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Acute Complications of Major Sickle Cell Syndromes in Libreville, Gabon: Clinical and Paraclinical Aspects

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Abstract

Objective: To establish the epidemiological profile of complications of major sickle cell syndrome in acute situations. **Patients and Methods**: This was a prospective, longitudinal, multicenter, one-year cohort study, including patients over the age of 3 years with major sickle cell syndrome presenting for an acute complication in major university hospitals. Their history, clinical, and paraclinical data were reviewed. **Result**s: 67 patients were included, with a mean age of 19 years. The sex ratio was 1.23, with 36 men and 31 women. There was a clear predominance of the SS phenotype (87% of cases). In history, there was a clear predominance of VOC (77% of cases) and infections (malaria and pneumonia). Baseline hemoglobin was 7 g/dL. Usual analgesia included a combination of paracetamol and NSAIDs. Sixty-six percent of the included patients received no form of antimicrobial prophylaxis, and malaria prophylaxis was absent in 43% of cases. General signs were dominated by fever in 25% of patients. The main contributing factor was exposure to cold. Complications were dominated by VOC, decompensated by infection, in which malaria (53% of cases) and pneumonia (15% of these cases) were predominantly found. **Conclusion**: Acute complications of sickle cell syndromes affect young subjects with a history of SCD and infections. Prevention of these aggravating factors could significantly reduce the occurrence of these complications.

Keywords

Major Sickle Cell Syndrome, Complications, Epidemiology

1. Introduction

Sickle cell disease is a monogenic disease with autosomal recessive inheritance. It results from a point mutation in the sixth codon of the β-globin gene, which leads to the polymerization of the mutated hemoglobin (Hb βS) in a deoxygenated environment. HbS is responsible for hemolysis and vaso-occlusive events [1].

According to the Global Burden of Disease systematic review, 3.2 million people are living with sickle cell disease, 43 million people have the sickle cell trait, and 176,000 people die from complications of this disease each year [2].

Individuals with the sickle cell trait are asymptomatic, unlike homozygous SS, double heterozygous SC, or thalasso-sickle cell individuals, who are likely to present with major signs of sickle cell syndrome.

Major sickle cell syndromes are characterized by three types of clinical manifestations:

- Chronic hemolytic anemia;
- Vaso-occlusive events;
- Susceptibility to bacterial infections [3].

Numerous acute complications can occur during the course of sickle cell disease, including worsening anemia, Vaso-Occlusive Crisis (VOC), Acute Chest Syndrome (ACS), stroke, priapism, acute abdominal syndrome, and infections. Preventing these complications is therefore crucial and involves vaccination, clinical and paraclinical monitoring of patients, and lifestyle management. Despite the progress made in recent years aimed at increasing the life expectancy of people with sickle cell disease, prevention of complications remains inadequate in our country. We conducted a study on the complications of major sickle cell syndromes with the aim of understanding the epidemiological and clinico-biological profiles and evaluating their impact.

2. Patients and Methods

2.1. Study Type and Study Period

This was a prospective, longitudinal, multicenter cohort study. The study was conducted over one year, from April 1, 2019, to March 31, 2020.

This study took place in the emergency departments of the following healthcare facilities.

2.2. Public Facilities

—Omar Bongo Ondimba Military Teaching Hospital (HIAOBO)—Libreville University Hospital Center (CHUL)—Akanda Military Teaching Hospital (HIAA)

- Private Facility:

—Jean François ONDO University Clinic

The three public university hospitals account for four-fifths of the pediatric beds in Libreville. The Jean-François ONDO Clinic is an institution specializing in the care of sickle cell patients in Gabon.

2.3. Study Population

Patients with sickle cell disease were admitted to the emergency departments of the aforementioned facilities during the study period.

2.4. Inclusion Criteria

The inclusion criteria were:

—Patients aged 3 years or older;

—Patients with homozygosity for SS or compound heterozygosity (SC, SB0, or SB+ thalassemia);

—Patients with an acute complication, defined as any unscheduled medical or surgical consultation or hospitalization.

2.5. Exclusion Criteria

Patients who refused to sign the informed consent form were not included in the study.

2.6. Data Sources and Collection Techniques

Data was collected using a data collection form upon admission or during consultations with eligible patients. This form was supplemented during physical examinations and from medical records throughout the study period. Remote follow-up and additional data collection via telephone were possible.

The parameters studied were:

—Patient anthropomorphic characteristics: age, sex, height, weight; Phenotypes: SS, SC, SB thalassemia; General medical history: hand-foot syndrome, Vaso-Occlusive Crises (VOCs), Acute Spondyloarthritis (AS), chronic conjunctival jaundice;

—Number of hospitalizations and VOCs over the past year; History of each organ system; Baseline laboratory results: baseline hemoglobin; Long-term treatments: analgesics, anti-infectives, malaria prophylaxis, hydroxyurea;

—Triggering factors of the acute complication: date and type of care, predisposing factors, prodromal symptoms, and medication use; Clinical examination during the acute complication: general signs, oxygen saturation, respiratory signs, pulmonary auscultation; Laboratory findings during the acute complication: hemoglobin, platelets, white blood cells, etc.; Identification of the complication: infectious, hematological, respiratory, neurological, ophthalmological, urological, gynecological, abdominal.

2.7. Statistical Analysis

The data were analyzed using Microsoft Excel Pro version 2019.

3. Results

During the study period, 67 patients were included. We selected 67 patient records

from the different study facilities, broken down as follows:

—HIAOBO: 30 patients included;

—HIAA: 21 patients included;

—CHUL: 6 patients included;

—Clinique Jean François ONDO: 10 patients included.

3.1. Anthropometric Characteristics

The mean age of the included patients was 19 years; the median age was 20 years, with a range of 3 to 39 years. The most represented age groups were 15 - 20 years and 20 - 25 years. The pediatric population represented one-third of the total population, with a mean age of 8.4 years. Analysis of the male-to-female ratio showed a male predominance. The ratio was 1.23, with 36 men for every 31 women (**Figure 1**).

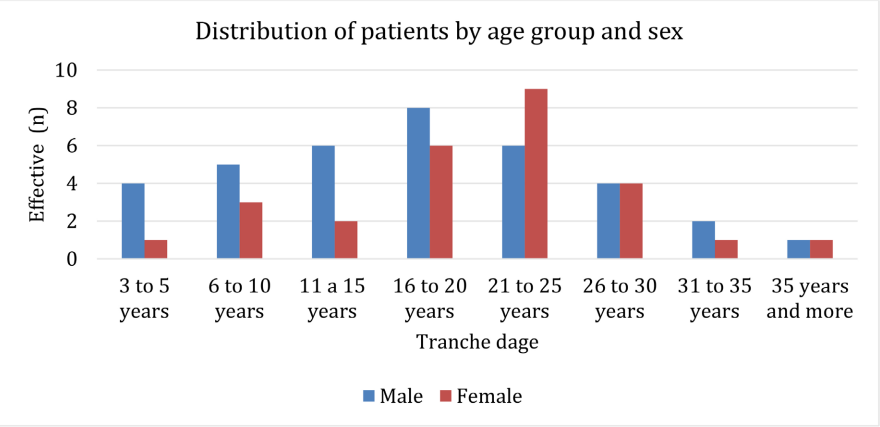

Figure 1. Distribution of patients by age group and sex.

The hemoglobinopathies identified showed a predominance of the SS phenotype, present in 87% of cases in the study. This was followed by the SC (4.47%), SB0 (5.97%), and SB+ (2.56%) phenotypes.

3.2. General Clinical History

The distribution of patients according to their general and sickle cell disease-specific medical history showed a predominance of Vaso-Occlusive Crises (VOCs) in 45% of cases, followed by hand-foot syndrome in 21% of patients in our study.

The number of previous hospitalizations was predominantly between 1 and 5 in the current year, in 88.1% of cases. We noted one case that had been hospitalized nearly 20 times before the complication leading to their inclusion in the study.

The patients predominantly experienced a maximum of 3 Vaso-Occlusive Crises (VOCs) in the current year, representing 77% of cases.

In their medical history, 80.6% of the included patients had previously experienced an infection. These infections were dominated by malaria (40% of cases)

and pneumonia (25% of cases). In terms of cerebrovascular history, only one case of ischemic stroke was described. Chronic headaches were the most frequent neurological history (26.8% of cases), followed by epilepsy (5.97% of cases). Only one history of psychiatric disorders was found. Regarding chronic respiratory history, 4 patients with asthma were included in the study. Asthma was the only significant respiratory history. Regarding splenic history, chronic splenomegaly represented 37.31% of the cases, with only one case of splenectomy already performed.

3.3. Baseline Hemoglobin

Regarding basic blood tests, in the medical histories of the study patients, 32% reported a lack of knowledge regarding their baseline hemoglobin level. When it was known, the most common baseline hemoglobin level was 7 g/dL in 26% of our patients. Only about 6% reported having a baseline hemoglobin level above 9 g/dL.

Basic biochemistry tests were not available. Renal and liver function tests, as well as previous LDH levels, could not be obtained through patient interview or review of medical records. Results from none of the routine imaging examinations were available.

3.4. Long-Term Treatment

In the context of standard management of painful manifestations of sickle cell disease, the combination of paracetamol and a Non-Steroidal Anti-Inflammatory Drug (NSAID) and paracetamol alone were used in 45% and 42% of cases, respectively.

Sixty-six percent (66%) of the patients included in the study were not receiving any form of antimicrobial prophylaxis. In the remaining cases, vaccinations against meningococcus and pneumococcus were administered in 17% and 28% of cases, respectively. Oral antibiotic prophylaxis was used in only 11 patients. Malaria prophylaxis was absent in 43% of cases. When it was used, mosquito nets alone were the most common method in 38.8% of cases, followed by combination with chemoprophylaxis in 14.9% of cases.

In the transfusion history of patients in our cohort, 60 patients (88.05% of cases) had already received at least one transfusion. Only one patient was enrolled in a chronic transfusion program, and 7 patients (10.4% of cases) had never received a transfusion. No history of transfusion problems was reported.

Fourteen (14) patients (20.8% of cases) were receiving hydroxyurea treatment. No patient had access to home oxygen therapy.

3.5. Major Syndromes

3.5.1. Predisposing Factors

Exposure to cold and heat are the triggering factors for the acute complication, found in 35% and 25% of cases, respectively. No predisposing factors were found in 45% of cases.

3.5.2. General Signs

At the initial clinical examination, during the acute complication, the general signs present were primarily jaundice, with or without fever. In our study, the general signs were dominated by fever in 25% of our patients, followed by the combination of jaundice and fever (20%) (Table 1).

Table 1. Distribution of patients according to general signs during the acute complication.

General signs	Incidence (n)	Percentage (%)
Hyperthermia	17	25.4
Conjunctival jaundice	12	17.9
Hyperthermia + Jaundice	13	19.4
None of these signs	25	37.3
Total	**67**	**100**

3.5.3. Respiratory Syndrome

Clinical signs affecting the respiratory system were dominated by tachypnea. Thirty-seven (37) patients presented with a respiratory rate between 16 and 20 breaths per minute. Lung auscultation was clear in 68.67% of patients, and the most frequent symptoms were cough and chest pain.

3.5.4. Hemodynamic Syndrome

Hemodynamically, the heart rate was normal in 70% of cases, with rare clinical signs, including prolonged capillary refill time and jugular venous distension in 5% of cases. Shock was observed in only one patient.

3.5.5. Neurological Syndrome

Neurologically, no complications were detected. No coma, focal neurological signs, or other specific neurological signs were found.

3.5.6. Paraclinical Data

Laboratory tests were performed in 68% of cases. A Complete Blood Count (CBC) was obtained in 67% of cases. Lactate Dehydrogenase (LDH) levels were never measured. Bilirubin and creatinine levels were measured in 1.4% and 17.9% of cases, respectively.

1) Hematological Profile

The mean hemoglobin level was 6.5 g/dL. The mean white blood cell count was 21,500/mm^3, with a range of 9500 to 50,000/mm^3. The mean platelet count was 308,200/mm^3, with a range of 74,000/mm^3 to 656,000/mm^3

2) Radiological Aspects

Primarily as part of the workup for a probable Thoracic Outlet Syndrome (TOS), fifteen (15) chest X-rays and five (5) CT scans were performed. None of the CT scans showed any signs of thrombosis.

3.7. Specific Complications

3.7.1. Vaso-Occlusive Crisis

In the study, among ischemic complications, Vaso-Occlusive Crisis (VOC) was

the predominant complication, occurring in 88% of the study population. In affected subjects, painful lesions were located in the limbs and back, in 37% and 23% of cases, respectively, as shown in Figure 2.

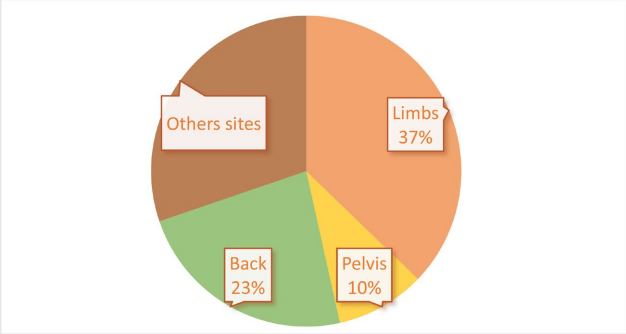

Figure 2. Preferential pain locations in CVO.

3.7.2. Anemia

Anemia was the main hematological complication. No other common hematological complications were observed, such as alloimmunization, bleeding, or delayed post-transfusion hemolysis.

3.7.3. Acute Chest Syndrome

AS was diagnosed in 10 cases, based on a combination of clinical and radiological findings. To support this diagnosis, 15 chest X-rays and 4 chest CT scans were performed during the study.

3.7.4. Abdominal Complications

Abdominal complications were observed in 9 cases. These complications were dominated by splenic sequestration, which accounted for 66% of abdominal complications. One case of acute cholecystitis warranted the only surgical intervention in the study.

3.7.5. Infectious Complications

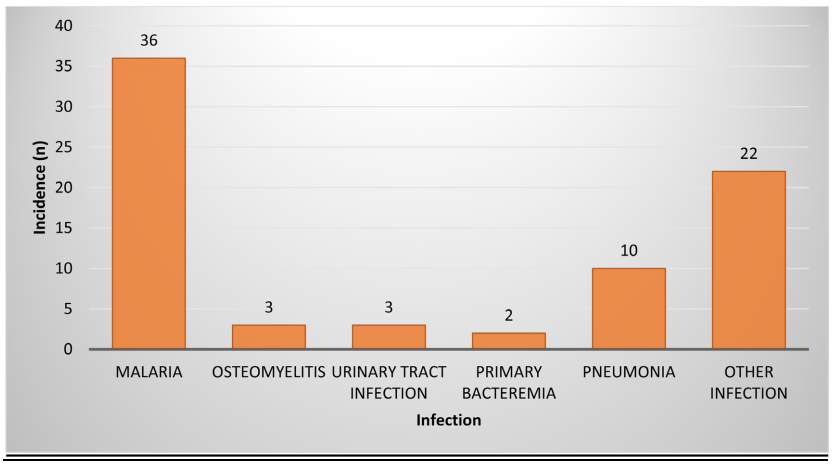

Figure 3. Distribution of acute infectious complications.

These complications were largely dominated by malaria (53% of cases) and pneumonia (15% of cases) when the source of infection could be documented, as shown in **Figure 3**. Several of our patients presented with septic episodes with SIRS without a clear focal cause, which improved with empirical antibiotic therapy. This scenario was observed in 32% of cases.

4. Discussion

4.1. Methodological Limitations

Our study was limited by its small sample size, given its cohort (67 patients). Furthermore, there is lack of technical support for certain paraclinical examinations (transcranial Doppler, pulmonary catheterization, etc.) and the unavailability of basic biochemical analyses, renal and hepatic function tests, and LDH measurement. could explain the underestimation of the majority of acute complications related to sickle cell disease.

However, this was a multicenter study conducted in the main hospitals of the capital, serving nearly half of the Gabonese population. Therefore, its analysis allows us to draw certain conclusions and compare them with data from the literature.

4.2. Anthropometric Data

In the study, the average age was 19 years. The most affected age group was 20 - 25 years, followed by 15 - 20 years. The pediatric population represented one-third of the total population, with a mean age of 8.4 years.

In Mali, Kpakoutou *et al.* in 2020, found a predominance in the 6 - 10 year age group [4]. This disparity could be explained by recruitment in a pediatric department with a maximum age of 15 years, unlike our study where there was no age limit. In Burkina Faso, Douamba *et al.* found a mean age of 6 years [5].

However, their study focused only on infectious complications, whereas the literature clearly describes the highest risk of infection in the first years of life.

A similar mean age to our cohort (15 - 24 years) was found in Cameroon in the study by Chemegni *et al.* in 2017 [6]. In Benin, Dodo *et al.* found a mean age of 24.2 years [7]. Perignon *et al.* in France, reported similar results with a mean age of 25 years [8].

These data, from studies including all patients, appear consistent with our study and suggest that acute complications increase with age. This could be explained by the natural history of sickle cell disease, a condition that mimics degenerative diseases par excellence.

Until the 1990s, sickle cell disease was considered a fatal illness, with studies reporting a life expectancy not exceeding 48 years, even in developed countries [9]. In 2005, Ondo *et al.* In Gabon, it was reported that at the time, "sickle cell patients did not reach adulthood" [10]. In our study, the maximum age was 39 years, demonstrating an overall improvement in the quality of care for sickle cell patients.

The male-to-female ratio in our study was 1.23. Chemegni *et al.* reported a male predominance with a male-to-female ratio of 1.5 [6].

This aligns with the findings of Lamine *et al.* in Senegal, Dodo *et al.* in Cotonou, and Mbika *et al.* in Brazzaville [7] [11] [12], who also observed a male predominance. In contrast, Nacoulma and Samira *et al.* reported a slight female predominance [13] [14].

Finally, in some cases, no predominance between the two sexes is observed, as reported by Dreux *et al.* in Grenoble (France) and Thuillez *et al.* in Gabon in 1997 [15] [16].

These differences are thought to be related to the demographic data of each country, since the transmission of sickle cell disease is not sex-linked.

4.3. Phenotypes

In the series, the SS phenotype was predominant, with an incidence of 87%. Studies reported by Kpatoutou *et al.* in Mali found the same results as in our series, namely a predominance of the SS phenotype at 91.1%, followed by the SC and Sβ° forms [4]. Dodo *et al.* in Benin found results close to those in the literature: homozygous SS (72.1%) and compound heterozygous SC (27.9%) [7].

In the study, only 4% of cases presented with the SC compound sickle cell syndrome. However, the literature considers that the SC type represents 20% to 30% of major sickle cell syndromes [17]. This could be explained by its predominance in West Africa in certain countries such as Ghana, Burkina Faso, and Nigeria [18].

It constitutes a distinct entity, very different from homozygous SS sickle cell disease, with attenuated clinical signs and subtle hematological abnormalities. This results in delayed diagnosis in adulthood, at the stage of irreversible sequelae [19] [20]. The SC phenotype appears to cause less severe complications but seems to be more specific for ocular complications such as proliferative retinopathy [18].

4.4. General History

The study is consistent with the literature, which recognizes painful manifestations as the cause of nearly 60% of patient consultations and 80% of hospitalizations [21]. In Cameroon, Chemegni *et al.* found 81% of consultations to be due to Vaso-Occlusive Disease (VOC), compared to 88% in our cohort [6]. This confirms VOC as the primary reason for emergency consultations, a finding that echocardiogram (Dodo *et al.*) made [7]. Seventy-seven percent (77%) of patients developed up to three Vaso-Occlusive Crises (VOCs) within one year of the acute complication. Darbari considers an increased frequency of VOCs to be a definite predictor of death [22].

In this series, only 15% of the included patients had a history of Acute Chest Syndrome (ACS). This differs from the literature, which considers ACS to be the second most common reason for consultation and the leading cause of death [23]. Furthermore, in the natural history of the disease, ACS is the first severe manifestation of sickle cell disease [5].

However, in Cameroon, Chemegni found 11% of patients with Sickle Cell Anemia (SCA) in his cohort, as in study [6]. SCA is a condition with a particularly high incidence in children [24] [25]. Since our study population is primarily young adults, this could explain the difference. Furthermore, in adults, bone vasculitis usually precedes ACS and can therefore be overlooked by healthcare professionals.

This two-stage progression of symptoms, often observed in adults, necessitates regular clinical monitoring of patients hospitalized for bone vasculitis without initial signs of pulmonary involvement [25].

4.4.1. History of Infections

Malaria is a common condition in sickle cell patients, primarily due to the strong geographical correlation between malaria-endemic areas and sickle cell disease foci [8]. The interactions between sickle cell disease and malaria are becoming increasingly well understood, but the belief that individuals with sickle cell disease are protected against malaria remains widespread [26].

Indeed, the sickle cell trait has been recognized as a protective factor against Plasmodium falciparum for nearly 70 years [27]. This is supported by more recent studies, with new discoveries regarding the cytoadherence of infected red blood cells [28].

In a study conducted in Gabon, Lell *et al.* demonstrated that, in conjunction with natural immunity, the sickle cell trait prolonged the inoculation-parasitemia interval and, more importantly, reduced the clinical manifestations of malaria [29]. However, malaria remains an infection that, like others, can trigger attacks, particularly vaso-occlusive crises.

4.4.2. History of Hospitalization

In Mali, the number of prior hospitalizations was 53%, unlike in our series, which was 100%. Our results are also higher than those of Bertholdt *et al.* [23] and Douamba S. *et al.* [5], who found 8% and 21.8% of prior hospitalizations, respectively.

This could be explained by a recruitment bias. Indeed, the aforementioned studies only concerned pulmonary complications for the Malian and Belgian studies, and infectious complications for the Burkinabe study.

Finally, given that the average age is significantly higher in our study (19 years versus 10 and 6 years), it seems logical that there are more prior hospital stays.

4.5. Baseline Laboratory Results

In our study, the baseline hemoglobin level was approximately 7 g/dL. In 1999, Ondo and Ngou Milama found a similar hemoglobin level of 7.4 ± 1.4 g/dL [26].

In Mali, Kpatoutou *et al.* found a hemoglobin level below 10 g/dL in 93.33% of patients, with a mean of 6.53 g/dL. Our results are comparable to those of Douamba *et al.* [5], who found a mean hemoglobin level of 6.7 g/dL in their study in Burkina Faso, and similar to those of Bertholdt *et al.* [23], who found a mean hemoglobin level of 8.3 g/dL. Hemoglobin levels are therefore uniformly low in the

literature and fluctuate around 8 g/dL.

The literature recognizes baseline hemoglobin levels below 7 g/dL at age 2 as a predictive factor for severe sickle cell disease [5]. Indeed, anemia is a constant feature in sickle cell patients due to chronic hemolysis and can worsen in acute situations.

Lack of knowledge of baseline hemoglobin was prevalent in this series. In Cameroon, Chemegni *et al.* considered this to be a consequence of inadequate patient follow-up, and in their study, they demonstrated a direct correlation between sickle cell disease monitoring and the educational level of patients' parents [6].

In this series, the mean white blood cell count was 21,500/mm^3, with a range from 9500 to 50,000/mm^3.

In 1999, Ondo *et al.* reported a mean white blood cell count of 13,500/mm^3 [26]. In Mali, leukocytosis was noted in 97.77% of patients, with a mean white blood cell count of 31,856/mm^3 and a range from 11,500 to 78,300/mm^3 [6]. Douamba *et al.* found that 84.9% of patients had leukocytosis, with a mean white blood cell count close to that of our study, of 22,945/mm^3 with a range from 6400 to 78,600/mm^3 [5].

Leukocytosis is commonly observed in homozygous sickle cell patients in the absence of bacterial infection. The mechanism underlying this increase in the number of white blood cells is still poorly understood. This appears to be linked to the chronic inflammation that characterizes sickle cell disease, inflammation promoted by adhesive interactions between various cells and the production of pro-inflammatory cytokines.

4.6. Other Basic Paraclinical Examinations

According to the recommendations for good management, sickle cell patients should undergo certain examinations as part of their regular follow-up, to be performed once or several times a year [3] [30].

From a biological standpoint, there was insufficient exploration of the minimal biological parameters required to assess the condition of a sickle cell patient. Hemoglobin S levels were not known. This baseline level is important to know, as its correction is the reason for the improvement of many acute complications, particularly in the context of Vaso-Occlusive Crisis (VOC), Acute Chest Syndrome (ACS), and even stroke [2] [5] [30].

Furthermore, its reduction is the objective of transfusion exchange programs. Therefore, it is important to have the baseline value to assess the program's effectiveness [31] [32].

Only one patient in our cohort benefited from one of these exchange programs but was unable to provide us with their baseline HbS level.

Similarly, we were unable to obtain baseline hemoglobin F levels. Its protective effect on the incidence of clinical manifestations and complications should make this level known to all sickle cell patients [33]. Hydroxyurea, an essential drug in the management of sickle cell disease, acts primarily by increasing the synthesis

of this fetal hemoglobin.

The indication for this therapy should, according to recommendations, be based on basic knowledge of Hb F [30], which was unknown to all patients in our cohort despite the 14 patients included who were receiving hydroxyurea.

In the series, none of the patients underwent systematic echocardiography or transcranial Doppler. These examinations should be performed annually according to best practice guidelines [34]. This demonstrates a lack of follow-up in our patients.

As early as 1985, Ondo *et al.* emphasized the importance of performing certain complementary examinations in the follow-up of sickle cell patients, particularly radiology and ultrasound [31].

4.7. Long-Term Treatment

The maintenance treatment, according to recommendations, involves analgesics to antimicrobials [34].

4.7.1. Analgesia

Ondo had already developed, in 1999, an acronym combining the key principles of managing a sickle cell patient: H. A. A. T. O. P.: Hydration, Analgesia, Antibiotic Therapy, Transfusion, Oxygen Therapy, Psychotherapy [31]. These recommendations, 20 years later, are still broadly relevant in the management and follow-up of our patients.

Painful manifestations recommend the use of paracetamol and NSAIDs [34]. Chemegni *et al.* in Cameroon mainly used ketoprofen alone or in combination with paracetamol if fever was present [6].

The use of step 2 pain relief was rare in our series, unlike theirs, where 58% of patients were prescribed tramadol. The absence of opioids in outpatient home care seems to be the norm in the various sub-Saharan studies reviewed. [6] [7]

4.7.2. Antimicrobial Prophylaxis

Severe septic states can be largely prevented by pneumococcal prophylaxis (vaccine and penicillin). This oral penicillin prophylaxis should begin at 2 months of age [34].

Combined with vaccination, this prophylaxis leads to a significant reduction in invasive pneumococcal disease.

In the study, this prophylaxis was administered in only 28% of cases, despite being an emergency. Indeed, the peak mortality period occurs between 6 and 12 months, during the paucisymptomatic phase of the disease. At this time, there is an increased risk of death from septic shock.

4.7.3. Hydroxycarbamide (Hydroxyurea)

In April 2013, the WHO included hydroxyurea in its lists of essential medicines for children and adults for the treatment of sickle cell disease [1], which spurred its widespread use worldwide.

However, in the series, only 14 patients, or 20.8% of cases, were not receiving hydroxyurea treatment. By increasing the synthesis of fetal hemoglobin, this molecule helps to reduce the severity and recurrence of crises.

The 1995 Multicenter Hydroxyurea (MSH) trial was the main randomized controlled trial on hydroxyurea that demonstrated a reduction in vaso-occlusive events of nearly 50% [33]. However, its use was long left to the discretion of clinicians. Indeed, cytotoxic effects were suspected, and its indications were therefore initially restricted.

Subsequently, several studies examined its medium- and long-term tolerability. After following 299 patients for almost 18 years, Steinberg *et al.* not only found very few adverse effects, but also demonstrated a significantly reduced mortality rate compared to patients not receiving hydroxyurea. After a 9-year follow-up, a mortality reduction of almost 40% was already observed [35].

The MSH study had already demonstrated an increase in total hemoglobin and Hb F with a reduction in the incidence of acute chest syndrome, transfusion requirements, and mortality compared to those receiving placebo [33].

In this series, of the 14 patients receiving hydroxyurea treatment, 10 came from the Clinique Jean François Ondo, a clinic specializing in the management of sickle cell disease. This reflects the importance of increasing the number of referral centers for the monitoring and management of sickle cell disease patients, as recommended by the National Sickle Cell Disease Control Program in 2007.

4.7.4. Blood Transfusion

The mainstay of sickle cell disease treatment is red blood cell transfusion, with more than 90% of adults receiving at least one transfusion during their lifetime [34].

Chronic transfusions help prevent long-term complications by replacing rigid, sickle-shaped red blood cells with malleable cells and suppressing sickle cell formation.

Kpe Faget *et al.*, in Côte d'Ivoire, found a history of prior transfusion in 32% of patients in their series of 91 [34]. In our study, more than 80% of patients had already received transfusions. This difference is primarily explained by the difference in mean age (6 years vs. 19 years in the series) but mainly by the easier access to blood products to date, due to their reduced price and improved availability. Ondo *et al.* found that 64% of patients in Gabon had a history of transfusions in 1999 in their series [36]. Exchange transfusions are rarely found in sub-Saharan studies.

In Europe, they are extremely common in the management of acute complications, particularly Acute Chest Syndrome (ACS), but also in the prevention of these acute complications, such as stroke [25].

4.8. Major Syndromes

Predisposing Factors

In Cameroon and Mali, various authors identified cold as the main predisposing

factor [4] [6].

Old age has long been recognized as a predisposing factor in Gabon: Ondo *et al.* in 1999, observed a resurgence of sickle cell crises and hospitalizations during the very cool month of June, at the transition between the short rainy season and the long dry season [37]. This observation was also made by Mekontso in France, where multivariate analysis of data from his study identified a daily drop in temperature and an increase in average wind speed as independent factors associated with a higher risk of crises and hospital admission of sickle cell patients [39].

Sickle cell disease is exacerbated by lower temperatures. Physiological studies have demonstrated a link between skin cooling and vaso-occlusion [39] [40].

In this study, cold was also identified as a predominant contributing factor. However, other recognized factors such as stress were more frequent in this series, as the patients included were significantly older than in most sub-Saharan series.

4.9. Specific Complications

The acute complications admitted in our study were vaso-occlusive and then infectious. In Gabon, after anemia, infection is the second leading cause of death (30.4%) [41].

4.9.1. Vaso-Occlusive Crisis (VOC)

In this series, nearly 88% of VOCs accompanied various complications.

VOC is not the earliest pathology in the natural history of sickle cell disease, but it is responsible for nearly 95% of hospitalizations [5]. Therefore, the identification, treatment, and prevention of Vaso-Occlusive Crisis (VOC) must maintain a significant impact on the natural history of the complication, as VOC usually precedes other, more serious complications, notably Sickle Cell Angioedema (SCAE) [22].

Topographically, sickle cell pain syndrome is ubiquitous, with a clear osteoarticular predominance, making bone pain the primary reason for hospital admission. The lower limbs and spine appear to be affected in more than half of cases, and the upper limbs in approximately 40% of cases, with preferential metaphyseal involvement.

This description is consistent with the study that identified the limbs (37%) and the back (23%) as the preferred sites of pain.

4.9.2. Acute Chest Syndrome

In this series, the diagnosis of ACS was made 10 times. The diagnosis, primarily radiological, is suggested by chest X-rays and CT scans showing infiltrates (no thrombosis was found in the 10 CT scans performed).

The incidence in this study is lower because chest syndrome is more common in early childhood [21], which contrasts with the average age of the series.

Our incidence is significantly lower than that reported by Bartolucci *et al.* (17.8%) [42].

In Mali, Kpakoutou *et al.* found 86.7% of cases of Acute Chest Syndrome (ACS)

in their study, but their work focused only on respiratory complications of sickle cell disease, hence the disparity in results due to a clear recruitment bias [4]. However, our incidence remains low, especially considering the high number of Vaso-Occlusive Crises (VOCs) in our series, which precede ACS in almost 50% of cases [21] [24]. This suggests an underestimation of cases due to numerous differential diagnoses (dyspnea of ACS mistaken for the respiratory manifestation of severe anemia, etc.).

This error is facilitated by the very different clinical presentations of ACS between adults and children, suggesting the existence of pathophysiological differences between these two patient groups.

In fact, an initial chest X-ray should be performed routinely in all patients with sickle cell disease, regardless of the reason for hospitalization, which occurred in only 15 patients in our series [34].

4.9.3. Strokes

We did not record any cases of stroke during the study period. This can be explained by the fact that they occur early in the natural history of the disease [5].

Strokes affect children much more than adults, with a predilection age between 2 and 10 years. Across all ages, the incidence is estimated to be around 7 to 10% in homozygous sickle cell disease and 11% in sickle-thalassemia syndromes [43]. Today, the term "silent stroke" is used and is a recognized complication. According to some studies, its incidence can reach 35% - 40% of cases.

In Senegal, Ndiaye *et al.* found that 45% of patients in their cohort had experienced stroke and 28.2% had epilepsy, but this was a retrospective study focusing only on the neurological complications of sickle cell disease [44]. To screen for these complications, the literature has demonstrated the value of transcranial Doppler ultrasound [3]. A velocity greater than 200 cm/s defines a likely pathological vascular axis with a stroke risk of approximately 40% within the following 3 years [45]. However, no transcranial Doppler ultrasounds were performed in the study facilities, despite it being an accessible examination. This reflects a continued lack of awareness of best practices for monitoring sickle cell patients.

As part of its prevention, the most effective alternative remains the implementation of a transfusion exchange program. This program is available in Gabon (one patient in our cohort benefited from it), but it also does not yet appear to be part of our practices.

The relative risk of developing a stroke in sickle cell disease is approximately 1 in 300. Early and regular pediatric screening for vasculopathy using transcranial Doppler and a transfusion strategy targeting an HbS level below 30%, on the other hand, considerably reduces this risk, which would then decrease from 40% to 2% [46].

4.9.4. Infectious Complications

In the study, 56% of patients experienced infectious complications.

Douamba in Ouagadougou found 21.8% and 35% of infectious complications,

respectively, in their series [5]. The hospital frequency of infections found in the study (56.3%) differed from those of Koreissi *et al.* in Bamako and Mabiala *et al.* in Brazzaville, which were 26% and 36.6%, respectively [47] [48].

Difficulties in bacteriological analysis complicate the optimal management of infectious complications, which are nevertheless numerous in sub-Saharan Africa. This observation is confirmed by the study, and by that of Dembele and Latoudji *et al.* [49] [50].

Functional asplenia exposes children to an increased risk of potentially fatal pneumonia, septicemia, and meningitis. The absence of chemoprophylaxis found in our study could explain the predominance of infectious complications. The expanded immunization program, which is free in Gabon, does not cover pneumococcal vaccines, which are relatively expensive in Gabon. Furthermore, even after a possible splenectomy, antibiotic chemoprophylaxis is rarely administered due to the difficulty of obtaining and adhering to long-term antibiotic therapy.

In the series, these complications were largely dominated by malaria and pneumonia. Malaria is frequently found as a factor in decompensation in our cohort, as well as in that of Dodo *et al.* (27.6%) [7]. Mbika *et al.* reported a frequency of 18% [12]. This discrepancy could be related to the methodology: a positive thick blood smear was required to confirm the diagnosis in the Congolese study. In our cohort, this was not the case; the combination of clinical and biological findings was sufficient, and a negative thick blood smear did not rule out the diagnosis.

Perignon demonstrated, despite a small cohort study, that carriers of hemoglobin SS experience malaria attacks, frequently complicated, regardless of the parasite species involved [8].

Furthermore, in his study concerning imported malaria in sickle cell patients in France, he showed that all types of Plasmodium are potentially responsible for severe malaria attacks in sickle cell patients. However, the prognosis remains unchanged when the infection progresses to a severe form.

In fact, mortality is high in sickle cell SS, hence the absolute necessity of prevention. Numerous experimental studies have described a greater protective effect of Hb SS, but also acknowledge higher mortality and morbidity once the infection has developed [51].

5. Conclusions

Despite the progress made in the management of sickle cell disease, acute complications remain frequent. This study has allowed us to outline a clinical profile of the sickle cell patient in an acute situation.

These are young patients with a history of Vaso-Occlusive Crises and multiple hospitalizations, with primarily vaso-occlusive complications; decompensated by numerous episodes of infections of various origins, predominantly malaria and pneumonia.

However, many potentially serious complications may have gone undetected due to the infrequent use of certain paraclinical examinations, which are never-

theless essential for the management of sickle cell disease and strongly recommended (imaging). Regular consultation of best practice guidelines by those involved in sickle cell disease care could improve these oversights.

But for now, the most frequent complications identified in our study are largely preventable through measures such as vaccination, antibiotic prophylaxis, and the use of insecticide-treated bed nets. Greater rigor in the application of these measures could therefore significantly reduce the incidence of acute complications in sickle cell patients. Along the same lines, given its recognized effectiveness on the incidence of vaso-occlusive manifestations, a wider use of hydroxyurea prescription could be an attractive alternative to reduce the resurgence of these complications.

Ethical and Legal Considerations

We obtained the approval of the management of the facilities selected for the study. As this was an observational study, without an intention to treat, its implementation did not interfere in any way with the therapies being administered.

The signing of an informed consent form by the study patients or their parent (s) was required and obtained from all included patients. Confidentiality and anonymity were maintained.

Conflicts of Interest

The corresponding author and the other contributors declare no conflict of interest.

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