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Children with Sickle Cell Disease in Northern Benin: Follow up of a Cohort at the Borgou/Alibori Branch of Integrated Medical Healthcare Center for Infants and Pregnant Women with Sickle Cell Disease from 2017 to 2022

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Abstract

Introduction: Sickle cell disease is a public health problem in sub-Saharan Africa. A national referral center for the management of infants and pregnant women with sickle cell disease (CPMI-NFED) was created three decades ago in Cotonou, in the south of Benin with two regional branches including that of Parakou in the North for better access of patients to specialized care. This work is a review of five years of activities in order to describe the epidemiological, clinical, hematological and evolutionary profiles of the children followed up in the said branch. **Method:** This was a descriptive and retrospective cross-sectional study on the medical records of children with sickle cell disease, followed up at the regional branch of CPMI-NFED in Borgou/Alibori from June 1, 2017 to May 31, 2022. The variables studied were epidemiological, clinical, biological and evolutionary. **Results:** A total of 101 children with sickle cell disease were included in the study, including 78 homozygous SS (77.2%) and 23 heterozygous SC (22.8%). Their mean age at inclusion was 51.2 ± 37.6 months [6 - 204]. The sex ratio was 1.4. Vaso-occlusive crises were the main diagnostic circumstances in 42.3% of homozygotes. More than half of the children (51.5%) had a regular follow-up. The average baseline level of hemoglobin (Hb) in homozygous children was 8.8 ± 1.4 g/dl [5.8 - 11.5]; and the

rate of Hb S varied between 61.9 and 94.7%. In heterozygous SC children, the mean baseline level of Hb was 10.7 ± 0.6 g/dl [9.7 - 11.5]. Acute complications observed during follow-up were dominated by pneumonia and vaso-occlusive crises in both phenotypes. The overall mortality was 3% and only affected homozygous patients. **Conclusion:** On average, three out of four children were homozygous in our cohort. The main acute complications were infectious and vaso-occlusive. The mortality only affected homozygous carriers. Specialized follow-up has contributed to improving the quality of life of children with sickle cell disease. This could be implemented on a large scale for better survival of children with sickle cell disease.

Keywords

Sickle Cell Disease, Children, CPMI-NFED, Parakou, Benin

1. Introduction

Sickle cell disease is an autosomal and recessive disease caused by a mutation of the β-globin gene, characterized by clinical manifestations such as hemolytic anemia and recurrent episodes of vascular occlusion [1]. Every year 300,000 newborns come to life with the disease [2]. Although present throughout the world, sub-Saharan Africa remains the most affected region with more than 90% of births. Morbidity and mortality related to sickle cell disease in children before five years of age are significant, especially in countries with limited resources. The number of pediatric hospitalizations can reach 2.5/child/year. The rate of infant and child mortality varies between 50% and 80% [3] [4] [5]. The World Health Organization (WHO) has recognized that sickle cell disease had a global impact with remarkable implications for public health in Africa [6] [7]. However, it is not yet a health priority in many African countries.

In Benin, the prevalence of sickle cell disease is estimated at 4.8% [8] [9]. There is no systematic neonatal screening program. Over the last three decades, a national referral center for the management of infants and pregnant women with sickle cell disease (CPMI-NFED) has been created in Cotonou, in the South with two regional branches within the country. The aim of this center was to design and implement political and strategic guidelines for the prevention and control of sickle cell disease, in particular in children under five years of age and pregnant women who constitute the most vulnerable groups [10]. As a result, specialized care is provided to these children in an African context generally characterized by a lack of access to comprehensive health care [5]. The pediatric department of the Regional Teaching Hospital of Borgou and Alibori (CHUD-B/A), located in Parakou in the north of Benin is a referral department receiving children from the northern region of the country. It houses one of the regional branches of CPMI-NFED. This work is a review of five years of activities in order to describe the epidemiological, clinical, hematological and evolutionary profiles of

the children followed up in the said branch.

2. Methods

This was a descriptive and cross-sectional study with retrospective data collection, conducted from May to September 2022. It focused on the medical records of children with major sickle cell syndrome (SS, SC, Sβ), followed up at CPMI-NFED of Borgou/Alibori over the period from June 1, 2017 to June 1, 2022. The diagnosis of major sickle cell syndrome was established on the basis of the hemogram and hemoglobin electrophoresis, carried out by high performance liquid chromatography (HPLC). The medical records of patients meeting the following criteria were included in the study:

- Medical records including at least two medical consultations for annual follow-up.
- Complete medical records including data relating to the general information of the child and his parents, the physiological and pathological history of the child, the clinical and biological parameters monitored at each consultation and complications developed by the child during the follow-up.

Were excluded:

- Medical records of children lost to follow-up during the first year after their integration into medical follow-up and not found after an active search.
- Unusable medical records, that is to say without essential information such as biological parameters of the child, in particular baseline level of hemoglobin.

Exhaustive recruitment of all children meeting the inclusion criteria was carried out.

The variables studied were:

- Epidemiological: age, sex, ethnicity, origin, educational level of the child and his parents, profession of the parents, size of the siblings and number of children with sickle cell disease in the siblings.
- Clinical: medical history (age and circumstances of discovery of the disease, frequency of vaso-occlusive crises, number of previous hospitalizations, history of blood transfusion, previous complications developed before inclusion), anthropometric parameters of children during the follow-up with reference to WHO growth charts, data from physical examination in interictal situation.
- Paraclinical: type of hemoglobinopathy, percentage of the different fractions of hemoglobin S, C and F, A2; hemogram during periods of clinical stability; rhesus blood group;dosage of G6PD; HIV serology; HBs antigenemia and anti-HCV antibodies. Reticulocytes were not taken into account because they were very rarely available in the medical records of patients.
- Evolutionary: regularity of follow-up, number of hospitalizations, number of blood transfusions, acute complications (infectious, thromboembolic, hemolytic), chronic complications and vital status.

To be eligible for the program of follow-up of children with sickle cell disease

at the regional branch of CPMI-NFED in Borgou/Alibori, the subject must be under five years old. Some older children, previously in the pediatric department of CHUDB/A in accordance with the protocol of CPMI-NFED before the creation of the Borgou branch in 2015, were also taken into account for the purposes of the study.

The period of clinical stability or stationary period was defined as any clinical situation in the child characterized by an absence of acute complications (fever, painful crises, acute hyperhemolysis). Vasoocclusive and infectious complications were those observed during the last two years of follow-up.

The management at the center was multidimensional, holistic with components of care, support, accompaniment, education of patients and their parents. Regarding the care, it was based mainly on prevention, notably: chemoprophylaxis (penicillin V, chloroquine, folic acid), immunizations, compliance with hygiene rules and avoidance of factors triggering painful crises, hydration, palpation of the spleen and nutrition of children. Curative measures were based on the management of various acute or chronic complications through defined protocols. At the paraclinical level, the follow-up assessment included a blood count every six months and a package of additional examinations from the age of five to assess the impact of the disease on the most exposed organs. The follow-up was said to be regular when the patient had at least three systematic visits in an Intercritical situation within a year.

The data collected were subject to verification to ensure their completeness and consistency. They were then analyzed using Epi info software version 7.1.3.3. The qualitative variables were analyzed independently and expressed as number (n) and proportion (%). Quantitative data were expressed as means and standard deviations for symmetrical distributions and as median with interquartile range (Q1, Q3) for asymmetrical distributions. The data were used with strict confidentiality.

3. Results

3.1. General Characteristics of the Study Population

3.1.1. Phenotypic Profile

Our study included 115 children with major sickle cell syndrome. Among them, 14 were excluded because they were lost to follow-up (9) or had unusable medical records (5). The study involved 101 children including 78 homozygous SS (77.2%) and 23 double heterozygous SC (22.8%).

3.1.2. Socio-Demographic Characteristics of Children and Their Families

Male children were the most represented (58.4%). The sex ratio was 1.4. The mean age at inclusion was 51.2 ± 37.6 months [6 - 204]. Children under 60 months were the most represented (66.3%). Table 1 shows the sociodemographic characteristics of children of the cohort included in the study.

Table 1. Distribution of children according to their socio-demographic characteristics.

	N	%
Sex		
Male	59	58.4
Female	42	41.6
Age (month)		
[0 - 24[	30	29.7
[24 - 60[	37	36.6
60 or over	34	33.7
Ethnic group		
Fon and related	42	41.6
Yoruba and related	23	22.8
Bariba and related	22	21.8
Dendi and related	10	9.9
Peulh/Boo/Yom/Lokpa	4	3.9
Residence		
Parakou	82	81.1
Outside of Parakou	19	18.8

Regarding the educational level of the parents, fathers with higher level of education were the most represented (57.4%) while among mothers, 40.5% had at least secondary level. In terms of profession, officials were the most represented with respectively 64.4% of fathers and 38.6% of mothers. The parents lived as a couple in 68.3% of cases. The average number of children with sickle cell disease per sibling was 1.35 ± 0.65 with the extremes of 1 and 5.

3.2. Clinical Profile of Children

3.2.1. Medical History

Among homozygous SS children, the age at diagnosis was less than 24 months in 61.5% of cases. Acute complications were the main diagnostic circumstances in 62.8% of cases. They were dominated by vaso-occlusive crises (VOCs) in 42.3% of cases including 24.4% hand-foot syndrome (19/78) and worsening of anemia (16.7%). Among heterozygous SC children, the age at diagnosis was less than 24 months in 43.3% of cases. The circumstances of diagnosis were dominated by VOCs (30.4%), including hand-foot syndrome (4.3%) and repeated infections (13%). Screening was initiated by the parents or the attending physician in 47.8% of cases.

Homozygous children before joining the follow-up had been hospitalized at least once in 55.1% of cases and transfused at least once in 24.3% of cases. Heterozygous children had been hospitalized at least once in 39.1% of cases and transfused at least once in 17.4% of cases. Table 2 shows the history of children before their inclusion in the medical follow-up.

Table 2. Distribution of children with sickle cell disease according to their medical history before inclusion in the medical follow-up.

	SS		SC	
	n = 78	%	n = 23	%
Age at diagnosis (months)				
[0 - 24]	48	61.6	10	43.5
[24 - 60]	20	25.6	9	39.1
60 or over	10	12.8	4	17.4
Circumstance of diagnosis				
Acute complications	49	62.8	11	47.8
Screening initiated by parents or the doctor	29	37.2	11	47.8
Systematic screening	-	-	1	4.4
Types of acute complications				
VOCs	33	42,3	7	30,4
Recurrent anemia	13	16.7	2	8.6
Recurrent bacterial infection	5	6.4	3	13.0
Recurrent priapism	1	1.3	-	-
Hospitalization				
Yes	43	55.1	7	39.1
No	35	44.9	14	60.9
Blood transfusion				
Yes	23	29.5	4	17.4
No	55	70.5	19	82.6

3.2.2. Clinical Status of Children at Initial and Stationary Phase

The main clinical signs found at the initial evaluation in homozygous SS children were pallor (83.3%), jaundice (46.1%) and splenomegaly (16.7%). In heterozygous SC carriers, it was pallor (21.7%), jaundice (17.4%) and splenomegaly (8.7%). These signs were also found in the stationary phase at lower proportions: pallor (74.4%), followed by jaundice (17.9%) and splenomegaly (12.8%) in homozygous SS children. The signs were essentially jaundice and splenomegaly in 4.3% of cases among heterozygous SC children.

3.2.3. Nutritional Status of Children at Inclusion and during the Five Years of Follow-Up

We focus on acute and chronic malnutrition.

At the start of the follow-up, children regardless of their phenotypes had a good nutritional status in 89.5% of cases. Acute malnutrition affected 10.5% of them, including 9.2% with moderate forms and 1.3% with severe forms. After five years of follow-up, 97.4% of children had a good nutritional status and 2.6% suffered from moderate acute malnutrition. No child was suffering from severe acute malnutrition.

At the start of follow-up, chronic malnutrition affected 10.6% of the children,

2.6% of whom were severely malnourished. After 5 years of follow-up, 13.6% were at risk of developing chronic malnutrition.

3.3. Hematological Profile of Children

Homozygous children had a mean baseline level of hemoglobin (Hb) at 8.8 ± 1.4 g/dl [5.8 - 11.5]. The mean hemoglobin S level was 79.6% ± 8.8% [61.9 - 94.7]. Hemoglobin F was 16.7% ± 9.9% and hemoglobin A2 was 2.9% ± 0.8%. In terms of white blood cells (WBC), 81% of children had a WBC count greater than 10,000/mm^3 with an average WBC count of 14.1 ± 5.4 G/L. As for the heterozygous (Hb SC) children, they had a mean baseline level of Hb at 10.7 ± 0.6 g/dl [9.7 - 11.5]. The average level of hemoglobin S was 47.6% ± 0.4% [41.1 - 52.4]. That of hemoglobin C was 42.9% ± 2.4% [38.6 - 46.5]. Table 3 shows a summary of the data from the baseline blood count and the hemoglobin study of children with major sickle cell syndrome included in the cohort.

3.4. Evolution

3.4.1. Acute Complications

Acute complications were dominated by infections in both phenotypes. These were pneumonia, septicemia found respectively in 55.4% (56/101), 28.7% (29/101). Malaria was a comorbidity associated with sickle cell disease in 87.1% of cases. Non-infectious complications were dominated by osteoarticular VOCs, 52.4% (53/101). Stroke and acute chest syndrome (ACS) were found only in homozygotes, in the same proportions (2.6%). Worsening of anemia was found exclusively in homozygous carriers in 35.9% of cases. Table 4 illustrates the acute complications presented by phenotype during the follow-up.

Table 3. Data from the blood count and the hemoglobin study of children with sickle cell disease followed up in Parakou.

	SS			SC		
	Averages	Standard deviation	Extremes	Averages	Standard deviation	Extremes
Hb (g/dl)	8.8	1.4	5.8 - 11.5	10.7	0.6	9.7 - 11.5
MCV (fl)	73.2	6.6	59.9 - 86.1	77.6	4.5	60.7 - 80.2
MCH (pg)	26.7	5.3	20.1 - 62.8	25.0	2.6	21.0 - 30.9
MCHC (g/dl)	35.4	1.5	31.4 - 39.3	35.9	1.5	33.1 - 37.7
WBC (G/L)	14.1	5.4	4.5 - 30.1	9.7	3.3	4.5 - 80.2
PNN (G/L)	5.8	2.5	1.9 - 16.3	4.5	1.6	2.2 - 8.7
Platelets (G/L)	381.3	124.8	126.6 - 781	347.2	103.4	126.6 - 538.3
Hemoglobin S (%)	79.6	8.8	61.9 - 94.7	47.6	0.4	41.1 - 52.4
Hemoglobin F (%)	16.7	9.9	1 - 35.9	7.7	5.83	1 - 17.5
Hemoglobin C (%)		-	-	42.9	2.4	38.6 - 46.5
Hemoglobin A2 (%)	2.9	0.8	0.80 - 4.7	3.0	1.51	0.3 - 4.7

Table 4. Distribution of children with sickle cell disease according to acute complications presented during the follow-up.

	SS		SC	
	N	%	n	%
Vaso-occlusive crises	43	55.1	10	43.5
Priapism	3	3.8	-	-
Stroke	2	2.6	-	-
Acute chest syndrome	2	2.6	-	-
Pneumonia	48	61.5	8	34.8
Tonsillitis	26	33.3	6	26.1
Sepsis	26	33.3	3	13.0
Osteomyelitis	2	2.6	-	-
Meningitis	1	1.3	-	-
Severe anemia	28	35.9	-	-

3.4.2. Frequency of Hospitalizations and Blood Transfusion

During the study period, 43.5% of homozygous children had been hospitalized at least once. The average number of hospitalizations per child was 2 ± 1.53 with the extremes of 1 and 9. They had been transfused at least once in 38.4% of cases with an average number of transfusions per child of 2.2 ± 3.3 and the extremes of 1 and 12. As for heterozygous (Hb SC) carriers, 21.7% had been hospitalized. The average number of hospitalizations per child was 1 ± 0.1 with the extremes of 0 and 3. None of them had been transfused.

3.4.3. Chronic Complications

The main chronic complications observed were aseptic osteonecrosis of the femoral head in a homozygous SS child and leg ulcer in a double heterozygous SC child aged 15 years.

3.4.4. Regularity of Follow-Up and Overall Mortality of Children in the Cohort

In 51.5% of cases, the children had regular follow-up. Three homozygous children died, representing an overall mortality in the cohort of 3%. The causes of death were severe malaria, splenic sequestration, and septicemia.

4. Discussion

This study took stock of children with sickle cell disease followed up for five years in the branch of CPMI-NFED in Borgou/Alibori. It made it possible to describe their clinical, hematological and evolutionary profiles. Despite the retrospective nature of the study, the exhaustive recruitment of medical records which were well completed and archived made it possible to reduce selection bias. The methodological approach used was safe enough to guarantee the validity of our results.

In our study, 78 children were homozygous SS (77.2%) and 23 heterozygous

SC (22.8%). In sub-Saharan Africa, several authors have reported a predominance of Hb SS phenotypes with proportions varying between 50% and 95%; those of SC phenotypes varying between 47% and 4% in Senegal and Burkina Faso [11] [12]. These differences could be explained by the variability of the cohorts studied as well as that of the prevalence of sickle cell trait in these countries. But the predominance of Hb SS phenotypes remains an observation in most studies, demonstrating the importance of this homozygosity in major sickle cell syndromes [5] [11] [12].

The average age of the children at inclusion in the cohort was 51.2 + 37.6 months. There was a high representation of children less than 60 months (66.3%). This same predominance was observed by Shongo and Rahimy [13] [14]. Other authors [11] [15] reported a mean age greater than 60 months in their cohorts. The high proportion of children under 60 months reflects the target population followed up by the center which favors children under 60 months.

The age of children at diagnosis of sickle cell disease was 24 months in 61.5% and 43.3% of cases in homozygous and double heterozygous children, respectively. Thiam *et al.* in Senegal [16] made the same observation in homozygous (Hb SS) patients. In the DRC an average age less than 12 months had been found at diagnosis for this same phenotype [13] [17]. On the other hand, among double heterozygous SC carriers, Diagne *et al.* in Senegal found an average age at diagnosis of eight years with the extremes of three and fourteen years [11]. Indeed, around 12 to 48 months, hemoglobin S almost replaces completely hemoglobin F, which thus promotes the occurrence of acute complications, particularly vaso-occlusive ones. These acute complications were the main diagnostic circumstances for both phenotypes, dominated by VOCs including hand-foot syndrome (24.3%) in homozygous SS children. This is similar to the observations of other authors [13] [17]. These clinical manifestations have been described in the literature as being the main warning signs of the disease. The high proportion of hand-foot syndrome in homozygous SS carriers results from the age of children in the cohort because the majority was less than 24 months old at the time of diagnosis.

During the follow-up, the signs observed in the stationary period were mainly pallor (64.1%), jaundice (17.9%) and splenomegaly (12.8%) in homozygous children. The same observation had been made in Senegal [16]. Jaundice and splenomegaly were found in 4.3% of cases in double heterozygous SC children. These signs reflect chronic extravascular hemolysis. Jaundice appears following anemia and classically after the age of six months; the age at which fetal hemoglobin begins to be replaced by hemoglobin S which then becomes predominant [16]. As for splenomegaly, the hypothesis of splenic regression after the age of 5 years is commonly described [18]. Its presence in the children of the cohort could be related to the age of our patients, and the chronic hemolysis, but also the possibility of an interaction with malaria due to the high prevalence of malaria in our context [19].

Acute malnutrition affected 10.5% of children at the start of follow-up and

2.6% after five years. Chronic malnutrition was present in 10.6% of children at the start of follow-up. After five years, 13.6% of them were at risk of developing acute malnutrition. In Nigeria a frequency of 9.1% of emaciation and 55.4% chronic malnutrition had been reported [20]. The negative impact of sickle cell disease on the nutritional status of children is well known. Poor nutritional status is associated with a deficient immune response to infections. Sickle cell disease also affects the nutritional status of children through several mechanisms such as increase in resting energy expenditure, reduced food intake, the combination of protein turnover due to increased erythropoiesis and increased cardiac activity secondary to anemia and hypoxia [21] [22] [23]. The reduction in cases of acute and chronic malnutrition in our cohort could probably reflect the good follow-up of patients and the importance given to the nutritional management of these children.

Regarding the hematological profile, homozygous children had on average a baseline level of hemoglobin at 8.8 ± 1.4 g/dl. These results are similar to those reported by several authors in Africa with averages of hemoglobin level varying around 8.6 g/l [11] [13] [16]. Anemia is explained by chronic hemolysis. Likewise, the average white blood cell count was 14,100/mm^3. Hyperleukocytosis is physiological in sickle cell disease and could be explained by the hyperactivity of the marrow and inflammations [24]. The mean level of Hb F was 16.71% ± 9.9% [1 - 35.9]. In Nigeria an average level of Hb F of 9.9% ± 6.0% had been observed [0.8 - 27.6] [25]. Thiam in Senegal reported an average rate of Hb S of 86.8% [54.6 - 98.4] and an average level of Hb F of 4% [0 - 37.6] [16]. These differences in results remain a finding. Indeed, the Senegal haplotype of the beta-globin gene should be associated with a higher level of fetal hemoglobin compared to the Benin haplotype commonly observed in Benin and Nigeria. Furthermore, the possibility of hereditary persistence of fetal hemoglobin in some children in the study cannot be excluded. Heterozygous SC carriers had a mean baseline level of Hb of 10.66 ± 0.60 g/dl [9.70 - 11.53]. These data are similar to those of other authors who reported levels of hemoglobin varying between 9.8 g/dl and 10.5 g/dl [12] [26].

In terms of evolution, acute infectious complications, especially bacterial, were at the forefront for both phenotypes in our cohort. These were pneumonia (61.5%), septicemia (33.3%) in homozygous children, similar to the observations of other authors [11] [17]. The same infectious complications were observed in heterozygous children at a lower frequency than in homozygous. Paulo *et al.* made the same observations in heterozygous children [26]. These infectious complications arise from the pathophysiology of sickle cell disease characterized by early functional asplenia with greater vulnerability to infections related to encapsulated germs. Other factors such as neutrophil dysfunction, impaired cell-mediated immunity, phagocytosis and the presence of ischemia, have been identified as factors promoting bacterial proliferation [27]. Malaria was comorbidity in more than 80% of cases in both phenotypes. Malaria increases pre-existing anemia and promotes the occurrence of VOCs [28].

The non-infectious complications found in our study among homozygous children were characterized by VOCs (55.1%), priapism (3.8%), stroke (2.6%), acute chest syndrome (2.3%), similar to those observed in DRC [17]. These crises result from the obstruction of sickled red blood cells at the level of the microvessels leading to vaso-occlusion with stasis and ischemia. The stroke only affected two children, representing 2.6% of cases. Sickle cell disease is the leading cause of stroke in children with an estimated risk of 0.76 per 100 patients. In regions where access to transcranial Doppler (TCD) is easy, the frequency of stroke is 1 in 10 children. In sub-Saharan Africa where the majority of children do not have access to this examination, frequencies vary between 2.9 and 16.9% [29]. It is a major vaso-occlusive complication because it seriously affects the vital and functional prognosis of affected children. Other complications were worsening of anemia (32.1%) with splenic sequestration among the mechanisms (3.8%). Rahimy reported 23.7% of acute anemia [14] with 1.7% of splenic sequestration. Acute anemia can be the consequence of several mechanisms such as erythroblastopenia, splenic sequestration, acute hyperhemolysis following among other things, malaria and septicemia. In most cases, our patients had acute anemia related to acute hemolysis or splenic sequestration. Splenic sequestration is a serious and fatal complication in homozygous carriers. In sub-Saharan Africa, its frequency varies between 2% and 27.3% [30]. In heterozygous SC carriers, non-infectious acute complications were VOCs (43.5%), similar to the observations in Brazil [26].

The main chronic complication observed in our cohort was aseptic osteonecrosis of the femoral head in a homozygous SS child. Leg ulcer was found in a double heterozygous SC child at 15 years of age. Serjeant *et al.* in Jamaica, found leg ulcers in 7.7% of its population with an age of onset between 10 and 15 years [31].

In terms of follow-up, more than half of the children (51.5%) had a regular follow-up. The overall mortality of the cohort was 3% and only concerned homozygous SS children. The main causes of death were severe malaria, splenic sequestration and sepsis in our cohort. They are reported as a cause of death in the literature in Sub-Saharan Africa [11] [14] [18].

5. Conclusion

At the end of five years of follow-up, it appears that on average three children out of four are homozygous SS in our cohort. Hand-foot syndrome constitutes one of the main diagnostic circumstances. The main acute complications are infectious and vaso-occlusive and the mortality only concerned homozygous children. Specialized follow-up has contributed to improving the quality of life of children with sickle cell disease. This could be implemented on a large scale for better survival of children with sickle cell disease.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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