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ORIGINAL ARTICLE

Sickle cell disease: Clinical and laboratory aspects

Enfermedad de células falciformes: Aspectos clínicos y de laboratorio

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What do we know about the subject matter of this study?

Sickle cell disease (SCD) is a genetic hemoglobinopathy defined by the presence of sickle hemoglobin in erythrocytes. Patients are heterogeneous, have multiple comorbidities, and are at higher risk of hospitalization. Due to migration, it is an emerging disease in Chile and there are no studies in large populations.

What does this study contribute to what is already known?

It describes the clinical and laboratory characteristics of 51 patients with SCD from the Hospital Roberto del Río, being one of the studies with the largest pediatric population in Chile. In addition, it highlights that 75% were diagnosed before the age of 5 years, the most frequent ancestry was Haitian, and the most observed complications were infections.

Abstract

Sickle cell disease (SCD) is a genetic hemoglobinopathy defined by the presence of sickle hemoglobin (HbS) in erythrocytes. The migration phenomenon has transformed SCD into an emerging disease in countries where it was previously unknown. **Objective**: To describe the clinical and laboratory characteristics of patients with SCD diagnosed and under follow-up in a hospital in Santiago, Chile. **Patients and Method**: Retrospective study of clinical and laboratory characteristics of 51 patients under 15 years of age with SCD, diagnosed and under follow-up at the *Hospital Roberto del Rio* (HRR) in Santiago, Chile, from March 2016 to December 2023. Epidemiological data, clinical manifestations, complications, analytical results, and treatments received were collected. **Results**: The mean age was 3.7 years (75% diagnosed before age 5 years). 67% of patients were male. The most common ancestry was Haitian (73%), followed by Venezuelan (14%) and Colombian (8%). The most frequent finding was anemia (mean hemoglobin 10.3 gr/dL). Hemoglobin electrophoresis results were available in 49/51 patients (20/49 Sickle cell trait, 10/49 Homozygous, 3/49 Sickle cell-β-thalassemia, 14/49 Sickle cell-β+thalassemia, and 2/49 HbSC. Infections were the most frequent complications, followed by vaso-occlusive crises. Forty children were hospitalized and 27.5% required IMCU/PICU admission. 24% of patients needed transfusions and 33% were treated with hydroxyurea. **Conclusions**: The study reproduces what is described in the medical literature. With diagnosis, early preventive treatment, and good medical care, morbidity can be minimized. Due to the increasing incidence of SCD, genetic counseling and the establishment of therapeutic guidelines are recommended.

Keywords:
Sickle Cell Disease;
Drepanocytosis;
Hemoglobinopathy;
Erythrocyte;
Anemia

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Introduction

Sickle cell disease (SCD) is an autosomal recessive genetic hemoglobinopathy defined by the presence of sickle hemoglobin (HbS) in erythrocytes. It includes sickle cell anemia (homozygous mutation), sickle-beta thalassemia, and hemoglobin SC disease, among others[1-3].

Sickled red cells disrupt blood flow within small vessels, leading to distal tissue ischemia and inflammation, with acute symptoms, including painful crises. Recurrent crises lead to endothelial dysfunction and vasculopathy, which result in chronic organ damage with significant morbidity and premature mortality.[4-7]

This group of patients is very heterogeneous, characterized by multiple comorbidities and, a higher risk of hospitalization, in addition to requirements of health care by multiple specialties. Diagnosis is based on hemoglobin analysis by electrophoresis; however, DNA analysis is increasingly used[1,2].

SCD was not known in the Chilean population, however, secondary to a rapid epidemiological and demographic transition during the last decades, its incidence has increased. As of December 2022, there are an estimated 1,625,074 foreign residents (295% increase compared to 2014), of which 55.9% are from Venezuela, Haiti, and Colombia, countries where the prevalence of SCD is higher[8,9].

The objective of this study is to describe the clinical and laboratory characteristics of patients with SCD diagnosed and under follow-up at the *Hospital de Niños Dr. Roberto del Río* (HRR).

Patients And Method

Design

Retrospective study of clinical and laboratory features of children under 15 years of age with SCD.

From a total of 58 patients with SCD, 51 under 15 years of age diagnosed and under follow-up in the Oncohematology Service of the HRR, in Santiago, Chile, from March 2016 to December 2023 were included, with the respective informed consent and assent. Seven patients were excluded, 5 returned to their country of origin and 2 moved house.

Variables analyzed

Data were obtained from the patients' electronic medical records, laboratory software (Bioslis), and imaging software (Synapse). The following were considered: gender, age at diagnosis, ancestry, reason for consultation, symptoms and clinical findings at diagnosis, laboratory parameters (complete blood count, peripheral blood smear, sodium metabisulfite test, hemoglobin electrophoresis, biochemical profile), imaging characteristics (chest X-ray, abdominal ultrasound, transcranial Doppler ultrasound, densitometry), number of consultations, hospitalizations due to acute complications [infections, vaso-occlusive crisis (VOC), hemolytic crisis, aplastic crisis, splenic sequestration, acute chest syndrome (ACS)], and chronic complications (malnutrition, asplenia, cholelithiasis, chronic pain, neurological, respiratory, osteomyelitis). The number of hospitalizations in basic beds, ICU/PICU, and the treatment received were also reviewed.

The diagnosis was based on the presence of hemoglobin S (HbS) in hemoglobin electrophoresis and/or sickle cell formation in the sodium metabisulfite test.

According to the results of hemoglobin electrophoresis, syndromic diagnosis and phenotype were made in each patient, by relating the values of HbA, HbS, HbF, HbA2, HbC, % Hb, and MCV.

Definitions

Sickle cell trait (clinically healthy), Homozygotes (severe phenotype), Sickle-βthalassemia (severe phenotype), Sickle-β thalassemia (mild to intermediate severity), and Sickle-HbC (intermediate severity).[1]

Ethical Aspects

This study was approved by the management of the *Hospital de Niños Dr. Roberto del Río* (HRR) and the Scientific Ethical Committee of the North Metropolitan Health Service. Informed consent was requested from the legal guardian and informed assent, and patient anonymity was ensured.

Statistical Analysis

For each variable under study, the frequency and percentage were estimated for categorical variables, and the median (Me) and interquartile range (IQR) were calculated for quantitative variables. The information was presented using tables. Excel and Stata software were used for data management.

Results

General characteristics

Of 51 patients with SCD, 6/51 (11.8%) were diagnosed before March 2018. Table 1 shows the demographic and clinical data. 67% were male and 33% female. The mean age was 3.65 years, and 75% were younger than 5 years at diagnosis.

73% of the children were of Haitian descent, 14% Venezuelan, 8% Colombian, and 4% Dominican; however, we also found 1 Chilean patient (2%).

69% of the patients were referred to hematology from primary care, while 31% were referred through

internal consultation. At the time of diagnosis, 82.4% of the patients reported having no symptoms. Table 1 shows the most frequent clinical manifestations of the symptomatic patients.

Laboratory and diagnostic imaging features

Anemia was a frequent finding, with a median hemoglobin of 10.3 g/dL. In the smears of patients with SCD, sickle cells were found in 22% (100% with severe phenotype) and codocytes were found in 20%.

The sodium metabisulfite test was positive in 61% of the patients, in 37% it was not performed, and 2% was negative, however, 1 of them with HbS (46.7%) in hemoglobin electrophoresis. 2/51 patients had no hemoglobin electrophoresis result (both with positive sodium metabisulfite test). For patients with available results, the median HbS was 37.7, and fetal Hb was 9.3.

The most altered parameters of the biochemical profile were LDH (IQR 248 and 574 IU/L) and total bilirubin (IQR 0.19 and 1.37 mg/dL).

Hemoglobin electrophoresis was obtained in 49/51 patients of which 20 presented with sickle cell trait, 10 were homozygotes, 3 were sickle-βthalassemia, 14 sickle-β thalassemia, and 2 were sickle-HbC.

The median number of outpatient consultations for all patients was 4 (IQR 2 to 7). Table 2 describes the details of the consultations. Of the 49 patients, 81.6% were hospitalized due to acute complications and development of chronic complications (Table 2). 78.4% of the patients required hospitalization during their lifetime and, out of these, 27.5% required admission to the IMCU/PICU (Table 3).

24% of the patients received transfusions, all the indicated transfusions were simple, while 2/51 patients received chronic transfusions. 51% received antibiotic prophylaxis with amoxicillin, 33% treatment with hydroxyurea, 78% supplementation with vitamin D, and 57% with folic acid (Table 4). On evaluation of hemoglobin electrophoresis after hydroxyurea treatment, 35.2% had elevated (> 20%) fetal hemoglobin (HbF) levels.

In addition, the vaccination schedule for protection against encapsulated pathogens was adjusted for all patients.

Discussion

SCD is recognized by the World Health Organization (WHO) as a public health problem.[2,10,11] Diagnosis is made by hemoglobin electrophoresis, peripheral blood smear, and sodium metabisulfite test.[6,12]

Martinez et al. reported a predominance of male sex, similar to that observed in our study (42/74 vs 34/51, respectively). Furthermore, the most frequently observed morphological alteration in the peripheral blood smear was sickle cell disease (35.1% vs. 22%).[10] In this study, similar to that observed by Greppi et al., no patient presented quantitative platelet alteration.[13]

The median number of outpatient consultations observed by Martínez et al. was similar to that we observed, with 3 and 4 consultations (IQR 1-9 vs 2-7, respectively). Likewise, 97.2% of the patients were hospitalized due to SCD complications during the study period, similar to 81.6% in our study.[10]

Multiple authors point out that patients with sickle cell trait do not present clinical manifestations[3,14] which was confirmed since the patients with sickle cell trait in this study were asymptomatic and the infectious events that caused hospitalization were comparable to what occurs in the general pediatric population.

Patients with SCD experience a range of acute and chronic events.[3,14] In severe phenotypes, the clinical presentation and frequency of manifestations were similar to those described in the medical literature, with infections as the most frequent, followed by VOC and episodes of hemolytic anemia[10,12-14]. Splenic sequestration is considered a marker of severity[15], 6% of the patients in our study presented such a manifestation.

Authors indicate that dactylitis is an early manifestation directly attributable to SCD being more frequent in infants[6,15] (in our study, we had 1 case of a 2-year-old patient with severe phenotype), while VOC in older children, the involvement is more frequent in long bones, thorax, abdomen, and back[5] which was also evidenced in this work.

As for infections, their spectrum and course can be modified according to the phenotype of the disease and, the availability of prophylaxis and treatment, including safe blood transfusions.[4,15,16]

Reparaz et al. observed in their work that 71.8% of the patients received antibiotic prophylaxis with penicillin; in our study, amoxicillin was administered in 51% of the cases; in addition, 67.1% were on folic acid treatment vs 57% in our study[14]. All the patients in this study were asked to complete a vaccination schedule against encapsulated microorganisms.

ACS is more common in individuals with homozygous SCD (HbSS), is the second most common cause of hospitalization in SCD patients, and is the main cause of admission to the intensive care unit.[5,17] These statements correlate with what was observed in our study.

Klein, et al. suggest that children with sickle cell disease are at increased risk of malnutrition due to insufficient caloric intake.[18] However, only 2% of our patients (1 patient with sickle cell trait) presented this complication, which could be explained by the great clinical variability of patients with SCD[15,18].

Table 1. Demographic, clinical, laboratory and imaging characteristics

		N = 51
Demographic and Clinical Characteristics		
Gender	F	17 (33%)
	M	34 (67%)
Age at diagnosis	< 5	38 (75%)
	5-10	11 (22%)
	> 10	2 (4%)
Ancestry	Chile	1 (2%)
	Colombia	4 (8%)
	Haiti	37 (73%)
	Rep. Dominicana	2 (4%)
	Venezuela	7 (14%)
Reason for consultation	Internal consultation	16 (31%)
	External consultation	35 (69%)
Symptoms at diagnosis	No	43 (82.4%)
	Yes	9 (17.6%)
Clinical findings at diagnosis	Pallor	3 (5.9%)
	Icterus	3 (5.9%)
	Splenomegaly	3 (5.9%)
	Hepatomegaly	3 (5.9%)
	Infection	3 (5.9%)
	Extremity pain	1 (1.9%)
	Dactylitis	1 (1.9%)
Laboratory parameters		
Hemogram	Hemoglobin (g/dl)	10.3 (9-11.2)
	MCV (fL)	70.8 (66.2-75.7)
	Platelets (mm^3)	362500 (249000-431000)
	Reticulocytes (%)	1.7 (1.2-4.4)
Peripheral blood smear	Normal	3 (6%)
	Codocytes	10 (20%)
	Sickle cell	3 (6%)
	Codocytes + Sickle cell	8 (16%)
	Other*	27 (53%)
Sodium metabisulfite test	Positive	31 (61%)
	Negative	1 (2%)
	Unrealized	19 (37%)
Hemoglobin electrophoresis	HbS (%)	37.7 (33.4-59.7)
	HbF (%)	9.3 (4.2-20.5)
	HbA (%)	55.4 (1.5-57.9)
	HbA2, C, E (%)	2.8 (1.8-3.4)
Biochemical profile	LDH (UI/L)	346 (248-574)
	Total bilirubin (mg/dl)	0.41 (0.19-1.37)
Imaging characteristics		
Chest X-ray	Normal	24 (47%)
	Altered	20 (39%)
	Unrealized	7 (14%)
Abdominal ultrasound	Normal	22 (43%)
	Splenomegaly	5 (10%)
	Hepato-splenomegaly	3 (6%)
	Splenomegaly + splenic microinfarcts	1 (2%)
	Unrealized	20 (39%)
Transcranial Doppler ultrasound	Normal	28 (55%)
	Altered	2 (4%)
	Unrealized	21 (41%)
Bone densitometry	Normal	3 (6%)
	Altered	0 (0%)
	Unrealized	48 (94%)

F: female, M: male, MCV: mean corpuscular volume, Hb: Hemoglobin, LDH: Lactate dehydrogenase. *Includes: Anisocytosis, poikilocytosis, microcytosis, schistocytes.

Table 2. Relation between syndromic diagnosis and phenotype, with number of consultations, hospitalizations for acute complications and development of chronic complications

			Total	Sickle cell trait (clinically healthy)	Homozygotes (severe phenotype)	Sickle - □0 thalassemia (severe phenotype)	Sickle-□+ thalassemia (mild to intermediate severity)	Sickle-HbC (intermediate severity)
			N = 49	N = 20	N = 10	N = 3	N = 14	N = 2
Number of emergency consultations (Me, IQR)			4 (2-7)	2 (1-4)	6 (3-14)	6 (5-7)	3 (2-6)	5.5 (5-6)
Hospitalizations N = 40	Infections	No	27 (55%)	13 (65%)	5 (50%)	1 (33%)	7 (50%)	1 (50%)
		Si	22 (45%)	7 (35%)	5 (50%)	2 (67%)	7 (50%)	1 (50%)
	Vaso-occlusive crisis	No	36 (73%)	20 (100%)	2 (20%)	1 (33%)	13 (93%)	0 (0%)
		Si	13 (27%)	0 (0%)	8 (80%)	2 (67%)	1 (7%)	2 (100%)
	Hemolytic crisis	No	40 (82%)	20 (100%)	3 (30%)	2 (67%)	13 (93%)	2 (100%)
		Si	9 (18%)	0 (0%)	7 (70%)	1 (33%)	1 (7%)	0 (0%)
	Aplastic crises	No	49 (100%)	20 (0%)	10 (100%)	3 (100%)	14 (100%)	2 (100%)
		Si	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Splenic sequestration	No	46 (94%)	20 (100%)	8 (80%)	3 (100%)	14 (100%)	1 (50%)
		Si	3 (6%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	1 (50%)
	Acute thoracic syndrome	No	48 (98%)	20 (100%)	9 (90%)	3 (100%)	14 (100%)	2 (100%)
		Si	1 (2%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
Chronic complications	Malnutrition		1 (2%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Asplenia/splenectomy		1 (2%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
	Cholelithiasis		1 (2%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
	Chronic pain		1 (2%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)
	Neurological		4 (8%)	3 (15%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
	ROBS/ Asthma		2 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (14%)	0 (0%)
	Osteomyelitis		1 (2%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)
	None		38(77%)	16(10%)	7 (20%)	1 (33%)	12(85%)	2 (100%)

ROBS: Recurrent Obstructive Bronchial Syndrome.

Small case-control studies have suggested that asthma occurs more frequently among people with SCD compared with the general population[1,17]. In this work, we observed this chronic complication in 4% (2 patients with Sickle-βthalassemia), however, we cannot attribute such a complication directly to SCD as larger research cohort studies have not conclusively demonstrated this to be the case[1,17].

Primary prevention of ischemic strokes in children (one of the main causes of disability) can be achieved by transcranial Doppler ultrasound.[5,14,15,19-21] In our study, transcranial Doppler ultrasound was performed in 30/51 patients, resulting altered in 2/30 patients.

Treatment with hydroxyurea (approved by the FDA in patients older than 2 years), stimulates the production of HbF to levels above 20% by inhibiting the polymerization of deoxyhemoglobin S, inducing changes in the erythrocyte membrane and reducing adhesion to endothelial cells[12,22]. It reduces the frequency of painful crises and the need for transfusions and is the only approved and available treatment in many regions[4,5,17,23].

Martinez et al. published that 68.9% of their pa-

Table 3. Distribution of total hospitalizations

		N	%	Total
Hospitalized N = 40	IMCU/PICU	11	27.5%	78.4%
	Basic bed	40	100.0%	
Not hospitalized		11		21.6%

IMCU: Intermediate Care Unit. PICU: Pediatric Intensive Care Unit.

Table 4. Treatment received

		Total N = 51
Transfusions	No	39 (76%)
	Yes	12 (24%)
Folic acid	No	22 (43%)
	Yes	29 (57%)
Amoxicillin	No	25 (49%)
	Yes	26 (51%)
Hydroxyurea	No	34 (67%)
	Yes	17 (33%)
Vitamin D	No	11 (22%)
	Yes	40 (78%)

tients received treatment with hydroxyurea,[10] Reparaz et al. in 41.4%[14] and 33% of the patients received it in our study, observing in the hemoglobin electrophoresis evaluation an increase of HbF over 20% in 35.2% of the cases, a lower value than that observed by Gomez et al., where in their work 67% of the patients had elevated HbF levels over 20%.[12]

One of the milestones of treatment is transfusions and they can be administered acutely or chronically (simple transfusion, manual or automated exchanges), according to the guidelines of the American Society of Hematology.[20,24-26] Martinez et al. described transfusions in 19% of their patients,[10] Greppi et al. in 53%,[13] while in our study, 24% had been transfused (simple transfusion in all patients, 2 patients received chronic transfusion).

Few studies analyze the characteristics of children with SCD requiring admission to the PICU. Reparaz et al. reported that 12.6% of their patients required admission,[14] in this study, it was 27.5%. Mortality of children with SCD requiring admission to the PICU is very low.[14,27] No patient deaths were recorded during the study period. Early diagnosis allows the implementation of measures to reduce morbidity and mortality.[12-14] Despite optimal treatment, people with SCD have a life expectancy of 30 years lower than that of the general population.[4,13]

This is one of the studies in Chile with the largest number of cases describing the characteristics of SCD. As limitations we can mention those derive from its retrospective nature, similar to what was observed by Reparaz et al., the characteristics of this population (frequent changes of address, low awareness of the disease) may generate an underestimation of the real complications with consultations and admissions to other centers and loss of follow-up.[14]

In conclusion, this study reproduces what is described in the medical literature. With diagnosis, early preventive treatment, and good medical care, morbidity can be minimized. Given the increasing incidence, prognostic studies, genetic counseling, and the establishment of therapeutic guidelines are recommended.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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