of the disease caused by malaria, a selective pressure that favored Hb S (Hb AS) heterozygous individuals began[3].

Although children with sickle cell trait have a lower incidence of parasitemia, erythrocytes become infected with parasites in an ordinary way. Consequently, the inhospitable nature of erythrocytes with Hb AS is subsequently manifested in a symbiotic relationship. In this aspect, the multiplication of parasites is prevented by the sickle cell process and premature destruction of parasite-infected erythrocytes with a sickle cell trait, cell oxidation by iron released from denatured Hb S, cell potassium depletion and deficient nutrition of parasites by Hb S[19].

It is possible that the heterozygous state for Hb S (sickle cell trait) gives the individual a biological advantage against the infection caused by *P. falciparum*, thus being the reason why the frequency of the Hb S gene reached, through natural selection, such high levels in geographic regions where malaria is endemic, i.e. Equatorial Africa, known as the malaria belt[14].

The laboratory diagnosis of sickle cell anemia is performed using hemoglobin electrophoresis, isoelectric focalization or high-performance liquid chromatography (HPLC)[16].

Alkaline hemoglobin electrophoresis on cellulose acetate continues to be the basic methodology to qualify a great number of mutant hemoglobins. Currently, the introduction of alternative techniques, such as isoelectric focalization and high resolution liquid chromatography has enabled a better analysis of variant hemoglobins[1].

Early diagnosis is essential, once it would prevent complications resulting from the disease, and it can even be performed in the pre-natal period. At this stage, the clinical expression of Hb S homozygosis has been associated with high morbidity and mortality in childhood, due to bacterial sepsis, splenic sequestration crisis and acute chest syndrome[20,24].

As regards sickle cell anemia, it is expected that the *Programa Nacional de Triagem Neonatal* (National Program of Neonatal Screening), associated with certain therapeutic measures, such as prophylactic penicillin-therapy between three months and five years of age, specific vaccination (Pneumococcus, Haemophilus, Hepatitis B) and regular outpatient follow-up, guarantee higher levels of survival and quality of life for those who have this disease[21].

As Brazil has a population with different levels of miscegenation, an early diagnosis should be performed in all newborns, regardless of their ethnic group. Miscegenation in the Brazilian population is significant and progressive, and classification by skin color and other characteristics cannot currently be used as the only way to assess ethnic groups[20].

Brazil's Ministry of Health's Decree 822/01 regulated Neonatal Screening of several metabolic disorders, including sickle cell diseases and other hemoglobinopathies, guaranteeing equal access to screening tests for all Brazilian newborns, regardless of their geographic origin, ethnic group and socioeconomic class[22].

Early diagnosis and treatment of such hemoglobinopathies

significantly increase survival and quality of life of those suffering from such diseases, reducing their sequelae and clinical complications. Thus, the importance of their neonatal diagnosis. In the last years, expectations regarding morbidity and mortality by sickle cell disease have changed significantly, partly due to the greater accuracy and earliness of diagnosis, in addition to the growing volume of new knowledge about the disease. The other part is due to the gradual sensitivity of public health institutions in Brazil, motivated especially by social movements related to the black population and associations of individuals with the Hb S gene[3].

These data suggest that the inclusion of universal neonatal screening for hemoglobinopathies in projects that have already been implemented for phenylketonuria and congenital hypothyroidism shows advantages and should be considered by health programs[20].

DISCUSSION

The studies mentioned here showed that the researchers' concern about sickle cell diseases is aimed at the implementation of programs that enable screening and early diagnosis of sickle cell diseases.

This reveals that these diseases, ac a phenomenon studied in the population of certain Brazilian regions, oftentimes caused by social pressure, have led to specific laws that promote early diagnosis and treatment, thus contributing to a reduction in morbi-mortality.

The nursing studies selected for the present study show such care for this clientele, founded on the nursing process. In addition, one of them describes care according to a theoretical framework, revealing how the patients' adaptive process to sickle cell anemia occurs.

Although the literature includes many aspects of hereditary diseases, the authors' intention in this study was to contribute to health professionals, in the sense of drawing attention to the importance of early screening and diagnosis to enable treatment to be effective.

CONCLUSION

Analysis of scientific production on hemoglobin S has allowed information about the following to be generated: concept, history, national and international distribution, interaction with other variant hemoglobins, diagnostic tests, neonatal diagnosis and specific legislation on sickle cell changes. The results provide resources for reflection on the great, ongoing need for investigation on prevention, promotion and rehabilitation of sickle cell patients by health professionals, especially nurses.

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