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Hemoglobinopathy detection through an institutional neonatal screening program in Colombia

Detecção de hemoglobinopatias por meio de um programa institucional de triagem neonatal na Colômbia

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ABSTRACT

Introduction: Hemoglobinopathies are among the most common genetic disorders of hemoglobin worldwide and a public health problem. In Colombia, even though geographical areas with high incidence of this disorder have been reported, the absence of a national screening program does not permit us to determine its prevalence. **Objective:** Establish the prevalence of hemoglobin variants in a population covered by the neonatal screening program of Clínica Colsanitas S.A., between June 2000 and December 2014, including eight capital cities in Colombia. **Methods:** A retrospective cross-sectional study was conducted. We collected data from reports of the neonatal hemoglobinopathy-screening program for full-term newborn babies between 5 and 15 days old. Qualitative hemoglobin analysis was performed using gel electrophoresis of blood samples taken from the babies' heels. **Results:** The overall prevalence of abnormal Hb was 1.3%. Within the groups of newborns affected with any hemoglobinopathy ($n = 400$), the most frequent abnormal structural hemoglobins found were HbS (43%), HbC (9%), fast Hb (8%). For quantitative hemoglobins, HbA2 was 3.7% and HbA kept slightly elevated in 14.7% of cases. Frequency of homozygosis for HbS was 0.01%. Barranquilla, Cartagena and Cali were the cities with the greatest frequency of hemoglobinopathies. No correlation between sex and abnormal hemoglobin was found. **Discussion and conclusion:** Taking in consideration data from the World Health Organization (WHO) on hemoglobinopathies, our prevalence of $> 1\%$ is considered high. Therefore, a more extended coverage and the need for a national screening program are priorities.

Key words: hemoglobinopathies; sickle-cell anemia; hemoglobin C disease; abnormal hemoglobins; neonatal screening.

INTRODUCTION

Hemoglobin (Hb) disorders, also called hemoglobinopathies, are inherited hemoglobin abnormalities commonly distributed throughout the world[1, 2]. According to the World Health Organization (WHO), hemoglobinopathies are a serious health problem affecting 71% of the countries[3] and contribute to 3.4% of mortality in children aged less than 5 years worldwide[4].

At least 5.2% of the world population and over 7% of pregnant women carry significant hemoglobin variants, as well as around 1.1% of couples worldwide are at risk of having children with a hemoglobin disorder[4].

This situation can lead to the birth of more than 300,000 children affected annually, of which 83% develop sickle-cell anemia or one of its variants, and 17% develop thalassemia[4, 5]. Also, children under the age of 5 born in high-income countries affected by this disorder survive better into adult life than those born in low-income countries[4, 5].

The structural hemoglobinopathies identified worldwide include hemoglobin S (HbS), hemoglobin C (HbC), hemoglobin E (HbE), and hemoglobin D (HbD)[6, 7]. To date, more than 1,200 hemoglobin variants have been described[8]; and mutations, identified at the molecular level, are mostly rare and harmless[8]. Forty percent of hemoglobinopathies carriers present HbS. This hemoglobin causes more than 80% of the disturbances due to their high prevalence in the population. HbS causes 85% of the clinical detected hemoglobin disorders worldwide, with 70% of them present in Africa, and a mortality rate of 7%, yearly[4, 9].

Since Diggs[10] discovered the sickle-cell anemia in 1929, a series of events led to the definition of this disease clinical history.

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In 1967, Perutz[10] was awarded the Nobel Prize in Physiology and Chemistry for the study of the structures of hemoglobin and myoglobin, increasing the interest in the chemical analysis of HbS[10]. Later on, the United States signed the first act for the control of sickle-cell anemia (Public Law 92-294 of 1972), recognizing this and other hemoglobinopathies as of public health interest, and the first federal program towards the screening of a genetic disease was implemented[11].

The main purpose of a neonatal hemoglobinopathy-screening program is the early detection not only of sickle-cell anemia cases, but of other different hemoglobinopathies (including in the parents of the affected children)[12]. In 1987 the US National Institutes of Health (NIH) recommended the universal neonatal screening for hemoglobinopathies independently of ethnic origin[13].

The rapid identification of these patients enables the immediate introduction of preventive and therapeutic measures. For example, the use of a prophylactic treatment with penicillin in neonates with sickle-cell anemia reduces the mortality and morbidity rates due to secondary infections with encapsulated bacteria, as reported by Gaston *et al*. (2015)[14, 15].

Considering the negative impact on public health due to these disorders, several countries, including Brazil[3, 16-19], Cuba[20-25], Costa Rica[26], Spain[27], Italy[28] and 43 out of 50 states of the United States, have national neonatal screening programs for the detection of abnormal Hb. In South and Central America, only Brazil and Costa Rica, respectively, have mandatory screening of this Hb alteration in neonates[29].

In Colombia, several independent studies for hemoglobinopathies have been reported from cities such as Cartagena, Buenaventura, Cali, San Andrés and Providencia, due to their large Afro-descendant population[30-39]. No data has been obtained from other parts of the country, where a different population mix is present and, therefore, the real incidence of hemoglobinopathies at a national level is unknown. The present study was designed to determine the prevalence of hemoglobinopathies as part of the Neonatal Screening Program at Clínica Colsanitas S. A. in eight cities of our country (Armenia, Bogotá, Cali, Medellín, Cartagena, Barranquilla, Bucaramanga and Villavicencio) between June 2000 and December 2014.

METHODS

A retrospective cross-sectional study was conducted. Data were collected from all results of the neonatal screening program of full-term newborns aged between 5 and 15 days, from mothers included in the pre-paid medicine program of Colsanitas S.A. After a signed consent form was obtained, blood samples were taken from each child's heel in eight cities of Colombia. Premature babies were enrolled in this study after they reached a full-term development, and samples were drawn five to 15 days later. Samples were collected in BD Microtainer® tubes with ethylenediaminetetraacetic acid (EDTA) and stored between 2ºC to 8ºC until processing.

For qualitative and semi-quantitative hemoglobin analysis, alkaline gel electrophoresis was carried out using a SPIFE 2000 system (Helena Laboratories, Beaumont, TX, USA). Analysis of these hemoglobin bands and the quantification of each percentage were done using the QuickScan machine (Helena Laboratories, Beaumont, TX, USA).

Every abnormal positive test result was confirmed by a new sample, and samples from the respective parents were analyzed in order to confirm the inherited trait.

Each qualitative variable result was reported as counts and relative frequencies, and the overall prevalence was obtained using the number of positive cases (confirmed cases) divided by the total number of newborns registered in the neonatal screening program. The frequency of each variant of hemoglobin was distributed by city and sex according to the total number of newborns for each city, and the frequency of the genetic trait for each individual in the study was assigned. The frequency of homozygotes for HbS was calculated in two ways: 1) positive cases (HbSS) over the group of infants affected with any confirmed hemoglobinopathy (n = 339); and 2) positive cases (HbSS) over the whole population (n = 27,869). The statistical analysis was performed using the StataCorp version 13.0 software.

The research study protocol was approved by the Research Ethics Committee (CIEI) of Fundación Universitaria Sanitas. A consecutive code was assigned to each sample in order to maintain confidentiality of information.

RESULTS

A total of 27,869 newborn children were admitted to the study from June 2000 to December 2014. The geographical distribution was: Bogotá (67.95%), Cali (19.2%), Medellín (6.61%), Barranquilla (3.45%), Bucaramanga (1.64%), Cartagena (0.76%), Villavicencio (0.39%) and Armenia (0.03%). Each child admitted to one of our laboratories in each city follows a flow chart as described in **Figure 1**.

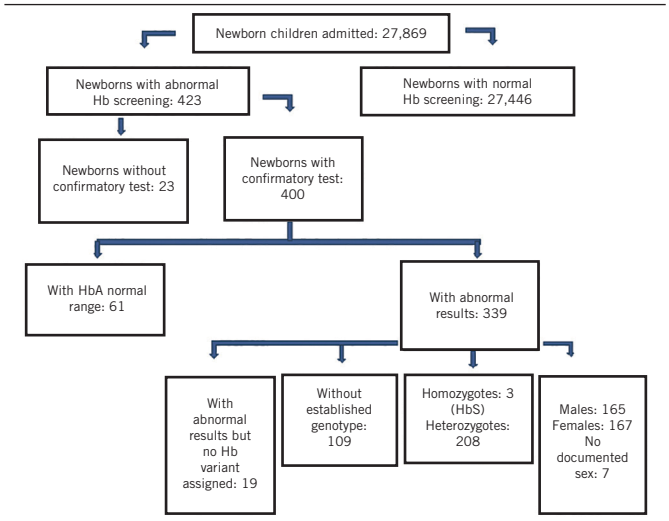

FIGURE 1 – *Sample selection – flow chart*

Flow chart showing the process followed by every newborn in our institution and then used in the present study to select our study population.

The overall prevalence of hemoglobinopathies was 1.3%. Among them, the frequency of presentation of an abnormal migration pattern was, in a descending fashion: HbS, HbC, rapidly migrating Hb and slowly migrating Hb. Also, the analysis of the quantitative abnormal Hb showed elevated HbA2. In some cases, HbA was slightly elevated in the first test and, after a confirmation test in a new sample of newborn and one of the parents, 14.7% kept showing slightly elevated HbA levels for age, **Figure 2**.

Interestingly, 4.75% of the screened population presented an abnormal electrophoretic pattern, but it was not possible to know the type of hemoglobin alteration because the final result of the variant was not registered in the data base.

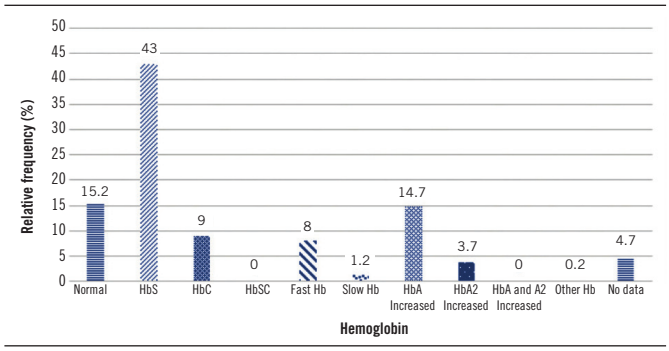

FIGURE 2 – *Hemoglobinopathy frequency*

Relative frequency for each hemoglobin variant. Every case was confirmed and assigned a pattern after the confirmatory test conducted in affected newborns and parents. The "no data" category corresponds to cases in which an abnormal electrophoretic pattern was obtained and could not be assigned to any Hb variant. The relative frequency (%) was calculated based on positive cases for each hemoglobin variant within the newborn group with confirmation test (n = 400).

The rapidly migrating Hb variant found in 8% of the population was later categorized by high-performance liquid chromatography (HPLC) and sequencing as either HbJ-Oxford or HbJ-Baltimore in 69% of this group (data supplied by an external lab).

Analyzing the type of Hb alteration (structural and quantitative) in the studied cities, we found that Barranquilla, Cartagena and Cali had higher frequencies of structural hemoglobinopathies, whereas Bogotá and Medellín had higher frequencies of quantitative hemoglobinopathies. Armenia and Villavicencio did not report any variation on the Hb, as observed in **Figure 3**. Comparing the types of Hb (**Figure 4**) among the studied cities, Barranquilla had a high frequency for HbS, Cartagena and Bucaramanga for both HbC and rapidly migrating Hb, and Bogotá for the slowly migrating Hb. Bogotá was the place where all the studied structural hemoglobinopathies were present (Figure 4A); and Medellin, Bogotá, Barranquilla and Cali were the cities where all the different quantitative altered Hb were found (Figure 4B).

Distribution of hemoglobinopathies by sex shows that HbS, slowly migrating Hb and elevated HbA were more frequent in the female group; whereas rapidly migrating Hb, HbC and elevated HbA2, in the male group. Nevertheless, this data is not of statistical significance (**Table**).

A part (5.44%) of the study population was lost due to the lack of a second confirmatory test from the initial abnormal electrophoretic pattern obtained.

Regarding genetic trait, a prevalence of 0.88% was found for HbSS in the groups of newborns affected with any confirmed

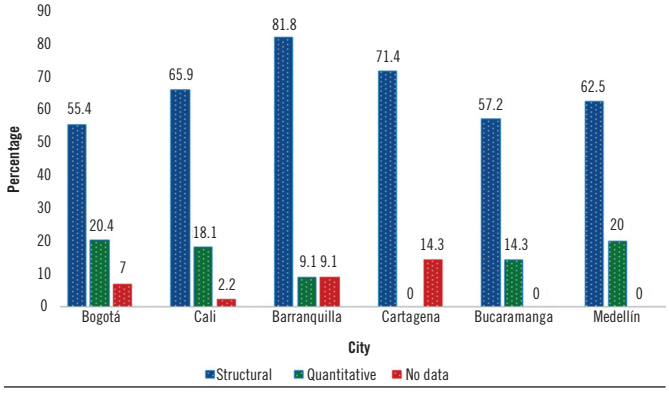

FIGURE 3 – *Percentage distribution of hemoglobinopathies by city*

The included structural hemoglobinopathies are: HbS, HbC, HbSC, rapidly migrating Hb, slowly migrating Hb, and other possible variants. The included quantitative hemoglobinopathies are: elevated HbA, elevated HbA2, and elevated HbA/HbA2 simultaneously. The "no data" group included results without a clear Hb electrophoretic pattern in the first sample, and lack of a confirmatory sample. Each percentage was calculated using the total number of cases per category over the total number of subjects with a confirmatory sample.

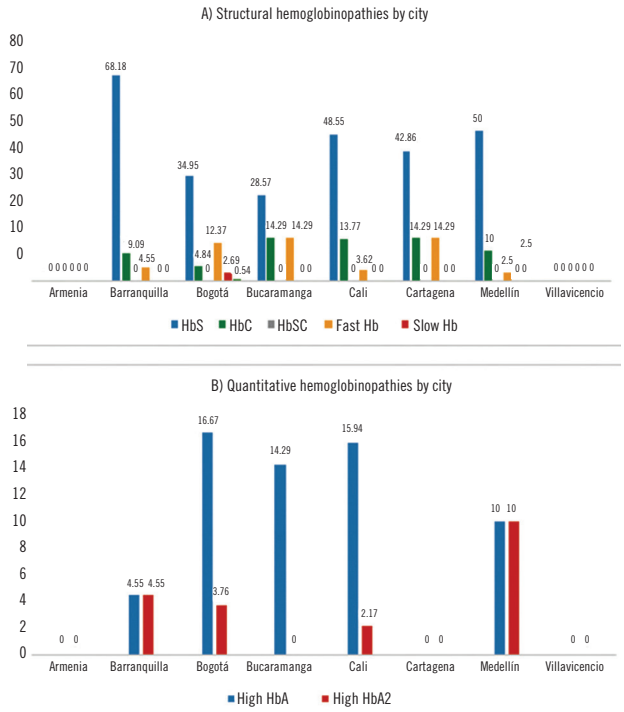

FIGURE 4 – *Percentage distribution of structural and quantitative hemoglobinopathies by city*

Tabulated data correspond to results with a confirmatory analysis for each Hb variant.

TABLE – Hemoglobinopathy frequency distribution by sex

Results	Sex				
	Female (n = 167)		Male (n = 165)		p value
	n	%	n	%	95%
HbS	85	50.9	82	49.7	0.83
HbC	16	9.58	19	11.52	0.57
Fast Hb	12	7.19	20	12.12	0.13
Slow Hb	3	1.8	1	0.61	0.62
Increased HbA	34	20.36	25	15.15	0.21
Increased HbA2	4	2.4	11	6.67	0.07
Other Hb	0	0	1	0.61	0.50
No data	13	7.78	6	3.64	0.10
HbSC	0	0	0	0	-
Increased HbA and A2	0	0	0	0	-
%	50.3		49.7		

We found an overall frequency of 50.3% among females and of 49.7% among males in the studied population. No data about sex was found in 0.12% of the cases.

hemoglobinopathy; and 0.01% in the overall study population (n = 27,869). No other hemoglobinopathies showed homozygous trait. In 12.7%, no available information was obtained due to either absence of one of the parents or a discordant genotype.

Among newborn babies positive for HbC and rapidly migrating Hb disorders with a parental Hb record available, all (100%) showed a heterozygous trait for these genetic alterations. In 33.3% of the HbC cases, no parental records were found.

In the quantitative Hb group, only a heterozygous trait was determined in 47% of the elevated HbA2 disorder. No parental Hb test record was found for the remaining population with this genetic trait.

DISCUSSION

The present study is the first approach to understanding the global prevalence of hemoglobinopathies in Colombia. Our global prevalence result is in agreement with previously reported data on global prevalence of hemoglobin disorders in different countries, such as Brazil with 1.6%[17] and 1.9%[19], Venezuela with 1.97%[40] and 1.96%[41], and Costa Rica with 1.26%[26], where global screening programs for hemoglobinopathies are in place, and the benefits and positive impacts on the health system are evident.

This similarity could be due to the close intertwining of ethnic groups in the whole Latin America, allowing the penetrance of Caucasian and African genes in our region[42]. These variables must be taken into consideration in the design of a new neonatal national screening program in our country, where areas of high prevalence of hemoglobinopathies (Pacific and Atlantic coast) have been detected, and human migration from these areas to regions of low prevalence of this disorder is taking place. This study also showed the importance of taking samples from many different centers or regions in our country in order to evaluate the degree of heterogeneity in the distribution of this hemoglobin disorder within short geographical distances, as previously reported[5]. Massive human mobilization between continents in the latest decades has become an issue due to the introduction of carriers of Hb disorders to regions with an absent trait for this disease; therefore, the need for an urgent neonatal screening program for treatment and prevention of this pathology is evident[43].

Regarding all the hemoglobin variants analyzed in this study, HbS and HbC are the two most prominent disorders found, similar to previously reported data from cities such as Cali, Barranquilla, Cartagena, Medellín, Buenaventura and San Andres and Providencia, with frequencies ranging from 2% to 6.9% for HbAS and 0.17% to 5.8% for HbAC[30-39]. The same pattern is observed if we compare it to countries such as Panama: 7.72%

for HbAS and 0.9% for HbAC[44]; Costa Rica: 0.26% for HbFSS, 1.07% for HbFAS and 0.07% for HbFAC[26]; Venezuela: 1.33% for HbFAS and 0.45% for HbFAC[41]; and Brazil: 4.06% for HbFAS and 0.05% for HbFSS[3].

Most of the structural hemoglobinopathy cases reported in this study were observed in cities such as Cartagena, Barranquilla, Cali and Medellín due to the fact that 50% of the national Afro-descendant population dwell in these cities[45]. Furthermore, the appearance of HbS and HbC variants in cities where a different population mix is present could be related to the advance process of human migration from the countryside to the urban cities. Also, global human population movements which have had a substantial effect on the distribution of the HbS allele[46] together with the introduction of new natural induced mutation on the hemoglobin gene have made us aware of the importance of a national screening test in our newborn population in order to implement new specific public health interventions. On the other hand, the homozygous frequency (HbSS) found in our study is similar to that previously reported in national localized data that range from 0.01% to 0.2%[34-37], as well as the prevalence found in other Latin American countries such as Brazil, with 0.05%[19]; and Costa Rica, with 0.55%[41]. This could be due to the prevalence of this type of Hb in the African-American population in the US, Brazil and several countries of the Caribbean region[46]. Additionally, studies have shown that haplotypes of the beta-globin gene can demonstrate the origin of the sickle-cell anemia gene in the Latin America region, which is distributed at a similar level in this ethnic group[47, 48].

The increased values of HbA2 in our study and their association with thalassemia syndromes would be a new goal for evaluation in the future, using more accurate techniques like HPLC, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH), to corroborate this association in our population[16, 49]. A previous study in a different region of Colombia showed frequencies of 1.7% for beta thalassemia and 2% for HbS + beta thalassemia[34].

The persistence of elevated levels of HbA after a confirmatory test can be explained because the production of hemoglobin chain proteins in the newborn is not homogenous and a high differential expression of one of them can be observed (false positive). Additionally, some parents showed increased levels of HbA. Therefore, it is very important, during the evaluation of this type of disorder in a health care neonatal unit, to obtain a double confirmatory result from newborns and their parents[50].

The absence of a neonatal program that screens these kinds of pathologies and the scarcity of public health resources to support the affected population explain the lack of information on prevalence, morbidity and mortality rates in our Latin-American countries. The opposite can be seen in countries such as the US, Brazil and Costa Rica, where a good neonatal screening program is in place together with an interdisciplinary national program of education for the diseased and carrier patients, families and medical personnel[51].

Some limitations were observed during the conduction of the present study. The fact that this is a retrospective analysis, there is deficiency in some medical information and there was a lack of participation from the parents in the confirmation of the genetic trait made us lose valuable data; although the coverage percentage was satisfactory.

Finally, according to the WHO[52], from an epidemiologic point of view, we must consider the percentage value of more than 1% for a hemoglobin variant like the one in Colombia, an endemic area of prevalence for hemoglobinopathies.

CONCLUSION

The diversity and heterogeneous distribution of hemoglobinopathies around the world make it necessary to develop strategies at the country level. In Colombia, the lack of a national screening program for this genetic disease does not allow us to identify and recognize the magnitude of this problem. Therefore, the establishment of a new national health policy that involves the detection of carriers, introduction and access to prenatal diagnosis centers in the community, information and education for parents, and genetic counseling for hemoglobin disorders will lead to a fall in births and deaths of affected children.

CONFLICT OF INTERESTS AND FINANCING

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RESUMO

Introdução: *As hemoglobinopatias são doenças genéticas comuns em todo o mundo e representam um problema de saúde pública. Na Colômbia, embora existam áreas geográficas com maior risco de apresentá-las, não há programas de triagem nem estudos para estabelecer sua prevalência na população.* ***Objetivo:*** *Estabelecer a prevalência de variantes de hemoglobina (Hb) na população pertencente ao programa de triagem neonatal da Clínica Colsanitas S.A. entre junho de 2000 e dezembro de 2014, em oito cidades do país.* ***Métodos:*** *Estudo transversal retrospectivo. Os registros do programa de triagem neonatal das hemoglobinopatias foram revistos para a informação dos resultados de eletroforese de hemoglobina em pH alcalino, praticada no sangue dos recém-nascidos com idades compreendidas entre 5-15 dias.* ***Resultados:*** *A prevalência geral de Hb anormal foi de 1,3%. Dentro dos grupos de recém-nascidos afetados com qualquer hemoglobinopatia (*n = *400), as hemoglobinas anormais estruturais mais frequentes foram hemoglobina S (HbS) (43%), hemoglobina C (HbC) (9%) e Hb rápida (8%). Para as Hb quantitativas, o aumento da hemoglobina A2 (HbA2) foi de 3,7%, e a hemoglobina A (HbA) aumentada permaneceu ligeiramente elevada em 14,7% casos. A frequência de homozigotos para HbS foi de 0,01%. Barranquilla, Cartagena e Cali foram as cidades com maior frequência de hemoglobinopatias. Não houve associação entre sexo e presença de algum tipo de Hb.* ***Discussão e conclusão:*** *A prevalência global de hemoglobinopatias em nosso estudo foi alta (> 1%) de acordo com os critérios da Organização Mundial de Saúde (OMS). Portanto, há a necessidade de implementação de programas de triagem neonatal com maior cobertura nacional para as hemoglobinopatias.*

Unitermos: *hemoglobinopatias; anemia falciforme; doença da hemoglobina C; hemoglobinas anormais; triagem neonatal.*

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