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ORIGINAL ARTICLE

Sickle cell disease in a reference pediatric hematology unit

Enfermedad de células falciformes en una unidad de referencia de hematología pediátrica

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

The frequency of sickle cell disease (SCD) may change with migrations. The suspicion, diagnosis, and treatment of SCD are well established in clinical guidelines and their proper implementation improves patient prognosis.

What does this study contribute to what is already known?

In Chile, this is the first report that describes the change in the frequency of SCD, its clinical characteristics of presentation, diagnostic process, and management, recognizing areas requiring improvements in standardization and access.

Abstract

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy. The prevalence of SCD can change especially by migrations. **Objective:** To describe the characteristics of patients with SCD at diagnosis, in a referral hospital over a decade. **Patients and Method:** Retrospective study of the clinical and laboratory characteristics of children under 15 years of age with SCD, diagnosed in the Onco-Hematology Service of the *Hospital Dr. Roberto del Rio*, Santiago, Chile, between April 2008 and March 2018. Sex, age, nationality, symptoms, blood count characteristics, and hemoglobin electrophoresis results were evaluated by descriptive statistical analysis. **Results:** Sixteen patients were included, 2 were healthy carriers so were excluded from the analysis. Of the 14 analyzed, the diagnosis was made before 2015 in 2 patients. Twelve were male, 9 were Chilean, 13 had foreign parents. Eight were less than 2 years old and 12 were symptomatic. The most frequent symptoms were limb pain and anemia. Median hemoglobin was 8.2 g/dL (6.2-12.3), in 11/14 sickle cells were observed, in 4 by metabisulfite test. In 13/14, hemoglobin electrophoresis was performed, median hemoglobin S 70.2% (28.2-87.1) and hemoglobin F 18.7% (0-32.3). Only one patient had a genetic study. Thirteen patients were still in follow-up, 84.6% of them received folic acid and amoxicillin, 53.8% required transfusions, and 69.2% started hydroxyurea. **Conclusion:** SCD has increased in Chile; therefore, a high degree of suspicion is required. The diagnosis, treatment, and follow-up of this pathology should be improved at the local level.

Keywords:
Sickle Cell Disease;
Sickle Cell Anemia;
Immigration;
Hemoglobinopathies;
Hemoglobin

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Introduction

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy[1], where the erythrocyte acquires a sickle shape that impedes its free circulation and causes endothelium disruption, resulting in hemolytic anemia and vascular occlusion[2].

Recent reviews describe the clinical manifestations, complications, treatment, and prognosis of SCD[3,4]. The manifestations can be classified into hematologic symptoms and signs such as hemolytic anemia, pain syndromes such as vaso-occlusive crisis, and hypoxic complications affecting different organs[5,6]. The diagnosis can be suspected by clinical manifestations, but confirmation by laboratory study is necessary, with electrophoresis being one of the most widely used techniques for diagnosis[6].

The severity of SCD can be established by reticulocyte count and alterations in transcranial Doppler ultrasound[7]. The approach to a patient with SCD should be multidisciplinary and include firstly prophylaxis strategies, with the use of hydroxyurea[1,6,8], antibiotics, and immunization against encapsulated bacteria[6,8]; secondly, early management of acute complications, such as pain, vaso-occlusive crisis, infections, stroke, and anemia[5,6,9]; and thirdly, the detection, management, and follow-up of chronic complications[5,6]. All these strategies aim to reduce the morbidity and mortality associated with SCD[6].

Despite optimal treatment, people with SCD have a life expectancy 30 years shorter than the general population, therefore, constant efforts are needed to better understand the genetic and environmental basis of the clinical manifestations, in order to perform prognostic studies and the early implementation of available treatments for all patients[2]. Although the only curative therapy for SCD is hematopoietic precursor transplantation[6,10], supportive care is essential.

The incidence of SCD varies in different regions around the world and migrations have generated local changes in its prevalence[11]. In Latin America, there are between 100,000 to 150,000 people with SCD[12] and it is especially frequent in Haiti[13], Brazil, Colombia, and Venezuela[12].

In Chile, the number of immigrants has increased by 400% in the last 10 years, according to estimates by the Department of Foreigners and Migration. People from Haiti, Colombia, and Venezuela now represent 54% of immigrants in Chile[14].

The objective of this report is to know the clinical and laboratory characteristics of the patients diagnosed in our hospital in the last 10 years.

Patients and Method

Retrospective, descriptive study based on the review of clinical records, to determine the number, clinical characteristics, and evolution of patients under 15 years of age with SCD, seen in the Hematology Service of the *Hospital Roberto del Rio* (HRR), between April 2008 and March 2018. This study was approved by the HRR management and the Scientific Ethics Committee of the North Metropolitan Health Service. Patients were identified from the HRR electronic registry, using ICD-10 codes D57.0 and D57.1.

The electronic records were reviewed, collecting the following data: sex, age at diagnosis, patient nationality, parents' country of birth, family history of SCD, symptoms at diagnosis, and laboratory tests at diagnosis, and regarding the laboratory tests: peripheral blood smear to confirm the presence of sickle cells, sickle-shaped red blood cells characteristic of SCD, sodium metabisulfite test by inducing the formation of sickle cells through the reduction of oxygen concentration in the sample, reticulocytes percentage, alkaline hemoglobin electrophoresis, and renal and liver function studies.

A case of SCD was defined as symptomatic patients with hemoglobin S (HbS) on hemoglobin electrophoresis or sickle cell on blood count or sodium metabisulfite test, also considering asymptomatic patients with sickle cell on hemoglobin electrophoresis or sodium metabisulfite test. Asymptomatic patients without evident sickle cell disease and with HbS ≤ 45% were defined as healthy carriers of sickle cell trait. We also recorded whether genetic confirmation tests were performed. In addition, imaging tests, treatment received, and whether they were followed up were reviewed.

Data management was done with Microsoft Excel for Mac, version 16.51(21071101). An anonymized database was created, and a descriptive analysis was performed. Absolute frequencies and percentages were used for categorical variables, while measures of central tendency and dispersion were used for quantitative variables, according to the distribution of the data.

Results

During the period studied, 16 patients were evaluated in the service, 2 before 2015 and 14 after that year (figure 1). Two asymptomatic patients, with 39% HbS, were classified as healthy carriers of sickle cell trait and excluded from further analysis. The excluded patients correspond to one patient from the Dominican Republic and one from Venezuela, both studied due to family history of SCD, with one of them presenting a genetic study that confirmed heterozygous inheritance.

Table 1 shows the demographic and clinical characteristics of the 14 patients with SCD. One of them already had the diagnosis at the beginning of his check-ups at the HRR. One patient did not have a hemoglobin electrophoresis study but had sickle cells in the blood smear. Of the thirteen patients with electrophoresis, four had HbS less than 45%; two of them were asymptomatic, but sickle cells were observed in the metabisulfite test. The other 2 were symptomatic, with anemia and bone pain, and were therefore considered as cases. In the latter, the other hemoglobin variants identified by electrophoresis were HbA1 in one case and HbA2 and HbF in the other, however, neither had a molecular analysis that allowed direct identification of the hemoglobin variant.

Eight of the fourteen patients had a family history of SCD. Figure 2 shows the clinical findings at diagnosis. None of the patients had quantitative platelet abnormalities and all had normal white blood cell counts, except for one patient with leukocytosis due to an infectious condition. Sickle cells were observed in 11 patients, 7 in the blood smear, and 4 with the metabisulfite test (table 1).

In patients with anemia at diagnosis, the median hemoglobin was 7.45 g/dL; 45.0% were macrocytic and 54.5% were normochromic, with a median reticulocyte percentage of 19.8% (2.5 to 40.1). Only one patient had a genetic study that confirmed SCD. In 6 patients, a complementary study was performed with bone scintigraphy, identifying bone infarcts in 5 of them. In only 1 patient a transcranial Doppler ultrasound was performed, which was not reported with the standardized criteria for follow-up. 13 patients remain in follow-up, 84% receiving folic acid and amoxicillin prophylaxis; 69% are on hydroxyurea with dose adjusted according to HbF levels, and 53% required red blood cell transfusions (table 2).

Discussion

During the last decade, the number of patients with SCD diagnosed in our service has increased, especially in the last 5 years. In Chile, SCD was an anecdotal diagnosis 5 years ago[15,16] and its increase coincides with recent migratory flows[14]. Changes in the prevalence of SCD in the world because of migration have been described for more than 20 years[11].

Patients with SCD can present severe clinical pictures, even fatal, due to hemolysis, vaso-occlusive episodes, and infections, so a high level of suspicion should be maintained and guidelines for early and appropriate management should be incorporated. These patients frequently require hospitalization, even in critical patient units, as can be seen in recent reviews published by Zúñiga P. et al.[3]. and Carrasco P. et al.[4].

Early initiation of treatment is associated with better quality of life[17]. Half of our patients were diagnosed before the age of 2 years. In 2 of the 10 patients with a family history, it was possible to make the diagnosis. In addition, healthy carrier status was established in two others. In the continent, there are national neonatal screening programs in Brazil[18], Colombia[19], and other Caribbean countries, but their implementation is not always easy[20].

The severity and complications of SCD may vary from one population to another[2]; therefore, it is important to know the local characteristics to improve

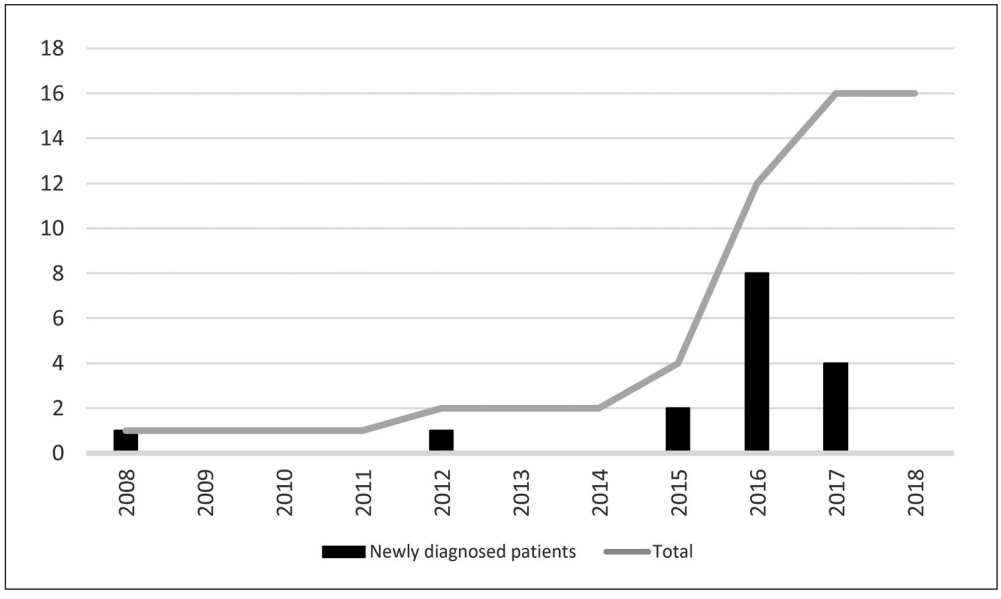

Figure 1. Yearly new patients diagnosed with sickle cell disease or sickle cell trait, at Hospital Dr. Roberto del Río, from April 2008 and March 2018.

Table 1. Demographic, clinical and laboratory characteristics of the 14 participants.

Demographic and clinical characteristics		N	%
Sex	Male	12	85.7
Age at diagnosis	< 2 years old	8	57.1
	2 to 5 years old	4	28.6
	> 5 years old	2	14.3
Patient nationality	Chilean	9	64.3
	Foreigner	5	35.7
Parent's birth country	Haiti	11	78.6
	Colombia	2	14.3
	Chile	1	7.1
Family history SCD		8	57.1
Symptomatic at diagnosis		12	85.7
Laboratory characteristics		**Median**	**Range**
Blood smear n = 14	Hemoglobin (g/dL)	8.2	(6.2-12.3)
	MCV (fL)	75.4	(59.8-96.3)
	MCHC (g/dL)	33.5	(30.3-36.2)
	Leucocytes (mm3)	13165	(5270 – 41330)
	Platelets (mm3)	462000	(171000-544000)
	Reticulocyte percentage (%)	16.7	(0.9-40.1)
	Sickle cells at smear	7/14 (50.0%)	
	Positive Metabisulfite	4/4 (100%)	
Hemoglobin electrophoresis n = 13	HbS (%)	70.2	(28.2 - 87.1)
	HbF (%)	18.7	(0 - 32.3)
	Hb Total (g/dL)	8.0	(5.1 - 11.5)

Hb: hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; SCD: sickle cell disease.

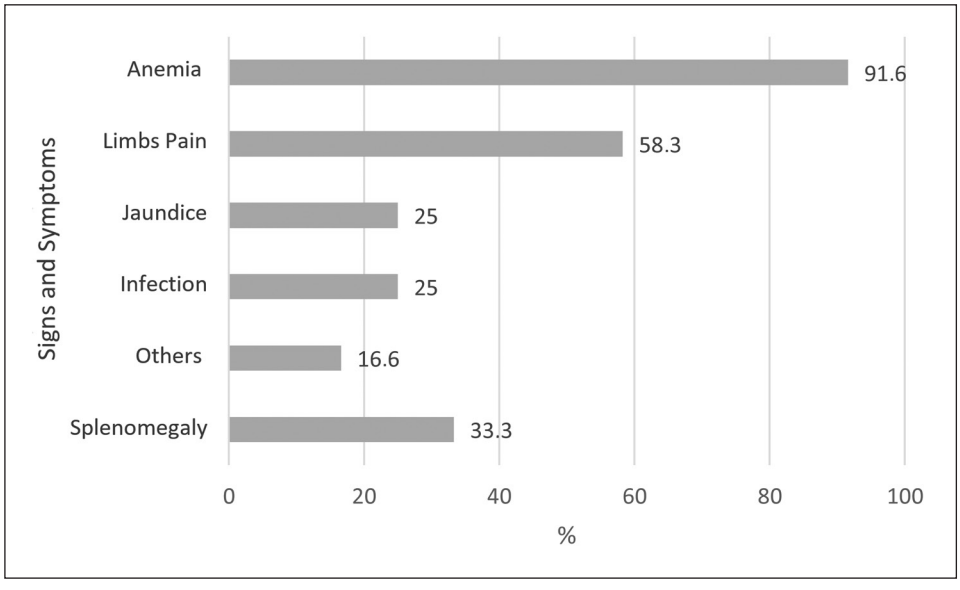

Figure 2. Clinical features present at diagnosis, in symptomatic sickle cell disease patients. Others: dactylitis and impure nephrotic syndrome.

Table 2. Treatment received by participants during follow up

Treatment	N	%
Folic acid	11	84.6
Ferrous sulfate	2	15.4
Amoxicillin	11	84.6
Transfusions	7	53.8
Hidroxiurea	9	69.2

suspicion, management, referral, and follow-up. In our study, the main clinical manifestations were those associated with hemolytic anemia and pain.

Among the laboratory findings, the observation of sickle cells in the blood smear is frequent, although their absence does not rule out SCD. Hemoglobin electrophoresis was not performed in all patients and the genetic study was only available in one patient, so it is not possible to rule out the concomitance of other hemoglobinopathies. The low number of complementary studies performed is of concern, which prevents optimal management according to international standards[17].

Most patients received the recommended treatment, antibiotic prophylaxis[21], transfusions[22], and hydroxyurea[17].

To our knowledge, this is the first report of a case series of SCD in pediatric patients in Chile. This summary of a decade of experience is restricted to a single center and there are few patients, so the results should be treated with caution and not generalized.

It is necessary to improve the suspicion, diagnosis, and management of patients with SCD in Chile by creating a registry of patients with SCD and coordinating the units that care for this type of patients at the national level. In addition, the vast experience of other Latin American countries in research[13,23], study[24,25], management[26,27], and education of health personnel in SCD[28] should motivate international collaboration.

Conclusion

The number of patients with SCD has increased, especially in the last 5 years. Most patients are not migrants, but their parents are. It is urgent to increase the level of diagnostic suspicion and improve access to complementary studies according to international standards. The necessary treatments are available in the country and most patients receive them once the diagnosis is established.

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

Authors state that no economic support has been associated with the present study.

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