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Clinical presentation of major sickle cell syndrome in children under 5 years at Kindu hospital environment, Democratic Republic of Congo (DRC)

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Abstract

Sickle cell disease is the most common genetic disorder of hemoglobin in the world today. Screening is the basis of any program aimed at its fight. Faced with the difficulties of implementing screening in countries with limited resources, it is important to resort to alternative strategies, in particular the optimization of clinical suspicion. This study was conducted with the objective of presenting the clinical characteristics of SS sickle cell disease revealed by laboratory screening in pediatric hospitals.

A cross-sectional, descriptive study with prospective collection was carried out in 5 health facilities in the city of Kindu in the DRC between December 2, 2019 to October 15, 2020.

Our results show that the hospital prevalence of major sickle cell syndrome was 12.7% in the study population. Boys accounted for 53% of cases. The most represented age group was 48 to 59 months with 56.1%. On the clinical level, the examination of our respondents objectified a malnutrition in 36.8% of cases, the presence of frontal bumps in 10.5% of cases, lymphadenopathy in 10.5% of cases, hypertrophy of the tonsils. in 8.8% of cases, conjunctival jaundice in 35.1% of cases, hepatomegaly in 7.0% of cases and splenomegaly in 21.1% of cases. There are significant associations between certain epidemiological characteristics studied in homozygous SS subjects, in particular the age of 48 to 59 months with jaundice ($p = 0.012$) and splenomegaly ($p = 0.028$), undernutrition with jaundice ($p = 0.037$) and the presence of lymphadenopathy ($p = 0.013$), presence of frontal lumps with enlarged tonsils ($p = 0.0001$) and hepatomegaly ($p = 0.008$), splenomegaly with jaundice ($p = 0.001$) and presence of lymphadenopathy ($p = 0.004$) and finally hepatomegaly and the presence of lymphadenopathy ($p = 0.008$).

In short, it emerges that many children with major sickle cell syndrome have a less expressive clinical presentation. This is probably linked to the fact that at this age they still have a level of hemoglobin F sufficient to attenuate the impact of hemoglobin S. The associations observed between various clinical parameters show that it is possible to develop a clinic score that can guide the suspicion of the disease and motivate a biological screening.

Keywords: Sickle cell disease; Clinic; Child under five; Kindu; DRC

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1. Introduction

Described as the most widespread genetic disease in the world, sickle cell disease is currently recognized as a public health problem by the WHO [1]. The prevalence of sickle cell disease varies by region and can be up to 45% of individuals carrying the genetic mutation [2,3]. The prevalence of the major form depends on that of the sickle cell trait. For a prevalence of the sickle cell trait greater than 20%, the prevalence of sickle cell disease is estimated to be at least 2% [2]. Almost ¾ of sickle cell sufferers live in sub-Saharan Africa [4].

Two phenotypic forms are to be distinguished in this condition; the homozygous SS form where the child carries the defect from two parents with a strong expression of the disease and the heterozygous form where the child carries the defect from a single parent without symptomatic expression of the disease. The asymptomatic heterozygous form must each time be distinguished from the composite heterozygous form which is an association of the homozygous form with other genetic abnormalities of hemoglobin [5].

The fight against sickle cell disease is based on three strategic axes. This involves the screening of all carriers of the mutation, the proper management of subjects with the major form and genetic counseling in favor of carriers of the S trait (heterozygotes) who are generally asymptomatic but likely to transmit the disease to their descendants following the Mendelian model [2]. The screening program is the basis of any strategy aimed at combating sickle cell disease. It is ideally intended neonatal and is presented as one of the guarantees for improving the life expectancy of patients because it allows an early start of therapeutic programs [2,6].

In sub-Saharan Africa, early detection of the disease is not universally guaranteed. This is linked to the high cost of access to standard diagnostic tools and their unequal distribution because they are often concentrated in large cities [4]. The alternative and palliative solution to this difficulty is to optimize the suspicion of the disease by clinicians, especially in children under 5 years old, and refer suspected cases to targeted screening. For this, knowledge of the clinical elements encountered in subjects with major sickle cell syndrome in each environment is important. However, the typical symptomatology of the disease is not evident during the first years of life because of the attenuating effect of fetal hemoglobin, the rate of which is still high at these times [7]. This situation underestimates the extent of sickle cell disease among young children, mainly those under 5 years of age, and thus delays their referral to biological screening. By the time the symptomatology becomes evident, more than 50% of children born with sickle cell disease major are estimated to have already died without being diagnosed. In addition to fetal hemoglobin concentration, other factors can modulate sickle cell symptomatology. This is in particular the haplotype, the atmosphere, the air quality and the altitude [8]. These factors vary from region to region.

To improve the early clinical suspicion of sickle cell disease, it is useful to identify the clinical characteristics which are significantly associated with it in young children and which can be integrated into a predictive score system for sickle cell status in the infant-juvenile population. The objective of this study is to present the clinical characteristics of major sickle cell syndrome in children under 5 years old admitted to hospitals in Kindu.

2. Methodology

We conducted a cross-sectional, descriptive study in 5 health facilities in the city of Kindu, Maniema province in the Democratic Republic of Congo (DRC).

The survey included children under the age of 5 admitted to the targeted health facilities during the period from December 2, 2019 to October 15, 2020. The criteria for inclusion in the survey were age under 5, major sickle cell status and the informed consent of the guardian.

Major sickle cell syndrome was defined by an electrophoretic profile of hemoglobin SS or SC. Heterozygotes carrying the sickle cell trait were not included.

The electrophoretic profile of hemoglobin was obtained after 3 biological tests in the following order; rapid immunological test HemoType SC, Isoelectrofocusing and Capillary electrophoresis. The first test was carried out as part of hospital screening and the last two were carried out for confirmation at the laboratory level of the Monkole Mother-Child Hospital Center in Kinshasa.

The study variables, contained in a previously tested sheet, have been grouped into 2 categories:

- Demographic variables : age, sex.
- Clinical variables: malnutrition, deformation of the head (frontal bumps), lymphadenopathy, enlarged tonsils, conjunctival jaundice, hepatomegaly and splenomegaly.

The information collected from the respondents was processed and analyzed by Excel 2016, SPSS 23.0 and XLSTAT 2016 software. We performed univariate and bivariate analyses. The univariate analyzes helped to determine the prevalence, the distribution of the respondents according to the modalities of the study variables. They also determined the measures of central tendency and dispersion of the respondents in relation to the quantitative variables. The bivariate analyzes made it possible to search for the association between the various characteristics of homozygous SS subjects. The significance threshold was set at $p<0.05$.

The study was conducted under cover of a favorable opinion from the Medical Ethics Committee of the University of Lubumbashi by its letter N° UNILU/CEM/023/2019.

3. Results

We recorded 448 children under 5 years old who took part in the screening and among them 57 were SS homozygotes, i.e., an infant-juvenile hospital prevalence of 12.7% of major sickle cell syndrome.

Of the 57 homozygous SS children, 53% were boys. The age group from 48 to 59 months was the most represented with 56.1% of cases (Table 1).

Table 1 Age and sex of children with major sickle cell syndrome

Variables	Number (n= 57)	Percentage
Age		
≤ 11 months	6	10.5
12 – 23 months	8	14.0
24 – 35 months	6	10.5
36 – 47 months	5	8.9
48 – 59 months	32	56.1
Sex		
Female	27	47.0
Male	30	53.0

Table 2 Distribution of children with major sickle cell syndrome according to clinical signs

Variables	Number (n= 57)	Percentage
Denutrition	21	36.8
Conjunctival jaundice	20	35.1
Splenomegaly	12	21.1
Frontal bumps	6	10.5
Lymphadenopathy	6	10.5
Enlarged tonsils	5	8.8
Hepatomegaly	4	7.0

Clinically, the examination of our respondents objectified malnutrition (36.8%), conjunctival jaundice (35.1%), splenomegaly (21.1%), the presence of frontal bumps (10.5 %), lymphadenopathy (10.5%), hypertrophy of the tonsils (8.8%) and hepatomegaly (7.0%) (Table 2).

Table 3 Comparison between the presence and absence of a clinical sign according to different age groups

Age	D (n=57)		B (n=57)		A (n=57)		HA (n=57)		I (n=57)		H (n=57)		S (n=57)	
	Oui	Non	Oui	Non	Oui	Non	Oui	Non	Oui	Non	Oui	Non	Oui	Non
≤ 11 months	1	5	0	6	0	6	0	6	0	6	0	6	0	6
12 – 23 months	2	6	0	8	0	8	1	7	1	7	0	8	0	8
24 – 35 months	1	5	0	6	0	6	1	5	0	6	0	6	0	6
36 – 47 months	2	3	0	5	0	5	0	5	2	3	0	5	3	2
48 – 59 months	15	17	6	26	6	26	3	29	17	15	4	28	9	23
Total	21	36	6	51	6	51	5	52	20	37	4	53	12	45
p-value*	0.408		0.264		0.264		0.795		0.012		0.499		0.028	

Legende: A= Lymphadenopathy, B= Frontal bumps, D= denutrition, H= Hepatomegaly, HA= Enlarged tonsils, I= Conjunctival jaundice, S= Splenomegaly.

In bivariate analysis of clinical characteristics in relation to age, Table III shows that there was a statistically significant association between age and the presence of conjunctival jaundice (p=0.012) as well as the presence splenomegaly (p=0.028).

After bivariate correlation analyzes between the clinical characteristics studied with our patients, Table IV shows the following statistically significant associations: malnutrition and jaundice (p= 0.037), malnutrition and presence of adenopathy (p= 0.013), frontal bumps and hypertrophy of the tonsils (p= 0.0001), frontal bumps and hepatomegaly (0.008), presence of lymphadenopathy and hepatomegaly (p= 0.008), splenomegaly and jaundice (p= 0.001) and finally splenomegaly and presence of lymphadenopathy (p= 0.004).

Table 4 Bivariate correlation between the clinical characteristics of the cases

	D	B	I	HA	A	H	S
Denutrition	1	0.109	0.037	0.261	0.013	0.101	0.288
Frontal bumps	0.109	1	0.087	0.0001	0.604	0.008	0.781
Conjunctival jaundice	0.037	0.087	1	0.459	0.0004	0.083	0.001
Hypertrophie des amygdales	0.261	0.0001	0.459	1	0.422	0.234	0.227
Lymphadenopathy	0.013	0.604	0.0004	0.422	1	0.008	0.004
Hepatomegaly	0.101	0.008	0.083	0.234	0.008	1	0.141
Splenomegaly	0.288	0.781	0.001	0.227	0.004	0.141	1

Legende: A= Lymphadenopathy, B= Frontal bumps, D= denutrition, H= Hepatomegaly, HA= Enlarged tonsils, I= Conjunctival jaundice, S= Splenomegaly.

4. Discussion

Infant-juvenile hospital prevalence of major sickle cell syndrome was 12.7% in our series. It corroborates WHO estimates on the hospital prevalence of major sickle cell disease in pediatrics in the DR Congo, which is 12% [2]. Our observation gives a high hospital prevalence of major sickle cell syndrome in pediatric settings compared to many studies that have reported this indicator without a systematic screening program.

In this study, the age group of 48 to 59 months is the most represented with 56.1% of cases. This finding can be explained by the gradual decline in the fetal hemoglobin level; which increases morbidity in patients with major sickle cell syndrome [7]. The observation made in this study is similar to that of Shongo and coll. [9] where the age group 36 to 59 months was the most represented (48.8%).

In our series, an association was observed between age and conjunctival jaundice (p= 0.012) as well as splenomegaly (p= 0.028). Jaundice and splenomegaly in a subject with major sickle cell syndrome are mainly explained by the almost permanent hemolysis of sickled red blood cells [8,10]. The extent of haemolysis increases proportionally with age in an unmonitored sickle cell patient and is multifactorial. The recurrent occurrence of hemolytic crises should lead to a search for the existence of comorbidities in sickle cell patients [10 – 12]. This monitoring is only possible when screening is carried out early and monitoring begins earlier. Apart from other causes of jaundice and splenomegaly, it may be recommended to carry out an exclusion survey for sickle cell disease in children presenting with these manifestations.

It appears from our series that 36.8% of SS homozygous subjects had malnutrition. Malnutrition is statistically correlated with jaundice and lymphadenopathy with a p-value of 0.037 and 0.013 respectively. The prevalence of undernutrition in subjects with major sickle cell syndrome, increasing with age, is explained by the chronic anemia and nutrient deficiency that accompany this condition [8,13 – 15]. The association between malnutrition and jaundice is justified by the fact that jaundice is primarily an indicator of chronic hemolysis in subjects with sickle cell disease, a phenomenon naturally associated with anemia. As for the association between malnutrition and the presence of lymphadenopathy; it is described that adenopathies are linked to the immune hyperstimulation of the lymphoid system by infections occurring on a ground of functional asplenia [16,17]. Recurrent infections, to which sickle cell patients are commonly predisposed, can justify both malnutrition and the presence of lymphadenopathy in major sickle cell syndrome. The antibiotic prophylaxis and vaccinations strongly recommended in children with sickle cell disease under 5 years of age are partly justified by this observation.

Frontal bumps were found in 10.5% of children with major sickle cell syndrome in our series. This proportion is low compared to observations made at advanced ages. This is probably because the organ abnormalities characteristic of sickle cell disease are less common at an early age [18]. Under the effect of chronic anemia, there is an increase in erythropoietic activity in the active marrow. This leads to a modification of the bone walls in their dimension and calcium load. Hence the appearance of bone dysmorphisms [18,19]. Charmot and coll. [18] had noted in his series that 2/3 of sickle cell patients presented with a dysmorphic anomaly of the skull. In bivariate analyses, frontal bumps were significantly associated with hepatomegaly and tonsil hypertrophy. We have not found an explanation for this observation.

The frequency of lymphadenopathy was 10.5% among children with major sickle cell syndrome in the present study. The presence of adenopathies in sickle cell disease is explained by the immune hyperstimulation of the lymphoid system but also by the functional asplenia occurring in sickle cell disease [16,17,20]. Bivariate analyzes showed that the presence of lymphadenopathy was correlated with malnutrition (p= 0.013), splenomegaly (p= 0.004) and hepatomegaly (0.008). Chronic and sometimes exacerbated hemolytic anemia is a common factor that explains the presence of frontal bumps, malnutrition, splenomegaly and hepatomegaly [8,10,14,15,21,22]. The repeated infections encountered in sickle cell patients can secondly justify the correlations between the presence of lymphadenopathy with splenomegaly, malnutrition and hepatomegaly. Measures to prevent hemolytic anemia and recurrent infections in children with major sickle cell syndrome are necessary to observe during their follow-up. Also, the associations between these different signs, having common physiopathological bases, can guide the clinical suspicion of major sickle cell syndrome even in young children for whom the typical symptomatology of the disease is considered poor.

Tonsil hypertrophy was found in 8.8% of cases. This is correlated with the presence of frontal bumps (p= 0.0001). The tonsils are also part of the lymphoid system and thus may be overstimulated in homozygous SS subjects due to splenic dysfunction [20]. Cristina and coll. [20] had found in his study that 55.3% of subjects with major sickle cell syndrome had enlarged tonsils. The statistical association between enlarged tonsils and the presence of frontal bumps in major sickle cell syndrome needs to be determined. However, it can serve as an orientation element for the clinical suspicion of major sickle cell syndrome.

Conjunctival jaundice was encountered in 35.1% of cases in our series. Jaundice in sickle cell disease is mainly due to almost permanent hyperhaemolysis of sickled red blood cells. The importance of this hemolysis varies with several genetic, morbid and environmental factors [8,10]. Our results are similar to those found by Thiam and coll. [23] in Senegal where 36.9% of homozygotes aged 2 to 21 had presented jaundice in the stationary phase. On the other hand, in the series of Shongo and coll. [9] in DRC and Camara [24] in Guinea Conakry, the frequency of jaundice in subjects with major sickle cell syndrome was 63.4% and 64% respectively. Our observations show a statistical association

between jaundice and certain other clinical characteristics such as malnutrition (p= 0.037) and splenomegaly (p= 0.004). There are many causes of jaundice in sickle cell patients apart from hyperhemolysis of sickled red blood cells [25]. The observed associations can be explained by chronic hemolytic anemia in sickle cell disease [10,14,22].

Hepatomegaly was present in 7.0% of SS homozygotes screened during the study. It was correlated with the presence of lymphadenopathy. Hepatomegaly in sickle cell disease can be explained by various etiological factors. It follows the participation of the liver in extramedullary erythropoiesis due to chronic anemia, delayed complications of multiple transfusions (haemosiderosis and hepatitis), repeated plasmodial infestations for subjects living in malarial regions, compensation of certain splenic functions when it establishes functional and/or anatomical asplenia. More often, its frequency increases with age [21,22]. Olaniyi and Abjah [21] in Nigeria found a frequency of hepatomegaly estimated at 59% in a population of children and adults with major sickle cell syndrome in the stationary phase. The association between hepatomegaly and the presence of lymphadenopathy can be explained by the hyperstimulation of other lymphoid organs where functional asplenia is observed in the face of infectious attacks [16,22]. Liver and lymph nodes are part of it.

Among the cases admitted in this study, splenomegaly was encountered in 21.1% of cases. It was statistically associated with jaundice (p= 0.001) and the presence of lymphadenopathy (p= 0.004). The spleen is one of the first organs affected by the pathophysiological consequences of sickle cell disease. Splenic dysfunctions are observed from 6 months in patients with major sickle cell syndrome. Splenomegaly is due to several mechanisms including hyposplenism or hypersplenism [26]. In the series of Olaniyi and Abjah. [21], splenomegaly was present in 21% of his patients. Variabilities in the prevalence of splenomegaly in sickle cell subjects are due to several factors that are not unanimously accepted by experts. These factors include age, sex, haplotype, comorbidities and treatment [9,26,29]. Regarding the statistical association observed between splenomegaly with jaundice and the presence of lymphadenopathy, plausible explanations have already been mentioned above.

5. Conclusion

The clinical features of major sickle cell syndrome were observed among the cases studied in our series. They are in small proportion probably because of the attenuating effect of fetal hemoglobin during the first years of life. Age is statistically associated with the expression of certain clinical signs such as jaundice and splenomegaly in children under 5 with major sickle cell syndrome. Statistically significant associations are also observed between different clinical signs presented by the patients. Chronic hemolytic anemia and recurrent infections partly explain most of these associations. It is possible that the combination of clinical signs described in this study could contribute to the development of a clinical suspicion score for the disease in young children.

Compliance with ethical standards

Acknowledgments

- Team having assisted in the recruitment of respondents.
- Guardians who consented to the children's participation in the survey.
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- The Monkole Mother-Child Hospital Center for the analysis of samples by electrophoresis.

Contribution of the authors

Abdala Kingwengwe Aimé is the principal investigator of this study. He ensured all stages of the work, starting from the design of the study to the writing of the final version of the manuscript. Nyenga Muganza Adonis has read and corrected the final version of the manuscript before submission. Shongo Ya Pongombo Mick has read and corrected the final version of the manuscript before submission. Shindano Mwamba Etienne has supervised the data collection and the drafting of the manuscript until the submitted version. Wembonyama Okitotsho Stanis supervised all stages of the study.

Disclosure of conflict of interest

The authors of this manuscript declare no conflict of interest.

Statement of ethical approval

This work has been approved by the University of Lubumbushi's Ethics Committee by its letter N° UNLU / CEM / 023/2019.

Statement of informed consent

The companions of the children who participated in this study gave their informed consent before the inclusion of their children.

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