Integrative review evaluation of newborn screening for the diagnosis of sickle cell anemia

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ABSTRACT

INTRODUCTION: Sickle cell anemia is a hereditary, chronic hemoglobinopathy, defined as a hemolytic anemia, caused by a deformation in the structure of erythrocytes due to the production of Hb "S", changing the natural biconcave format, to a "sickle" or "sickle" shape. half Moon". Data show that sickle cell anemia reached in the period from 2014 to 2020, the annual average of 1,087 new cases of children diagnosed with sickle cell disease. The test for initial diagnosis is the so-called "Heel Foot Test", which comes from neonatal screening and is performed using the High Performance Liquid Chromatography method.
PURPUROSE: The objective of this work is to carry out an integrative review on the evaluation of neonatal screening for the diagnosis of sickle cell anemia.
METHODS: This is an integrative literature review. The survey of scientific articles was carried out using the descriptors: "Neonatal screening"; "sickle cell anemia"; "Neonatal screening"; and "sickle cell anemia", using the Boolean operator "AND", in the Scientific Electronic Library Online (SciELO) and PubMed databases; in the period from April 1 to May 20, 2023
RESULTS: A total of 234 articles were found, of which 84 were excluded for not meeting the inclusion criteria (complete and free articles and temporal cut), leaving 150 publications. Of these, 100 articles were excluded, according to pre-established criteria and after reading the titles and abstracts of articles that did not meet the initial theme of this study. 50 works were submitted to readability evaluation, culminating with a quantitative of only 11 scientific articles included as object of study in this integrative review, being (2) Scielo and (9) PubMed.
CONCLUSION: Therefore, all the studies analyzed in this review demonstrated the importance of the presence and performance of neonatal screening for genetic diseases, especially for sickle cell anemia, since early detection of this chronic and severe disease is essential. This screening and subsequent early clinical intervention can reduce infant mortality, minimize comorbidities, generating better quality and increased life expectancy for patients with this main type of hemoglobinopathy.

Keywords: Foot test, Hemoglobinopathy l, Hemoglobin S Disease.

1 INTRODUCTION

Sickle cell anemia is a hemoglobinopathy belonging to the group of qualitative hemoglobin (Hb) diseases, characterized by a genetic mutation in chromosome 11 (eleven) of this protein, resulting from the replacement of a nitrogenous base, adenine (A), by another called thymine (T), in the codon of the beta globin gene, which passes from GAG to GTG. And it causes the replacement of the sixth amino acid in the chain, glutamic acid, with valine. This causes the appearance of hemoglobin variant "S" (NOGUEIRA, 2013).

It is a hereditary, chronic disease, defined as a hemolytic anemia, caused by a deformation in the structure of erythrocytes due to the production of Hb "S", changing the natural biconcave shape, to a "sickle" or "half moon" shape. Due to this rearrangement, these cell types lose their flexibility, becoming more rigid, shortening their average life, with a consequent chronic hemolysis, causing typical symptoms of this anemia, such as tiredness, paleness, jaundice and reticulocytosis. In addition to the high risk of blood vessel obstruction due to the presence of these drepanocytic cells (CARDOSO et al., 2021).

Sickle cell anemia, when it affects the organism of its carrier, reveals numerous correlated factors that feed back into permanent cycles of chronic inflammation. Drepanocytes, sickle cells, adhere to the vascular endothelium, causing obstruction, resulting in local hypoxia, aggravating the process called sickling. And, consequently, these alterations that exist in the cells and that affect the tissues trigger the inflammatory process characteristic of this pathology (CARDOSO, 2020).

There are two theories for the emergence of sickle cell diseases, the first theory would be that it arose from malaria, an infectious disease caused by the protozoan of the genus Plasmodium, transmitted by the bite of the mosquito of the genus Anopheles and thus would have contributed to the mutation of the HbS gene. for man has ceased to be a nomad. Its origin predominates in sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries (DALELLASTE; REISER; KUSE, 2022).

In 1910, James Bryan Herrick published in the Archives of Internal Medicine, pioneering the suggestion that sickle cells were the cause of sickle cell disease.

In 1935, Campbell, a surgical resident, drew the attention of physicians to the awareness of the clinical symptoms of sickle cell anemia, as the diagnoses were wrongly made, confusing it with other diseases such as appendicitis and any other that caused abdominal pain (RAMOS, 2020).

Sickle cell anemia reached an annual average of 2014 to 2020 1,087 new cases of children diagnosed with sickle cell disease, according to data from the national program that carries out the screening process in children under 5 years of age. This hematological alteration had an incidence of 3.78 per 10,000 live births. It is currently estimated that there are between 60 thousand and 100 thousand patients with sickle cell disease in the country and their geographical distribution is quite heterogeneous (STOCK, 2022).

Data from the mortality content system of the Unified Health System indicate that, between 2014 and 2019, most of these patients with sickle cell disease in the country died in the second or third decade of life (20 to 29 years old) (DE SOUSA, 2015). Between 2018 and 2021, the coverage of the transcranial Doppler ultrasound survey for children and adolescents with sickle cell anemia aged 2 to 16 years showed the importance of calculating cerebral blood flow to prevent a possible stroke (ALVES, 2019).

The clinical manifestations of sickle cell anemia can affect or target practically all organs and systems, occurring from the first year and extending throughout the patient's survival period. The main occurrences are pain crises; jaundice; anaemia; Infections; hand-foot syndrome; splenic sequestration crisis; accident in the cerebral blood vessels; priaprismo; severe chest syndrome; aplastic crisis; Ulcerations; Osteonecrosis; renal causes; Eye; among others (DOS SANTOS, 2021).

The main standardized treatment for this hemoglobin "S" disease is the use of the drug hydroxyurea, although it does not cure the disease. And among the therapeutic arsenal also used to minimize the consequences of this disease is folic acid supplementation, the use of analgesics, anti-inflammatories, intravenous hydration in pain crises, blood transfusions, the prophylactic use of antibiotics and vitamin supplements, and periodic immunizations (SOUZA, 2020). The therapeutic resource with the best results is hematopoietic stem cell transplantation (JARDULI-MACIEL et al., 2022).

Genetic counseling has important psychological, social, and legal implications, resulting in a high degree of responsibility toward women, institutions, and professionals who provide it. It is essential that it is carried out by experts qualified and with extensive experience, within the strictest ethical standards (RAMALHO, 2015). It is one of the best tools with regard to hereditary diseases, as it directly reflects on the quality of life of patients with specific genetic pathologies (DE ALCANTARA et al., 2021).

There are several methods for confirming the diagnosis of sickle cell anemia, these techniques can help patients detect the disease or sickle cell trait early. They are, the complete blood count and its complementary microscopy; o Reticulogram; Hemoglobin Electrophoresis, a standard test in the laboratory routine to identify variant hemoglobins, such as hemoglobin "S". There is also Isoelectric Focusing. And currently, Polymerase Chain Reaction (PCR). However, the initial diagnostic test is the so-called "Heel Test", which comes from neonatal screening and is performed using the High Performance Liquid Chromatography (HPLC) method (ARDUINI, 2017; PORTO et al., 2020; SOUSA et al., 2021).

The history of Newborn Screening (NT) began in the United Kingdom in the late 1950s, through the screening of metabolic disease that was detected in the urine test. Initially, it was just an organized phenylketonuria detection project with dietary counseling and carried out shortly after birth. In 1960, a conference held by the Medical Research Council recommended to local authorities the continuation and possible expansion of the phenylketonuria screening program (BONZO et al., 2013).

Since the 1960s, the World Health Organization (WHO) has identified the need for neonatal screening programs. In Brazil, neonatal blood screening, popularly known as the "Heel Test", was incorporated into the Unified Health System (SUS) through Ordinance GM/MS No. 22, of January 15, 1992, enforcing the obligation to perform the test on all live newborns, analyzing phenylketonuria and

congenital hypothyroidism. And in June 2001, there was an increase in the number of diseases screened by the National Neonatal Screening Program (PNTN), including the detection of sickle cell diseases and other hemoglobinopathies (MENDES et al., 2020).

In 2020, this screening program examined 964 cases of sickle cell disease and 60,094 heterozygous carriers of hemoglobin S, sickle cell trait. Studies show that if treatment is not carried out in the first years of life, only 20% of children will reach 5 years of age. The institution of the World Sickle Cell Disease Awareness Day in consideration of Sickle Cell Disease helped the Ministry of Health to highlight the need and the need for early identification of the disease, even in neonatal screening (Sickle Cell Disease Test). Foot) shortly after birth (POMPEO et al., 2021).

The previous identification of genetic diseases, based on a neonatal screening, can directly assist in early treatment and, possibly, avoid more severe conditions in carriers of these diseases. However, it is of fundamental importance that this screening process be publicized, publicly accessible and free of charge to the general population, and of a mandatory nature carried out by the related governments.

Thus, the objective of this study is to conduct an integrative review on the evaluation of newborn screening for the diagnosis of sickle cell anemia.

2 METHODOLOGY

2.1 TYPE OF SEARCH

This is a study in the integrative format of literature review, whose theme is "EVALUATION OF NEONATAL SCREENING FOR THE DIAGNOSIS OF ANEMIA SICKLE CELL"; Based on data collection carried out through consultation of journals and subsequent thorough reading of titles, abstracts and full papers.

The descriptors used for the search were: "Neonatal screening"; "sickle cell anemia"; "Neonatal screening"; and "sickle cell anemia", using the Boolean operator "AND", in the Scientific Electronic Library Online (SciELO) and PubMed databases; from April 1 to May 20, 2023.

For the pre-selection of the articles, previous readings were carried out through the titles and abstracts, and those that addressed the research theme were chosen. Only articles that portrayed the theme in a targeted way were considered.

2.2 INCLUSION AND EXCLUSION CRITERIA

Full and free articles published in the time frame from 2012 to 2023, in English and Portuguese, that addressed the initial theme proposed were included in the research.

Monographs, dissertations, theses, and articles were discarded as exclusion criteria incomplete and duplicates in the chosen databases, abstracts and expanded abstracts that did not portray the

purpose of this study or that were written in languages other than those mentioned above, and articles published outside the chosen period and articles that did not directly address the theme delimited in this research were excluded.

2.3 ANALYSIS OF THE RESULTS

The results of this review were organized in a flowchart (Flowchart 1) and in a chart (Chart 1) for better interpretation of the data.

3 RESULTS

A total of 234 articles were found, of which 84 articles were excluded because they did not meet the inclusion criteria (full and free articles and time cut-off), with 150 publications remaining. Of these, 100 articles were excluded, according to the pre-established criteria and after reading the titles and abstracts of the articles that did not meet the initial theme of this study. 50 papers were submitted to readability evaluation, culminating in a quantity of only 11 scientific articles included as an object of study in this integrative review, which make up the results of this research and whose distributions are described in Flowchart 1.

FLOWCHART 1 - Data Collection Flowchart

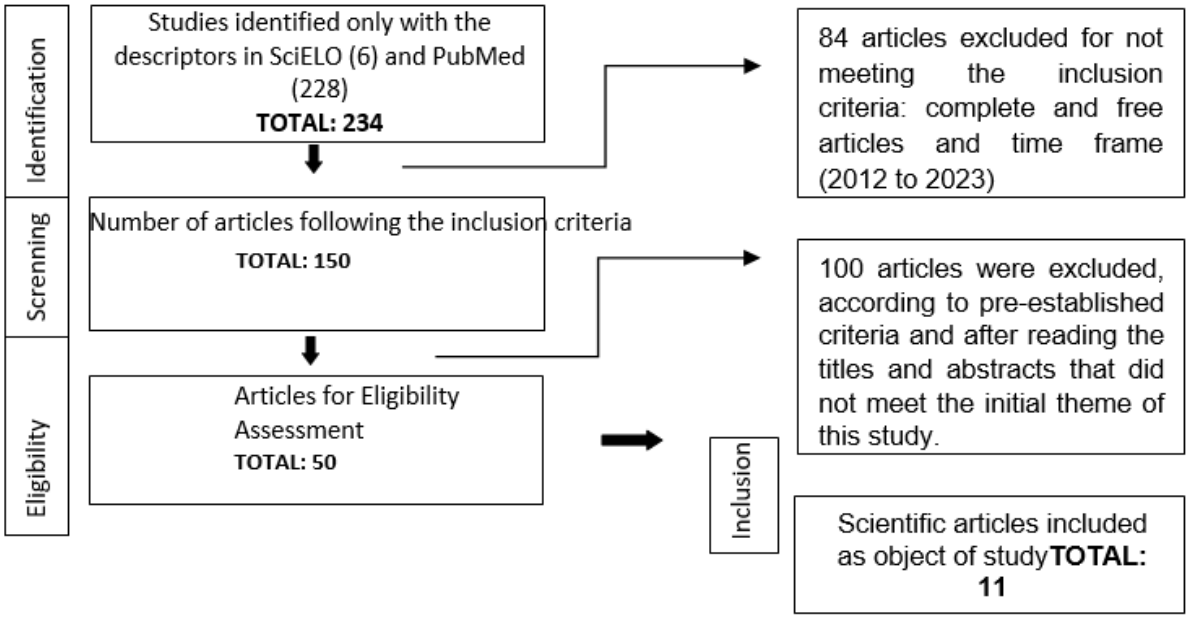

Chart 1 shows the origin, title of the study, authors, journals, and relevant considerations of the 11 scientific articles (SCIELO: 02 and PubMed: 09) included in this integrative review.

Chart 1 – Articles used in this integrative review.

No.	Origin	Job Title	Author /year	Newspapers	Relevant considerations at work
1.	PubMed	Neonatal Screening of Sickle Cell Anemia: A Preliminary Report	PANIGRAHI; PATRA; KHODIAR, 2012	Indian Journal of Pediatrics.	Newborn screening study for sickle cell disease conducted with 1,158 newborns, this study demonstrated the importance of early detection of sickle cell disease (SS) by newborn screening
2.	PubMed	Neonatal Screening for Sickle Cell Disease in Congo.	DOKEKIAS *et al.*, 2022	Anemia	The study was conducted with 2,897 children, aged or younger 5 days. As a result, they were abnormalities found hemoglobin in 20.81%, in which the main hemoglobin was Hb S
3.	PubMed	Neonatal Screening and the Clinical Outcome in Children with Sickle Cell Disease in Central India	UPADHYE *et al.*, 2016.	Plos one	A study conducted in Central India with 2,134 newborns showed that 48.7% were normal, but 45.8% were sickle cell and 4.9% were sickle cell homozygous (SS). Therefore, this study reinforces that sickle cell anemia is among the hereditary diseases with the greatest evidence that early diagnosis and treatment improve the clinical outcome of its carriers.
4.	Pubmed	Sickle cell screening in Europe: the time has come.	SHOOK; WARE, 2018	British Journal of Hematology	This study emphasized that it is also important to develop a clinical care program for sickle cell anemia, which should include: prophylaxis of infection with penicillin and prophylaxis of malaria; family training to identify severe or persistent early symptoms and the severity of crises.
5.	PubMed	Universal neonatal screening for sickle cell disease and other haemoglobinopathies in Ferrara, Italy	BALLARDINI *et al*., 2013	Blood Transfus	In this study, 24 patients with hemoglobinopathies were identified from nenonatal screening, 16 of whom had HbS.
6.	PubMed	Screening and Clinical Profile of Children With Sickle Cell Disease in a Tribal Area of Gujarat.	DAVE *et al*., 2022.	Indian Pediatre	Dave *et al*., (2022) screened 2,492 newborns with sickle cell trait using HPLC, 3.5% were diagnosed with SCD, which corresponds to 87 newborns.
7.	PubM|ed	. Dépistage néonatal de la drépanocytose en France [Newborn screening for sickle cell disease in France].	BROUSSE; BENKERROU, 2021	Medicine Science	A newborn screening program has demonstrated considerable efficacy in reducing infant mortality, as well as severe infectious, anemic, and neurovascular complications in childhood in patients with sickle cell anemia.

8.	PubMed	The Prevalence of Sickle Cell Disease and Its Implication for Newborn Screening in Germany (Hamburg Metropolitan Area). Pediatr Blood Cancer.	GROSSE *et al*., 2016.	Pediatric Blood & Cancer	This article highlights that sickle cell disease is among the hereditary diseases with the greatest evidence that early diagnosis and treatment improve clinical outcome, and newborn screening is important for this.
9.	Scielo	Incidence of variant hemoglobins in newborns attended by a public health laboratory.	REIS *et* al., 2018	Albert Einstein	A study at the Central Laboratory of Public Health of the State of Piauí (PI, Brazil). A higher occurrence of sickle cell trait was found in 4.1% of the sample, with emphasis on cases of homozygous hemoglobin S (0.1%). Therefore, we can conclude that neonatal screening programs are important for screening, guidance on health actions, and follow-up dasfamiliascom hemoglobinopathies, in order to reduce morbidity and mortality rates
10.	PubMed	Sickle cell disease in childhood: from newborn screening through transition to adult medical care.	QUINN, 2013	Pediatric Clinics of North America	A study highlights that in the first months of life of newborns they are asymptomatic, because very young infants still produce a significant amount of fetal Hb (Hb F), which ends up inhibiting the polymerization of Hb S. This period of protection conferred by Hb F usually lasts about 3 months, allowing the Newborn screening and intervention precocious.
11.	Scielo	(Lack of) knowledge of mothers about sickle cell trait and disease: a qualitative study.	ROCK *ET AL*., 2021.	Magazine Brazilian Nursing Degree,	The diagnosis cannot be restricted to the result of neonatal screening, requiring that preventive information on sickle cell crises be reinforced. It is recommended to seek out other affected family members to learn about their genetic condition, reflecting on Their Reproductive Decisions

4 INTEGRATIVE REVIEW

Newborn screening is a technique that can be performed using umbilical cord blood and by the isoelectric focusing methodology for early diagnosis of sickle cell disease (SCD), in which the confirmation of the results must be performed using another technique, such as citrate agar electrophoresis at acidic pH. A clinical care program for sickle cell anemia should also be conducted, which should include: penicillin infection prophylaxis and malaria prophylaxis; family training to identify severe or persistent early symptoms and the severity of seizures, as reported in the study by Shook, (2018).

Quinn (2013) had already highlighted that in the first months of life, newborns are asymptomatic, as very young infants still produce a significant amount of fetal Hb (Hb F), which ends up inhibiting Hb S polymerization and protecting against sickle cell anemia. As Hb F decreases in the first few months, there is a proportional increase in Hb S (rather than normal Hb A). This period of protection conferred by Hb F usually lasts about 3 months, allowing for newborn screening and early intervention.

In the newborn screening study for a type of sickle cell disease, sickle cell anemia, conducted by Panigrahi, (2012) with 1,158 newborns, between the months of February 2008 and January 2009 by the Department of Pediatrics and Neonatology, Pt. JNM Medical College & Dr. BRAM Hospital, Raipur (Chhattisgarh), it was possible to find sickle cell disease in 0.2% of the newborns, while the sickle cell trait was found in 5.8% of the individuals tested.

Another, more recent study by Dokekias et al., (2022) with 2,897 children, aged 5 days or less, between October 1, 2019 and March 31, 2020, where blood samples were collected and analyzed using the high-performance liquid chromatography (HPLC) machine. As a result, hemoglobin abnormalities were found in 20.81% of the newborns, the main hemoglobin was Hb S, which corroborates the neonatal screening data obtained in the study by Panigrahi (2012).

A study conducted in Central India, by researchers Grosse et al., (2016), with 2,134 newborns, showed that 48.7% were normal, but 45.8% were sickle cell and 4.9% were sickle cell homozygous (SS). After screening, these babies were followed, of which 75 of the SS (sickle cell anemia) had clinical complications, while 13 babies remained asymptomatic, demonstrating the importance of early diagnosis. This scenario reinforces the findings of Upadhye et al., (2016), that sickle cell anemia is among the hereditary diseases with the greatest evidence that early diagnosis and treatment improve the clinical outcome of its carriers (UPADHYE et al., 2016).

The study conducted in Ferrara, Italy, between September 26, 2010 and January 31, 2012, by researchers Ballardini et al., (2013), in which 1,992 neonatal tests were performed, analyzing umbilical cord blood by high performance liquid chromatography - HPLC, in which 24 patients with hemoglobinopathies were identified. 16 individuals had sickle cell anemia and the rest had other variant hemoglobins.

Recently, researchers Dave et al., (2022) also conducted a neonatal screening study, where 2,492 newborns with the so-called sickle cell trait were screened, according to the HPLC technique used and the life span restricted to two days after birth, in a hospital in the tribal area in Gujarat, in the period from 2014 to 2019. Confirming the presence of sickle cell anemia, of the newborns who underwent this type of screening, a representative percentage of 3.5% were diagnosed with this sickle cell disease, corresponding to 87 newborns.

Brousse and Benkerrou (2021) found that newborn screening for sickle cell diseases in France has been able to catalog the identification of 9,260 children since 1989 and adding up to 583 cases in 2019. This French screening program, combined with prophylaxis measures from a well-organized social health network in the country, has demonstrated considerable efficacy in reducing infant mortality, as well as severe infectious, anemic, and neurovascular complications in childhood, in patients with sickle cell anemia.

Neonatal screening was analyzed at the Central Laboratory of Public Health of the State of Piauí between February 1, 2014 and December 31, 2015, by the researchers Reis et al., (2018), in a very representative sample of 69,180 newborns, of which 3,747 were diagnosed with some hemoglobinopathy. A relevant occurrence of sickle cell trait was also found in 4.1% of the children evaluated. In this study, it was also evidenced that most hemoglobin alterations were present in male (49.8%) and brown (38.5%) newborns.

In a study developed by Rocha et al., (2021), carried out in the outpatient clinic of a public hospital, from October to December 2017, all participants had sickle cell trait. Allied to 20 children diagnosed with sickle cell disease by the "heel prick test" and 3 diagnoses, after hospitalization due to the disease. This research ratified the warning that the diagnosis cannot be restricted to the result of neonatal screening, requiring that the preventive information of possible sickle cell crises be reinforced during this process, and it was also recommended the complementary submission of a possible genetic counseling for the family members of these patients with sickle cell anemia and sickle cell trait.

5 CONCLUSION

Therefore, all the studies analyzed in this review demonstrated the importance of the presence and performance of newborn screening for genetic diseases, especially sickle cell anemia, since the early detection of this chronic and severe disease is essential. This screening and subsequent early clinical intervention can reduce infant mortality, minimize comorbidities, and generate a better quality of life and increase life expectancy for patients with this main type of hemoglobinopathy. Neonatal screening programs around the world are important for the selection, orientation to the appropriate health actions and follow-up of families affected by this sickle cell disease, who should also, as highlighted in this study, be submitted to the parallel process of genetic counseling. In addition, the possible complement of the diagnosis of sickle cell anemia and sickle cell trait was also observed by other techniques subsequent to the neonatal screening process, for the purpose of specific confirmation of the presence of the disease and the current clinical situation of the patient with this disease.

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