# ORIGINAL ARTICLES

## Sickle cell disease: Clinical and sociodemographic characteristics of children under five years in a Portuguese hospital

### Doença de células falciformes: Caracterização da população até aos cinco anos de idade num hospital Português

Inês Filipa Mendes[1], Adriana Costa[1], Joana Lage[1], Bernardo Monteiro[1], Teresa Ferreira[1], Helena Cristina Loureiro[1]

## ABSTRACT

**Introduction:** The global incidence of sickle cell disease (SCD) is approximately 300.000 births per year, and the condition is associated with significant morbidity and mortality in pediatric age. This study aimed to describe the sociodemographic and clinical characteristics of children up to five years of age with SCD in a Portuguese center.

**Methods:** This was a descriptive retrospective study of children aged until five years with a diagnosis of SCD and hematologic follow-up in a level II Portuguese hospital between January 2010 and December 2019.

**Results:** Eighty-six patients were included, mostly of African descendent and homozygotic for hemoglobin S. The median age at diagnosis was five months, obtained through neonatal screening in 44.2%, in the context of hospitalization in 34.9%, and in ambulatory observation in 17.4% of patients. A total of 96.5% of cases were compliant with the Portuguese National Vaccination (PNV) Program, and 48.8% completed the extra-PNV scheme. All patients were under folic acid supplementation, 98% were under amoxicillin prophylaxis, and 6.9% were under hydroxycarbamide. Transcranial Doppler was conducted in 68.6% of patients and was altered in only one, echocardiogram was performed in 72.1% of patients and showed left ventricle dilatation in 21%, and overnight polysomnography was performed in 24.4% of patients and revealed obstructive sleep apnea in 95.2%. Each child had an average of four hospitalizations during the study period, with the most common diagnosis being vaso-occlusive crisis in 38.3%, followed by fever of unknow origin in 23.4%, upper airway infection in 17.8%, bacterial pneumonia and splenic sequestration in 10.7% each, and worsening anemia in 9.5%.

**Discussion:** Given the chronicity of SCD and the multiplicity of associated comorbidities, it is essential to reinforce the importance of multidisciplinary follow-up and family engagement in treatment.

**Keywords**: anemia; Hematology; pediatric age; sickle cell disease

## RESUMO

**Introdução:** A doença das células falciformes (DCF) ocorre em cerca de 300.000 nascimentos por ano a nível mundial, associando-se a morbimortalidade significativa em idade pediátrica. Este estudo pretendeu fazer a caracterização sociodemográfica e clínica da população até aos cinco anos com DCF seguida num centro português.

**Métodos:** Estudo retrospetivo descritivo de crianças até aos cinco anos de idade com DCF e seguimento em consulta de Hematologia pediátrica num hospital português de nível II entre 2010 e 2019.

**Resultados:** Foram incluídas 86 crianças, maioritariamente de ascendência africana e homozigóticos para a hemoglobina S. A mediana de

1. Department of Pediatrics, Hospital Professor Doutor Fernando Fonseca. 2720-276 Amadora, Portugal.
ines.f.mendes@hff.min-saude.pt; adriana.costa@hff.min-saude.pt; joana.lage@hff.min-saude.pt; bernardo.monteiro@hff.min-saude.pt; teresa.m.faria@hff.min-saude.pt; helena.c.silva@hff.min-saude.pt

idades ao diagnóstico foi de cinco meses, tendo as idades sido obtidas obtida através de rastreio neonatal em 44,2% dos casos, em contexto de internamento em 34,9% e em contexto de consulta em 17,4%. O Programa Nacional de Vacinação (PNV) foi cumprido em 96,5% e 48,8% realizaram o esquema vacinal extra-PNV recomendado. Todos os doentes estavam a receber medicação com ácido fólico, 98% estava a receber amoxicilina em regime profilático e 6,9% hidroxicarbamida. No total, 68,6% efetuaram Eco-Doppler transcraniano, que esteve alterado apenas numa criança; 72,1% realizaram ecocardiograma transtorácico, que revelou dilatação do ventrículo esquerdo em 21%; e 24,4% realizaram polissonografia, que revelou síndrome de apneia obstrutiva do sono em 95,2%. Cada criança teve em média quatro internamentos durante o período do estudo, sendo os diagnósticos mais frequentes crise vaso-oclusiva (38,3%), febre sem foco (23,4%), infeção respiratória alta (17,8%), pneumonia bacteriana e sequestro esplénico (10,7% cada) e agudização de anemia (9,5%).

**Discussão:** Dada a cronicidade da DCF e a multiplicidade de comorbilidades associadas, é fundamental reforçar a importância do seguimento multidisciplinar e do envolvimento dos familiares no tratamento.

**Palavras-chave:** anemia; doença de células falciformes; Hematologia; idade pediátrica

## INTRODUCTION

Sickle cell disease (SCD) has been acknowledged by the World Health Organization as a global public health problem, with estimates indicating that 300.000 to 500.000 children are born each year with severe hemoglobinopathy.[1]

The term SCD refers to an heterogeneous group of inherited hemoglobinopathies in which the affected individuals have inherited an abnormal gene in the hemoglobin (the sickle hemoglobin [HbS]), either in homozygosis (HbSS or sickle cell anemia [SCA]) or in compound heterozygosis with another beta globin allele mutation, such as hemoglobin SC disease, sickle cell-beta thalassemia (which is divided into sickle cell-beta$^0$ thalassemia and sickle cell-beta$^+$ thalassemia), and others less frequent (sickle-alpha thalassemia, sickle-hereditary persistence of fetal hemoglobin, sickle-delta beta (0) thalassemia, sickle-Hb Lepore disease, sickle-HbD disease, sickle HbO Arab disease, and sickle-HbE disease).[2,3]

HbS results from a mutation in the normal beta globin gene that leads to an abnormal hemoglobin, which under adverse circumstances, such as hypoxia, polymerizes into intracellular fibers, becoming less soluble and causing sickle cell deformity. The pathological polymerization of deoxygenated HbS is a key feature in the pathophysiology of the disease and explains its main clinical manifestations, such as vaso-occlusive phenomena and hemolytic anemia.[2-4]

All forms of SCD are inherited in an autosomal recessive fashion, although there is considerable variability in severity according to the genotype. As such, individuals with HbSS and compound heterozygous for Sβ$^0$ thalassemia have the most severe clinical phenotype, and those with SC and Sβ$^+$ thalassemia have a milder clinical phenotype and increased life expectancy.[2,5]

The sickle cell trait is a benign condition that confers a relative protection against *Plasmodium falciparum* malaria infection, and therefore carriers are less likely to get this disease. Although the sickle hemoglobin mutation is currently globally widespread due to migrations, this survival advantage has contributed to a high frequency of the condition in areas with a history of malaria, as sub-Saharan Africa.[2,3]

About 75% of the global burden of SCD occurs in sub-Saharan Africa, where the resources to diagnose and manage this disorder are scarce. Therefore, many children in this area do not reach their fifth birthday and die undiagnosed due to disease complications.[6] In well-resourced countries, a holistic approach with family education and well-structured comprehensive care programs has been instituted, which has enabled an increase in the average life expectancy of sickle cell children, with almost all surviving into adulthood. Therefore, as these patients age, other comorbidities manifest, such as pulmonary hypertension, diastolic heart dysfunction, and end-stage renal disease.[3,7]

SCD testing is currently a standard component of newborn screening in some hospitals. Newborns with abnormal screening results should be referred to a pediatric hematologist, and a confirmatory testing should be performed.[1]

SCD has a variable presentation in pediatric patients. The first symptoms usually manifest around six months of life, when fetal hemoglobin dissipates, and include pallor, anemia, vaso-occlusive episodes, acute chest syndrome, and susceptibility to bacterial infections, amongst others. Infection is the most common cause of mortality, particularly in very young children, with several preventive strategies developed throughout the years, such as antibiotic prophylaxis with penicillin and vaccination.[1]

Antibiotic prophylaxis with penicillin or amoxicillin (used in Portugal, since the oral penicillin formula is not available) was shown to reduce the incidence of pneumococcal infections in children younger than five years and should be initiated at two months of age.[1]

According to the Portuguese National Vaccination (PNV) Program, all children with SCD should receive routine childhood immunization. In addition, they should also receive the influenza vaccine annually

since the age of six months, the 23-valent pneumococcal vaccine from the age of two years, and the meningococcal B vaccine and meningococcal ACWY conjugate vaccine since the age of two months.[1,4] Since October 2020, the meningococcal B vaccine has been included in the PNV Program for all children in the first year of life (not included at the time of this study). Daily folic acid supplementation is recommended to prevent bone marrow aplasia from folate deficiency.[4] Hydroxycarbamide is used to increase fetal hemoglobin levels, thereby increasing oxygen-carrying capacity, decreasing sickle hemoglobin levels, and reducing several morbidities related to chronic hemolysis.[1]

Stroke is a major known complication of SCD, primarily occurring in childhood. Routine screening with transcranial doppler ultrasonography (TCD) can identify vessel abnormalities by measuring the mean velocity artery flow that identifies children at high risk of stroke, and should be performed annually since the age of two years.[1]

Obstructive sleep apnea syndrome (OSAS) is a common pediatric disorder with an estimated prevalence of 1–5%.[8] It causes episodic upper airway collapse, which disrupts ventilation and therefore interferes with sleep quality. Hypoxia is one of the main triggers for vaso-occlusion, and desaturation is common in both OSAS and SCD.[8] According to several studies, the prevalence rates of OSAS are higher in children with SCD, reaching 41% when considering a cut point of obstructive apnea hypopnea index (AHI) superior to one.[8] Considering that SCD is a complex disease with many comorbidities and that OSAS is a treatable condition that may be associated with multiple adverse health outcomes, it is of utmost importance to implement measures for screening and managing this disease, particularly in such a vulnerable population as that of children under the age of five years.

The purpose of this study was to assess the sociodemographic and clinical characteristics, as well as management and follow-up of all children up to the age of five years with a diagnosis of SCD in the Portuguese hospital Professor Doutor Fernando Fonseca. This is a level II hospital in the region of Amadora and western Sintra covering a total population of 568,069 people, of whom 90,761 are children under 15 years old.[9] The latest data point to a foreign resident population of 8.65% in Sintra and 10% in Amadora, of whom 55.6% and 62% are African residents, respectively.[10,11] This demographic feature makes this region particularly interesting for the study of SCD.

## METHODS

A descriptive retrospective observational study was conducted between January 2010 and December 2019, with data collected from computerized inpatient records.

The following variables were assessed: sociodemographic and clinical parameters, comorbidities (including concomitant diseases and follow-up at other medical appointments), and disease management. Sociodemographic parameters included age, gender, date of birth, origin, family's birthplace, and surveillance during pregnancy. Pregnancies was considered well monitored if having at least six medical appointments, blood tests with serology in the three trimesters, and at least three ultrasounds performed. Clinical parameters retrieved included neonatal screening (which, since 2013, has become a standard approach in newborns of mothers with sickle cell or ancestry from countries with high risk for SCD), age at diagnosis, type of sickle cell disease, and steady-state hemoglobin. The hemoglobin analysis methods consisted of capillary electrophoresis in cases up to six months of age and high-performance liquid chromatography (HPLC) thereafter.

Management and surveillance of the disease included transcranial doppler ultrasonography screening, sleep evaluation (only from the age of two years), use of prophylactic medication, and compliance with the PNV Program and other recommended vaccines. For vaccines not included in the PNV Program, the following eligibility criteria were considered: age over two years for the Pneumococcal Polysaccharide vaccine (PPSV23); age over six months for the Influenza vaccine; age over two months for the Meningococcal B and ACWY conjugate vaccines (free for children with SCD since 2016); and age over 12 months for the hepatitis A vaccine.

OSA severity classification was established through the obstructive apnea hypopnea index (AHI): mild if AHI 1-5/h, moderate if AHI 5-10/h, and severe if AHI>10/h.

As this study aimed to describe sociodemographic and clinical features, as well as management and comorbidities of children up to five years of age with a diagnosis of SCD and at least two years of hematologic follow-up, children who were lost to follow-up at the study hospital for any reason were excluded from the analysis.

Statistical analysis was performed in Excel Microsoft 365, 2020 Microsoft Corporation©.

Ethics permission for the study was obtained from the Ethics Committee of the hospital.

## RESULTS

A total of 86 patients aged until five years were included in the study, 46 (53.5%) of whom were female. Most were of Portuguese (85%) followed by Angolan (8%) nationality. Regarding parents' origin, the most frequent was Angola, corresponding to 32.6% of cases, followed by Guinea-Bissau (16%) and São Tomé e Principe (11.6%; **Table 1**) Sixty-three (73.3%) pregnancies were monitored in Portugal.

The predominant type of SCD in the study cohort was HbSS (SCA), present in 80 (93%) cases, followed by HbSC (n=3; 3.5%). Only one case of HbS$\beta^+$ thalassemia (1.2%), HbS$\beta^0$ thalassemia (1.2%), and alpha thalassemia association (1.2%) each were identified. In one child, the simultaneous presence of glucose-6-phosphate dehydrogenase deficiency was identified.

Regarding diagnosis, 44.2% (n=38) of patients were diagnosed through neonatal screening (hemoglobin electrophoresis at birth),

34.9% (n=30) in the context of hospitalization, and 17.4% (n=15) in the context of a medical appointment with laboratory confirmation. The diagnostic setting could not be ascertained in three cases that had been diagnosed in Angola (n=2) and Cape Verde (n=1). Considering only children born after 2013 (n=38), 68.4% (n=26) had been diagnosed through neonatal screening, while only 25% (n=12) of children born before 2013 (n=48) had been diagnosed through this procedure at the study hospital.

The median age at diagnosis was five months (interquartile range [IQR] 1-12 months). Analyzing only children born before 2013, when neonatal screening was not implemented at the study hospital, the median age at diagnosis was eight months (IQR 3-17 months), and considering only children born after 2013, the median age at diagnosis was one month (IQR 0-6 months).

**Table 1 –** Birthplace of children in the study cohort and their parents

| Birthplace | Absolute number (n=86) | Relative frequency (%) |
|---|---|---|
| Children's Birthplace | | |
| Portugal | 73 | 84.9 |
| Angola | 7 | 8.1 |
| S. Tome e Príncipe | 1 | 1.2 |
| Brazil | 1 | 1.2 |
| Guinea-Bissau | 1 | 1.2 |
| Cape Verde | 1 | 1.2 |
| Netherlands | 1 | 1.2 |
| Senegal | 1 | 1.2 |
| Parents' birthplace | | |
| Angola | 28 | 32.6 |
| Unknown | 16 | 18.6 |
| Guinea-Bissau | 14 | 16.3 |
| S. Tome e Príncipe | 10 | 11.6 |
| Cape Verde | 7 | 8.1 |
| Brazil | 5 | 5.8 |
| S. Tome e Príncipe + Cape Verde | 3 | 3.5 |
| Senegal | 1 | 1.2 |
| Portugal + Cape Verde | 1 | 1.2 |
| Pakistan + Portugal | 1 | 1.2 |

Hemoglobin levels were assessed by considering 1 g/dL intervals, with 41.9% of children presenting a baseline hemoglobin level between 7-8 g/dL (**Table 2**).

**Table 2 -** Baseline hemoglobin levels of the study cohort

| Hemoglobin level (g/dL) | Absolute number (n=86) | Relative frequency (%) |
|---|---|---|
| ]6-7] | 10 | 11,6 |
| ]7-8] | 36 | 41.9 |
| ]8-9] | 22 | 25.6 |
| ]9-10] | 13 | 15.1 |
| ]10-11] | 5 | 5.8 |

All patients were regularly followed in Hematology outpatient consultation. In addition, 74% were also followed in Cardiology, 30% in Otorhinolaryngology, and 28% in Sleep Disorders consultation (**Table 3**).

**Table 3 -** Medical follow-up of the study cohort

| Medical consultation | Absolute number (n=86) | Relative frequency (%) |
|---|---|---|
| Hematology | 86 | 100 |
| Cardiology | 64 | 74.4 |
| Otorhinolaryngology | 26 | 30.2 |
| Sleep disorders | 24 | 27.9 |
| Pediatric surgery | 17 | 19.8 |
| Psychology | 5 | 5.8 |
| Neurology | 5 | 5.8 |
| Nephrology | 4 | 4.7 |

Regarding vaccination status, the vast majority of children (96.5%) were compliant with the PNV Program. Concerning vaccines not included in the Program but recommended, 85% had received the Pneumococcal polysaccharide vaccine (PPSV23), 87% the Influenza vaccine, and 80.6% the Meningococcal B vaccine. The lowest immunization rate was observed in children eligible for Meningococcal ACWY conjugate vaccine (39%). Additionally, 52.9% of the study population had also received the Hepatitis A vaccine.

Patients were only assessed for vaccines they were eligible to, which is why denominators are smaller for some immunizations compared to others. The complete immunization adherence rate, including recommended vaccines (all the previously mentioned, excluding Hepatitis A vaccine) was 49% (**Table 4**).

All patients were taking acid folic supplementation (n=86) and the majority was also receiving daily amoxicillin (n=84; 98%) as prophylaxis. One child was taking clarithromycin instead of amoxicillin due to allergic reaction to the latter. Ten children (12.6%) underwent treatment with an angiotensin-converting enzyme inhibitor, nine due to dilated cardiomyopathy (one of whom also had hypertension) and one due to persistent microalbuminuria. Six patients (6.9%) were under hydroxycarbamide therapy. All these patients had at least seven hospitalizations (average 9, minimum 7–maximum 17 hospitalizations) prior to treatment start, with at least two being due to vaso-occlusive crisis. One patient was hospitalized for acute chest syndrome. After therapy introduction, only one patient was hospitalized (two times, one for vaso-occlusive crisis). All patients started therapy after the year 2016 (the youngest was three years and seven months old).

Fifty-eight children (68.6%) performed transcranial doppler and one showed alterations, specifically middle cerebral artery stenosis.

Sixty-two children (72.1%) performed at least one echocardiogram. Left ventricle dilatation was the most frequent pathological finding, observed in 13 children (**Table 5**).

**Table 4 -** Adherence to the Portuguese National Vaccination Program and to other recommended vaccines in eligible patients of the study cohort

| Vaccine | Yes | No | Not applicable | n | Relative frequency (%) |
|---|---|---|---|---|---|
| PNV Program | 83 | 3 | 0 | 86 | 96.5 |
| Pneumococcal polysaccharide | 67 | 12 | 7 | 79 | 84.8 |
| Meningococcal B | 50 | 12 | 24 | 62 | 80.6 |
| Influenza | 74 | 11 | 1 | 85 | 87.1 |
| Meningococcal ACWY conjugate | 23 | 36 | 27 | 59 | 39.0 |
| Hepatitis A | 45 | 40 | 1 | 85 | 52.9 |
| Total adherence to vaccination program (excluding Hepatitis A vaccine) | 42 | 44 | 0 | 86 | 48.8 |

PNV, Portuguese National Vaccination

**Table 5 -** Echocardiogram findings in the study cohort (n=62)

| Echocardiogram | Absolute number (n=62) | Relative frequency (%) |
|---|---|---|
| Without pathologic findings | 45 | 72.6 |
| LVD | 8 | 12.9 |
| LVD + mitral regurgitation | 2 | 3.2 |
| LVD + tricuspid regurgitation | 2 | 3.2 |
| LVD + ostium secundum atrial septal defect | 1 | 1.6 |
| Pulmonary artery stenosis | 1 | 1.6 |
| Pericardial effusion | 1 | 1.6 |
| Patent ductus arteriosus | 1 | 1.6 |
| Interventricular communication | 1 | 1.6 |

LVD. left ventricle dilatation

Twenty-one children (24.4%) aged between 2.3–4.9 years underwent overnight polysomnography, 20 (95.2%) of whom had OSAS. Most children (n=12; 57.1%) had mild disease, six children (28.6%) had moderate disease, two children (9.5%) had severe disease, and only one child (4.8%) had a normal AHI (**Table 6**). Seven children underwent tonsillectomy, two in the context of severe OSA.

On average, each child experienced four hospitalizations during the five years. Sixteen children had no hospitalizations. The main acute complication requiring hospitalization during the study period was vaso-occlusive crisis (38.3%), followed by fever of unknow origin (23.4%), upper respiratory infection (17.8%), bacterial pneumonia and splenic sequestration (10.7% each), and worsening anemia (9.5%).

**Table 6 –** Obstructive sleep apnea and its severity in the study cohort

| OSA severity (nº events/h) | Absolute number (n=21) | Relative frequency (%) |
|---|---|---|
| Absent (AHI <1) | 1 | 4.8 |
| Mild (AHI 1-5) | 12 | 57.1 |
| Moderate (AHI 5-10) | 6 | 28.6 |
| Severe (AHI >10) | 2 | 9.5 |

AHI. apnea-hypopnea index; OSA. obstructive sleep apnea

## DISCUSSION

According to the literature, the most prevalent form of SCD is by far HbSS (SCA), followed by HbSC. This was confirmed in the present study, with the vast majority of cases (93%) presenting homozygosity for the S allele. The second most common form of SCD identified in the study was HbSC.

In agreement with previous reports from several other studies, a high prevalence of SCD was identified in families with origins in sub-Saharan Africa: 74.5%.[1,5,6,7]

Proper management of SCA begins with a correct diagnosis early in life, ideally during the newborn period. A significant proportion of cases in this study (44.2%) was diagnosed through neonatal screening, a number that is even higher (68.4%) if considering only the period after selective screening started (2013). Neonatal diagnosis allows early initiation of preventive interventions, including prophylactic antibiotics and vaccination, which help prevent complications, namely overwhelming sepsis, and thus the number of hospitalizations. In addition, it also allows prompt education of families in the recognition of early symptoms, enabling appropriate approaches and interventions.

SCA requires treatment and follow-up by a multidisciplinary team. Adherence to the PNV Program in SCD patients is essential to protect them from vaccine preventable diseases. This study showed that most children (96%) are compliant with the vaccination program. The lowest immunization adherence rates occurred with Meningococcal ACWY conjugate vaccine – the newest vaccine, only available for free to SCD patients since 2016 – and with Hepatitis A vaccine. The complete immunization adherence rate, including all recommended vaccines (excluding the Hepatitis A vaccine), was 48.8%. This contrasts with a U.S. study about immunization adherence in children with SCD, where the adherence rate to the recommended immunization schedule was 6% and the lowest immunization rate was observed in children eligible for the meningococcal B vaccine (25%).[12] In the present study, compliance with Meningococcal B vaccine was 80.6%. This emphasizes the need to reinforce the importance of vaccination and educate families and caretakers. Quality improvement measures should focus on increasing immunization adherence.

Hydroxycarbamide is the only approved treatment for SCD and the recommendations for treatment initiation have changed over time. For many years, its use was reserved for children older than two years and had specific eligibility criteria that included three or more hospitalizations for vaso-occlusive crisis; two or more hospitalizations for acute thoracic syndrome; or any combination of at least three hospitalizations with these two diagnoses per year or one episode of severe acute thoracic syndrome, priapism, stroke, or any other severe complication. More recently, there was a paradigm shift, with recommendations to introduce this therapy earlier in life and several sources, namely the British Society for Hematology, advising treatment start around the ninth month of life, regardless of other factors.[13] The present study was conducted over nine years, and hence most children were not under hydroxycarbamide therapy. Still, it should be noted that about 6.9% of children under five years of age were already under hydroxycarbamide therapy for having had at least three hospitalizations for vaso-occlusive crisis. Knowing that this treatment is, not only safe and effective, but also one of the only disease-modifying therapies available, it should be used early to prevent complications. Therefore, it can be anticipated that a change will be seen in upcoming years towards the introduction of hydroxycarbamide earlier in life. In this context, it would be interesting to conduct a study investigating if earlier treatment start influences hospitalizations and outcomes in children with SCD.

Cardiac complications are a common feature in SCD and an important cause of morbidity and mortality associated with the disease. A study of echocardiographic screening in children with ≥ 10 years of age and SCD documented 25% of left ventricle dilation.[14] In the present study, 21% of patients had left ventricle dilatation, which represents a non-negligible proportion in children under five

years old.

The prevalence of OSAS in children with SCD appears to be higher than in the general pediatric population.[8,15] In this study cohort of children younger than five years only, about a quarter underwent night polysomnography and OSAS was identified in the vast majority (95.2%, 38.1% with moderate to severe forms). This finding is in agreement with the literature, perhaps even more than the previous study that only included older children, between the ages of four and 18 years. [8] Since OSAS is a treatable condition and is associated with various adverse health outcomes (including minimum peripheral oxygen saturation significantly lower than non-SCD counterparts, behavioral problems, cognitive deficits, and cardiovascular changes, namely hypertension), this finding highlights the importance of early screening of the disease, since it has a direct impact on patients' quality of life, both in child and adulthood.[15]

One of the main limitations of this study was its small sample size, which makes it difficult to extrapolate results to the general population, namely the correlation between the type of SCD and disease severity.

A prompt diagnosis is the first step towards improving the outcomes of individuals with SCD, and is key for parental education, namely regarding symptom recognition and seek for immediate medical care.

## AUTHORSHIP

Inês Filipa Mendes - Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing – original draft; Writing – review & editing

Adriana Costa - Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft

Joana Lage - Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft

Bernardo Monteiro - Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft

Teresa Ferreira - Conceptualization; Methodology; Validation; Writing – original draft; Writing – review & editing

Helena Cristina Loureiro - Conceptualization; Methodology; Validation; Writing – original draft; Writing – review & editing

## REFERENCES

1. McCavit TL. Sickle Cell Disease. Pediatrics in Review 2012; 33(5) 195-206. Doi: doi: https://doi.org/10.1542/pir.33-5-195.
2. Piccone CM. Sickle Cell Disease. In: Florin TA, Ludwig S, Aronson PL, Werner HD. Netter's Pediatrics. Philadelphia; 2011. p.326-30.
3. McMahon C. Sickle Cell Disease. In: Arceci RJ, Hann IM, Smith OP. Pediatric Hematology, 3rd Edition. United Kingdom; 2006. p.213-30.
4. DeBaun MR, Frei-Jones MJ, Vichinsky EP. Hemoglobinopathies. In: Kliegman RM, Stanton BF, St Geme III JW, Schor NF. Nelson Textbook of Pediatrics, 20th Edition. Canada; 2016. p.2336-53.
5. Houwing ME, de Pagter PJ, van Beers EJ, Biemond BJ, Rettenbacher E, Rijneveld AW, *et al*. Sickle cell disease: Clinical presentation and management of a global health challenge. Blood Rev. 2019;37:100580. Doi: https://doi.org/110.1016/j.blre.2019.05.004
6. Williams TN. Sickle Cell Disease in Sub-Saharan Africa. Hematol Oncol Clin North Am. 2016;30(2):343-58. Doi: https://doi.org/110.1016/j.hoc.2015.11.005
7. Ogu UO, Billett HH. Comorbidities in sickle cell disease: Adult providers needed! Indian J Med Res. 2018;147(6):527-9. Doi: https://doi.org/110.4103/ijmr.IJMR_1019_18
8. Rosen CL, Debaun MR, Strunk RC, Redline S, Seicean S, Craven DI, *et al*. Obstructive sleep apnea and sickle cell anemia. Pediatrics. 2014;134(2):273-81. Doi: https://doi.org/110.1542/peds.2013-4223.
9. PORDATA, Base de dados Portugal contemporâneo. 2018 Database. Fundação Francisco Manuel dos Santos. [Retrieved May 2020]. Available at: https://www.pordata.pt/Home.
10. Diagnóstico Social do Concelho de Sintra Dinâmicas Demográficas e Habitacionais, Câmara Municipal de Sintra - Departamento de Solidariedade e Inovação Social. Março 2014. [Retrieved June 2020]. Available at: https://cm-sintra.pt/phocadownload/PDF/acao_social/diagnostico-scs.pdf.
11. Amadora XXI, DIG - divisão de informação geográfica, 2011. [Retrieved June 2020]. Available at: http://www.cm-amadora.pt/images/TERRITORIO/INFORMACAO_GEOGRAFICA/PDF/ESTATISTICAS/Populacao_2011.pdf.
12. Infanti LM, Elder JJ, Franco K, Simms S, Statler VA, Raj A. Immunization Adherence in Children With Sickle Cell Disease: A Single-Institution Experience. J Pediatr Pharmacol Ther. 2020;25(1):39-46. Doi: https://doi.org/110.5863/1551-6776-25.1.39
13. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M, *et al*. British Society for Haematology. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol. 2018;181(4):460-75. Doi: https://doi.org/110.1111/bjh.15235.
14. Allen KY, Jones S, Jackson T, DeCost G, Stephens P, Hanna BD, *et al*. Echocardiographic Screening of Cardiovascular Status in Pediatric Sickle Cell Disease. Pediatr Cardiol 2019; 40: 1670-8. Doi: https://doi.org/110.1007/s00246-019-02202-3
15. Mascarenhas MI, Loureiro HC, Ferreira T, Dias A. Sleep pathology characterization in sickle cell disease: case-control study. Pediatr Pulmonol. 2015;50(4):396-401. Doi: https://doi.org/110.1002/ppul.23074.

**CORRESPONDENCE TO**

Inês Filipa Mendes
Department of Pediatrics
Hospital Professor Doutor Fernando Fonseca
IC19. 2720-276 Amadora. Portugal.
Email: ines.f.mendes@hff.min-saude.pt

Received for publication: 05.09.2021
Accepted in revised form: 16.03.2022