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Prevalence of hemoglobinopathies in the Brazilian adult population: National Health Survey 2014-2015

Prevalência de hemoglobinopatias na população adulta brasileira: Pesquisa Nacional de Saúde 2014–2015

Luiz Gastão Rosenfeld[I]*, Nydia Strachman Bacal[I], Maria Alice Martins Cuder[II], Alanna Gomes da Silva[III], Ísis Eloah Machado[III], Cimar Azereido Pereira[IV], Maria de Fátima Marinho de Souza[V], Deborah Carvalho Malta[VI]

ABSTRACT: ***Objective:*** To describe the prevalence of hemoglobinopathies in the Brazilian adult population, according to laboratory tests from the National Health Survey. ***Methods:*** A descriptive study was carried out with National Health Survey laboratory data collected between 2014 and 2015. The hemoglobinopathies test was performed using the High Performance Liquid Chromatography method. The results of the individual tests were interpreted as providing normal, homozygous or heterozygous results for S, C and D hemoglobin, in addition to other possible hemoglobinopathies. Prevalence of hemoglobinopathies according to gender, skin color, region, age and schooling was estimated. ***Results:*** Hemoglobinopathies were present in 3.7% of the population. The main ones were the sickle cell trait (2.49%), thalassemia minor (0.30%) and suspected thalassemia major (0.80%). In relation to the sickle cell trait and suspected thalassemia major, there was a statistically significant difference for the skin color variable ($p<0.05$). The prevalences found for sickle cell trait according to skin color was: 4.1% among dark-skinned blacks, 3.6% among light-skinned blacks, 1.2% among whites, and 1.7% among others. ***Conclusion:*** The most prevalent hemoglobinopathies were the sickle cell trait and minor thalassemia, and were predominate among light- and dark-skinned black people. The study helps in identifying hemoglobinopathies and in genetic counseling in pre-conception.

Keywords: Sickle cell anemia. Sickle cell trait. beta-Thalassemia. Hemoglobin C. Fetal hemoglobin. Neonatal screening.

[I]Centro de Hematologia de São Paulo – São Paulo (SP), Brazil.

[II]Diagnósticos da América DASA – São Paulo (SP), Brazil.

[III]Graduate Program in Nursing, School of Nursing, Universidade Federal de Minas Gerais – Belo Horizonte (MG), Brazil.

[IV]Research Directorate, Instituto Brasileiro de Geografia e Estatística – Rio de Janeiro (RJ), Brazil.

[V]Graduate Program of the Department of Preventive Medicine, Faculty of Medicine, Universidade Federal Minas Gerais – Belo Horizonte (MG), Brazil.

[VI]Maternal-child Nursing and Public Health Department, School of Nursing, Universidade Federal de Minas Gerais – Belo Horizonte (MG), Brazil.

*in memoriam.

Corresponding author: Deborah Carvalho Malta. Departamento de Enfermagem Materno Infantil e Saúde Pública, Escola de Enfermagem, Universidade Federal de Minas Gerais. Avenida Professor Alfredo Balena, 190, Santa Efigênia, CEP: 30130-100, Belo Horizonte, MG, Brazil. Email: dcmalta@uol.com.br

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RESUMO: ***Objetivo:*** Descrever a prevalência das hemoglobinopatias da população adulta brasileira, segundo exames laboratoriais da Pesquisa Nacional de Saúde. ***Métodos:*** Estudo descritivo realizado com os dados laboratoriais da Pesquisa Nacional de Saúde coletados entre os anos de 2014 e 2015. A pesquisa de hemoglobinopatias foi feita pelo método da cromatografia líquida de alto desempenho. Os resultados dos exames individuais foram interpretados fornecendo os parâmetros normais, homozigotos ou heterozigotos para hemoglobina S, C e D, além de outras eventuais hemoglobinopatias. Foram estimadas prevalências das hemoglobinopatias segundo sexo, cor da pele, região, idade e escolaridade. ***Resultados:*** Houve presença de hemoglobinopatias em 3,7% da população. As principais foram o traço falciforme (2,49%), a talassemia menor (0,30%) e a suspeita de talassemia maior (0,80%). Em relação ao traço falciforme e à suspeita de talassemia maior, houve diferença estatisticamente significativa para a variável cor da pele ($p < 0,05$). As prevalências encontradas para traço falciforme segundo cor de pele foram: preta (4,1%), parda (3,6%), branca (1,2%) e outras (1,7%). ***Conclusão:*** As hemoglobinopatias mais prevalentes foram o traço falciforme e a talassemia menor, predominando entre pretos e pardos. O estudo ajuda na identificação das hemoglobinopatias e no aconselhamento genético na preconcepção.

Palavras-chave: Anemia falciforme. Traço falciforme. Talassemia beta. Hemoglobina C. Hemoglobina fetal. Triagem neonatal.

INTRODUCTION

Hemoglobin (Hb) is a protein present in red blood cells and its main function is to transport oxygen (O_2) from the lungs to peripheral tissues. It has a quaternary structure composed of two alpha (α) and two beta (β) globin chains[1,2]. Each chain is associated with a heme prosthetic group that is attached to an iron atom (Fe^{2+}), which allows oxygen binding in blood cells[1,2].

Some mutations can modify amino acids and cause changes in functional effects, such as erythrocyte elasticity and even affinity with O_2[3,4]. Thus, most abnormal hemoglobin result from the total or partial substitution of one amino acid for another in one of the globin chains[3,4]. These structural and functional changes are called hemoglobinopathies.

It is estimated that 1.1% of couples worldwide are at risk of having children with some hemoglobinopathy and 0.27% of newborns are affected[5]. In low-income countries, 3.4% of children with these diseases die before the age of 5, and in Africa this figure reaches 6.4%[5].

Among hemoglobinopathies, sickle cell disease (HbS) is considered to be the most common, followed by thalassemia, as well as other less prevalent ones, such as hemoglobin C (HbC), hemoglobin D (HbD), the persistence of fetal hemoglobin (HbF) and other rarer ones (over 200 subtypes)[6].

Sickle cell disease is caused by a single mutation in the composition of the β-globin chain, resulting in a conformational change called hemoglobin S (HbS)[7]. However, when the individual inherits the HbS gene from one parent and the hemoglobin A (HbA) from the other, he or she will carry the sickle cell trait. In this situation, sickle cell disease does not manifest itself; the individual is asymptomatic, has no physical abnormality, hematologic findings are normal, and life expectancy is similar to that of the general population[8,9].

Thalassemia is a syndrome characterized by the absence or marked decrease in the synthesis of one or more hemoglobin-forming globin chains (α, β, γ, δ)[10,11]. The most common forms of the disease are types α and β, which are the second most frequent and are of greater clinical importance. They present as major thalassemia (the most severe because it is a homozygous carrier) and minor thalassemia, or thalassemic trait, which is genetically characterized by the inheritance of a single mutant gene[10,11]. The reduction in the synthesis rate of β-globin is smaller, but it is sufficient to cause a slight degree of polyglobulia and anemia (reduction of hemoglobin), with intense microcytosis and hypochromia, as well as increased red cell osmotic resistance[12].

HbC carriers, also have β-globin chain mutations, but with the substitution of another amino acid. However, this mutation is considered to be benign in relation to sickle cell disease, since sickling is not part of its pathophysiology[13].

HbF is the predominant form of hemoglobin in fetuses during pregnancy and it is essential for the distribution of oxygen in the fetal phase. After birth, its expression gradually decreases and is replaced by HbA[14], however genetic factors may prevent this substitution, leading to a continuous synthesis of HbF, and thus a persistence of HbF[15,16].

A laboratory diagnosis of these hemoglobinopathies in children starting at 4 months of age can be made by electrophoresis or by high performance liquid chromatography (HPLC). The latter is a methodology with higher sensitivity and specificity, which increases the reliability of the results and the correct diagnosis. Additionally, it is recommended by the Brazilian National Neonatal Screening Program (*Programa Nacional de Triagem Neonatal* - PNTN), for diagnosing hemoglobinopathies in newborns[17]. In Brazil, the National Health Survey (*Pesquisa Nacional de Saúde* - PNS), which produces data on the health status and lifestyle of the Brazilian population, collected blood from a subsample of respondents for laboratory testing. Eleven types of exams were performed, including the screening for HbS and other hemoglobinopathies[18].

Information on hemoglobinopathy studies in the Brazilian population is important in order to know its epidemiological profile and establish a health care network, which allows genetic counseling and guidance to patients and their families.

The aim of this study was to describe the prevalence of hemoglobinopathies in the Brazilian adult population, according to sociodemographic characteristics, using laboratory tests from the PNS.

METHODS

The current study was a descriptive, epidemiological survey, and used data from PNS laboratory exams from 2014 to 2015.

The PNS is a nationwide household-based cross-sectional survey that uses three-stage probabilistic samples. The primary sampling units (PSUs) were the census tracts or set of tracts, the secondary units were the households, and the tertiary units were the adult residents, aged 18 years or older. Details on the sampling and weighting processes are provided in the publications on the PNS results[18,19].

The sample consisted of 8,952 people. Post-stratification weights were used for sample weighting. Further details on laboratory data collection can be read in other publications[18,19].

The research participants signed an informed consent form, and then peripheral blood was collected at any time of the day. The participant did not fast beforehand.

Hemoglobinopathies were investigated using the HPLC method. The results of the individual examinations were interpreted by providing the normal, homozygous or heterozygous parameters for HbS, HbC and HbD, as well as other possible hemoglobinopathies. Thalassemia and suspected thalassemia were presented together. The prevalence of hemoglobinopathies according to age, gender, education, skin color and region was described and analyzed. Bivariate analyses were performed using the Person χ^2 test, taking into account the sample weights. The analyses were performed with the aid of the statistical program Data Analysis and Statistical Software (Stata), version 14. The significance level considered was 5% ($p < 0.05$).

The PNS was approved by the National Research Ethics Commission (*Comissão Nacional de Ética em Pesquisa* — CONEP) of the National Health Council (*Conselho Nacional de Saúde* — CNS), of the Ministry of Health. Adult participation in the research was voluntary and confidentiality of their information was guaranteed.

RESULTS

A total of 8,952 tests were collected, and 237 results were excluded due to insufficient material, hemolysis, sample loss and other reasons, totaling 8,715 tests for analysis.

Hemoglobinopathies were present in 3.7% of the population (n = 327), and the following were found: sickle cell trait (2.49%), suspicion of major thalassemia (0.8%), minor thalassemia (0.3%), HbC carrier (0.04%) and probable carrier of persistent HbF (0.03%). When adding up minor thalassemia and suspected major thalassemia, the prevalence was 1.1% (Table 1).

Regarding the sickle cell trait and suspected major thalassemia according to sociodemographic characteristics, there was a statistically significant difference only for the skin color variable ($p < 0.001$). The prevalence found for sickle cell trait according to skin color was:

Table 1. Prevalence of hemoglobinopathies in the adult population. Brazil, National Health Survey (PNS), 2014–2015.

	N	%	95%CI
Normal	8,388	96.34	95.77 – 96.83
Sickle cell trait	234	2.49	2.10 – 2.97
Minor thalassemia and suspected major talassemia	87	1.10	0.84 – 1.43
HbC carrier	2	0.04	0.01 – 0.21
Probable carrier of persistant HbF	3	0.03	0.01 – 0.12
Association of sickle cell trait with HbC	1	0.003	0.00 – 0.02
Total	8,715	100	

HbC: = hemoglobin C; HbF: = fetal hemoglobin; 95%CI: 95% confidence interval.

4.1% in dark-skinned black people; 3.6% in light-skinned black people; 1.2% in white people; and 1.7% among those who declared another skin color. The prevalence of suspected major thalassemia according to skin color was: 1.4% dark-skinned black people; 1.1% in light-skinned black people; and 0.3% in white people. The frequency of major hemoglobin abnormalities (sickle cell trait, minor thalassemia, and suspected major thalassemia) according to the categories of gender, age, education, and skin color are shown in Table 2.

Table 2. Population prevalence of the sickle cell trait and the sum of minor thalassemia and suspected major thalassemia according to sociodemographic data. National Health Survey, Brazil, 2014–2015.

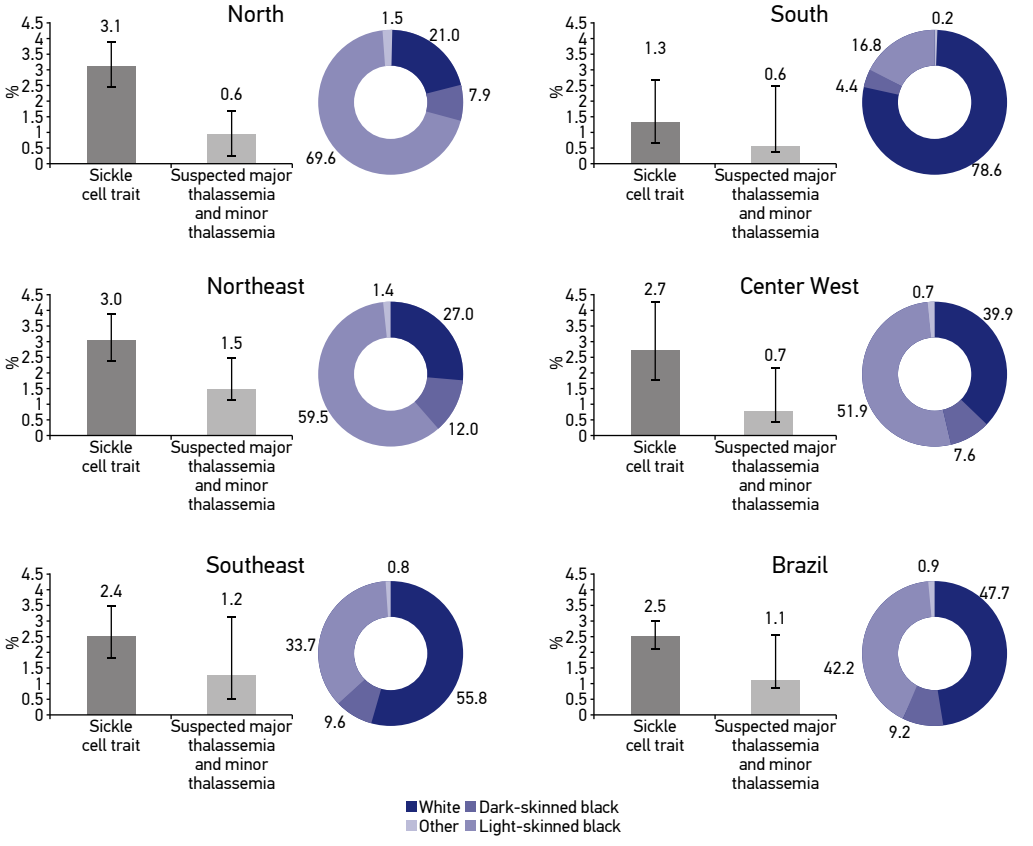
Variables (n = 327)	Sickle cell trait			Minor thalassemia			Suspected major thalassemia			Minor thalassemia + Suspected major thalassemia		
	%	95%CI	P	%	95%CI	P	%	95%CI	P	%	95%CI	P
Gender												
Male	2.6	2.0 – 3.4	0.653	0.3	0.1 – 0.7	0.778	0.6	0.3 – 1.0	0.20	0.9	0.6 – 1.4	0.227
Female	2.4	1.9 – 3.0		0.4	0.2 – 0.8		0.9	0.6 – 1.3		1.3	0.9 – 1.8	
Age group												
18 to 29	2.5	1.7 – 3.7	0.889	0.4	0.1 – 1.1	0.730	0.9	0.5 – 1.7	0.59	1.2	0.7 – 2.2	0.552
30 to 44	2.3	1.6 – 3.1		0.3	0.1 – 0.9		0.9	0.5 – 1.5		1.2	0.8 – 1.9	
45 to 59	2.7	2.0 – 3.6		0.5	0.2 – 1.1		0.7	0.3 – 1.2		1.1	0.7 – 1.9	
60 or older	2.6	1.8 – 3.7		0.2	0.0 – 0.8		0.5	0.3 – 0.9		0.7	0.4 – 1.2	
Education level												
No education and did not complete elementary school	3.0	2.4 – 3.8	0.166	0.4	0.2 – 0.9	0.664	0.8	0.5 – 1.3	0.22	1.3	0.9 – 1.8	0.234
Completed elementary school and did not complete high school	2.5	1.5 – 4.0		0.3	0.1 – 1.0		1.2	0.6 – 2.4		1.5	0.8 – 2.8	
High school or higher completed	2.1	1.5 – 2.8		0.3	0.1 – 0.7		0.6	0.3 – 1.0		0.8	0.5 – 1.3	
Skin color												
White	1.2	0.8 – 1.9	< 0.001	0.4	0.2 – 1.0	0.554	0.3	0.1 – 0.6	< 0.001	0.7	0.4 – 1.3	0.087
Dark-skinned black	4.1	2.7 – 6.0		0.4	0.1 – 1.7		1.4	0.7 – 2.8		1.8	1.0 – 3.3	
Light-skinned black	3.6	2.9 – 4.5		0.2	0.1 – 0.4		1.1	0.8 – 1.7		1.4	1.0 – 1.9	
Other	1.7	0.5 – 5.6		0.0			0.0			0.0		

95%CI: 95% confidence interval.

Figure 1 shows the frequency of major hemoglobinopathies by skin color in the Brazilian regions. These included the sickle cell trait and the sum of minor thalassemia with suspected major thalassemia. The northeast and north regions show a higher frequency of dark-skinned and light-skinned black people, and the southeast and south regions show a higher frequency of white people. The northeast and the north regions tend to exhibit a higher prevalence of the sickle cell trait and the northeast region shows a higher prevalence of thalassemia, however there is no statistical significance ($p > 0.05$).

DISCUSSION

The results from the PNS laboratory identified 3.7% of the adult population with some type of hemoglobinopathy. The sickle cell trait and minor thalassemia (thalassemia minor or suspected thalassemia major) were the most frequent.



Sickle cell trait: p = 0.106; suspected major thalassemia and minor thalassemia: p = 0.195.

Figure 1. Frequency of the sickle cell trait and minor thalassemia by skin color in Brazil and its regions (n = 327). National Health Survey, Brazil, 2014–2015.

With regard to the sickle cell trait and thalassemia, the prevalence was more frequent in dark-skinned and light-skinned black people. In this research, α-thalassemia was not studied, as its investigation in clinical practice is rare and difficult to detect, since it is performed by gene sequencing[10]. The prevalence of beta thalassemia is estimated to be low, with less than 1.5% of the Brazilian Caucasian population as carriers[12].

The sickle cell trait was the most frequent hemoglobinopathy in this research. It is worth noting that the presence of the sickle cell trait does not determine a disease and the carrier does not need treatment[20]. Nonetheless, its genetic condition should be taught, especially during the reproductive age[21,22]. With regard to sickle cell anemia, in this study no case of a homozygote was found.

The first mutations in the hemoglobin molecule were described on the African continent and sickle cell disease is prevalent across Africa. Genetic mutations for thalassemia can especially be found in the Mediterranean populations, such as in the Portuguese, Italian, Greek, Arab, Syrian and Lebanese[12], yet the phenomena of population migration and miscegenation has provided for the heterogeneous distribution of hemoglobinopathies to most countries of the world[23]. The dispersion of genes for variant hemoglobin in Brazil is related to the process of colonization and migration[24,25], as well as the miscegenation of black people from different African ethnic groups with the white population of Portuguese origin and, also, with the native indigenous population[26].

It was found in the study that the frequency of the sickle cell trait tended to be higher in the North and Northeast, which is justified because the population of light-skinned black people is more common in these regions, while dark-skinned black people are more present in the Northeast, especially in Bahia[27]. This finding coincides with the literature, which indicates a higher prevalence of sickle cell trait in the black population[26].

Previous research using PNTN data estimates that about 180,000 children/year with sickle cell trait are born[20]. According to state neonatal screening programs, the incidence of the sickle cell trait in live births in some states was: in Bahia, for each child with the sickle cell trait 17 did not have the trait, i.e. a 1:17 ratio; in Rio de Janeiro, 1:20; in Pernambuco and Maranhão, 1:23; in Goiás 1:25; in Espírito Santo, 1:28; in Minas Gerais, 1:30; in São Paulo 1:40; in Paraná, Rio Grande do Sul and Santa Catarina, 1:65[20]. Thus, a greater presence of the sickle cell trait is confirmed in Bahia, the state with the largest black population[27], as indicated in the present study.

It is important to emphasize that early diagnosis of hemoglobinopathies in the first week of life is essential to identify and ensure timely and continuous treatment and follow-up. Diagnoses are made by the State Neonatal Screening Programs (*Programas Estaduais de Triagem Neonatal* — PETN), which are regulated by the PNTN, and offered by the Public Health System (*Sistema Único de Saúde* — SUS)[12]. In 2015, there was 85.79% SUS coverage for neonatal screening[28]. By 2017, there were about 5.7 million newborns screened by the Minas Gerais Neonatal Screening Program and approximately 6,000 children/young people in follow-up and treatment for diagnosed diseases (May 2017 data)[29].

Given the findings, it is important to devote attention, investments and studies to better characterize and identify changes in hemoglobin in the Brazilian population, as well as to reduce morbidity and mortality, improve quality of life, and provide assistance to these people, families and society. In the adult carrier population, it is important to carry out

genetic counseling before conception, due to the chances that the child might inherit sickle cell anemia and thalassemia.

CONCLUSION

This is the first study to determine the prevalence of hemoglobinopathies in adults in Brazil and its regions. The most prevalent hemoglobinopathies were the sickle cell trait, minor thalassemia and suspected major thalassemia. The sickle cell trait and thalassemia between dark- and light-skinned black people predominated. The Brazilian population is characterized by a miscegenation of a diversity of races, ethnicities, peoples, social and economic segments. The racial origin and the predominance of dark- and light-skinned black people as carriers of the sickle cell gene and the presence of the thalassemia genes are important aspects when considering hemoglobinopathies from the point of view of collective health and strategies for control.

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