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Infections and Major Sickle Cell Syndromes at the Ziguinchor Peace Hospital / Senegal

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Sickle cell disease is an inherited disorder of hemoglobin. It poses a public health problem in Senegal and mainly affects children and adolescents. Infections are the main cause of morbidity and mortality in children with sickle cell disease. The objective of our work was to assess infections associated with major sickle cell syndromes at the Ziguinchor Peace Hospital (ZPH).
Methods: This was a retrospective study, from October 1, 2015 to October 31, 2020. Included were sickle cell patients homozygous SS and heterozygous SC, hospitalized with fever ≥ 39°C, in whom an infectious assessment was performed. Excluded from the study were patients whose complete blood count, C-Reactive Protein, and rapid diagnostic test for malaria were not performed.
Results: During the study period, we collected 66 patient files (43 boys and 23 girls). The mean age was 7.6 years [8 months – 21 years]. The population consisted of SS sickle cell disease patients in 98.5% of cases. The average body temperature was 39.6°C [39 – 40.5°C]. The clinical

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picture on admission was predominantly vaso-occlusive crisis and anemia. The positivity of the bacteriological examinations was 2 cases for the blood culture, 3 cases for the urine culture. The infections were dominated by bronchopneumonia (31.8%); ear, nose and throat infections (31.8%) and osteoarthritis (15.2%). Four children presented with severe malaria and the immediate course was favorable for all patients.

Conclusion: otorhinolaryngological infections; Bronchopulmonary and osteoarticular diseases are frequent in children with sickle cell disease at the Ziguinchor peace hospital. we recommend support for the microbiology unit and systematic sampling in febrile sickle cell patients.

Keywords: Hospitalization; infection; major sickle cell syndrome.

1. INTRODUCTION

Sickle cell disease is an inherited disorder of hemoglobin. According to the world health organization (WHO), nearly 5% of the world's population carry a gene responsible for a hemoglobin abnormality [1]. The majority of people with this disease live in black Africa with prevalence varying between 10 and 40% [2]. It poses a major public health problem in these developing countries. In Senegal, 1 in 10 people, regardless of ethnicity, geographic origin or social class, carry the sickle cell gene [3]. The majority only inherited it from one of the parents and show no signs. These are the carriers of the sickle cell trait (AS). However, from their union are born children with homozygous sickle cell disease (SS) with 25% of the risks in each pregnancy. Thus, approximately 1700 children are born each year with sickle cell disease in Senegal [4]. The homozygous form SS is manifested by anemia, susceptibility to infection, and painful attacks of the bones and / or abdominal pain [5]. Infections are the main cause of morbidity and mortality in children with sickle cell disease, especially before the age of 5 [6]. Otorhinolaryngological and respiratory infections are the most frequent, but the most severe attacks are meningitis, septicemia and osteoarticular infections [7]. The objective of our work was to determine infections associated with major sickle cell syndromes in children at the Ziguinchor Peace Hospital (ZPH).

2. MATERIALS AND METHODS

2.1 Period, Type and Setting of the Study

This was a retrospective descriptive study of children with sickle cell disease hospitalized in the pediatrics ward of the Ziguinchor Peace Hospital, during the period from October 1, 2015 to October 31, 2020. sickle cell children at the Ziguinchor Peace Hospital are attended to by medical staff made up of a university assistant pediatrician and two other hospital pediatricians. The hospital has a microbiology laboratory with medical staff consisting of a full professor, biochemist, two academic assistants, hematologist and microbiologist / virologist.

2.2 Study Population

The study involved all patients with major sickle cell syndromes (homozygous SS or heterozygous SC).

Inclusion criteria: Were included in the study patients with major sickle cell syndromes, hospitalized in the pediatric department of the Ziguinchor Peace Hospital during the study period for a fever greater than or equal to 39°C. , clinical signs (cough, dyspnea, headache, bone or abdominal pain, etc.), in which an infectious assessment was carried out: blood count, rapid diagnostic test (RDT) for malaria, blood culture, stool culture, bacteriological examination of the cerebrospinal fluid, urine, pathological fluid, C-Reactive Protein (CRP), chest x-ray. The diagnosis of the infection was made on the basis of clinical arguments and / or paraclinical arguments (imaging, biology). the diagnosis of sickle cell anemia was made by electrophoresis of hemoglobin by conventional method.

Exclusion criteria: Patients with complete blood count, CRP and RDT for malaria were not included in the study. The rest of the infectious assessment was carried out according to the clinical picture.

2.3 Data Collection

The data were collected from hospitalization records and using a collection sheet established for this purpose. We studied :

- Epidemiological and socio-demographic data: age, sex, geographical origin,

socioeconomic level, type of major sickle cell syndrome, circumstances of the diagnosis of sickle cell disease.

- Clinical data: reasons for consultation, temperature, clinical picture, radiography, ultrasound, blood count, CRP, RDT for malaria, blood culture, cytobacteriological examination of urine, cerebrospinal fluid, detection of *Mycobacterium tuberculosis (M. tuberculosis)* by PCR Xpert MTB/RIF, isolated germ.
- Location of the infection: digestive, respiratory, neuro-meningeal, osteo-articular,…
- Therapeutic and evolutionary data: anti-infectious treatment, length of hospitalization, immediate outcome of the child.

2.4 Operational Definitions

Originally, the urban environment was represented by the municipality of Ziguinchor, the suburban environment by the other departmental municipalities and the rural environment by the villages. The socioeconomic level was assessed on the basis of the family's assets (television, fridge, car, telephone, personal house, access to water and electricity, parents' profession). It can be low, medium, good [8].

Positive bacteriological test results were obtained within 48 hours of collection with identification of the germ in the culture and an antibiogram. In case of negativity, the final results of the bacteriological tests were obtained after 5 days.

2.5 Statistical Analysis

Data was entered using Microsoft Access software. Data processing was performed using Epi Info version 6 software from the CDC.
The variables were analyzed by determining the following characteristics: frequency, mean, minimum, maximum and percentage.

3. RESULTS

During the study period, we reviewed the records from 66 files of children with infection from 148 children with major sickle cell syndromes, ie a hospital frequency of 44.6%.

3.1 Epidemiological and socio-demographic Data

The mean age of the children was 7.6 years [8 months - 21 years] and 45.4% of the children were under 5 years old. In 42.4% of cases, the infectious episode was the circumstance of discovery of sickle cell disease. According to the schedule of the Expanded Vaccination Program in Senegal, 81.2% of the patients were up to date with their vaccines. The vaccines against the encapsulated germs, recommended by WHO in sickle cell patients, were given at 54.5% for pneumococcus, 33% for meningococcus and 33% for typhoid fever. Epidemiological data are shown in Table 1.

Table 1. distribution of sickle cell patients infected according to epidemiological data

Epidemiological data		Frequency (n=66)	Percentage (%)
Age range (year)	Under 1 year old	3	4.6
	1 – 4.11	27	40.8
	5 – 9.11	18	27.3
	10 – 15	15	22.7
	Over 15 years old	3	4.6
Gender	Male	43	65.1
	Feminine	23	34.9
Socioeconomic Lever	Low	47	71.2
	Way	14	21.2
	Well	5	7.6
Geographical Origin	Rural	12	18.2
	Sub-urban	10	15.1
	Urban	44	66.7
Major sickle cell syndrome	SS	65	98.5
	SC	1	1.5
Discovery of sickle cell anemia	Infectious episode	28	42.4
	Non-infectious episode	38	57.6

3.2 Clinical Findings at Presentation in the Hospital

The reasons for consultation were represented by fever (66 children or 100%), abdominal pain (26 children or 39.4%), bone pain (23 children or 34.8%), cough (17 children or 25.8%), headaches (13 children or 19.7%), osteoarticular swelling (11 children or 16.7%), dyspnea (7 children or 10.6%), others (vomiting: 3 children, diarrhea: 2 children, convulsion: 1 child, otorrhea: 1 child). The average temperature was 39.6 ° C [39 – 40.5 ° C]. Table 2 gives the distribution of children according to clinical presentation on admission.

Hyperleukocytosis was found in 54 patients (81.8%) with an average white blood cell count of 19295 [5700 - 64380 / mm3]. The average hemoglobin level was 7.2 [1.5 – 11 g/dl]. The C-reactive protein was positive in 53 patients (80.3%) with a maximum value of 192 mg/l. The rapid diagnostic test for malaria was positive in 4 children. The thick blood film was positive for plasmodium falciparum in 2 patients with a parasite density of 89700 and 875 trophozoites / mm3, respectively. The rate of completion of the infectious assessment was 40.9% for the chest x-ray (27 patients), 33.3% for the blood culture (22 patients), 16.7% for the cytobacteriological examination of the urine (CBEU) (11 patients). The positivity of the bacteriological examinations was 2 cases for the blood culture, 3 cases for the CBEU.

The cytochemical and bacteriological examination of the cerebrospinal fluid was carried out in 3 patients with a positivity in 1 child. All strains of bacteria were sensitive to penicillin.

The detection of *M. tuberculosis* by PCR Xpert MTB/RIF was carried out in 16 patients, it was positive and sensitive to rifampicin in 1 child. Two patients presented a positive molecular test for COVID 19 among 5 nasopharyngeal swabs. Table 3 gives the characteristics of the patients and of the type of sample according to the micro-organism isolated.

3.3 Diagnostic Data

The infections were dominated by bronchopneumonia (31.8%); ear, nose and throat infections (31.8%) and osteoarthritis (15.2%). Four children presented with severe malaria. The different infections are shown in Table 4.

Bronchopulmonary infections were found regardless of age, with a peak in children aged between 1 and 5 years. They were followed by otolaryngologic infections in patients aged ≥ 1 year and by osteoarticular infections. There was no malaria, acute gastroenteritis, or urinary tract infection in children under 1 year of age. The distribution of infections by age group of children is shown in Fig. 1.

3.4 Therapeutic and Evolutionary Data

Broad-spectrum probabilistic antibiotics therapy was prescribed in 100% (n = 66) of patients. The prescriptions were adapted to the laboratory results in 12.5% (n = 8) of the cases. Cefotaxime (100%), gentamicin (58.9%), oxacillin (26%) were the most prescribed antibiotics. Antibiotics were associated in 48 cases (75%). Patients with RDT positive for malaria received treatment including artesunate in injectable form. Major anti-tuberculosis drugs (rifampin, isoniazid, pyrazinamide, ethambutol) were used in the patient with the positive Xpert MTB/RIF PCR test.

Table 2. Distribution of sickle cell patients infected according to the clinical picture during hospitalization

Clinical data	Frequency (n=66)	Percentage (%)
Vaso-occlusive crisis	38	57.6
Anemia	52	78.8
Jaundice	18	27.3
Pulmonary condensation	18	27.3
Respiratory distress	15	22.7
Ostteoarticular swelling	11	16.6
Hepatomegaly	5	7.6
Splenomegaly	4	6.1
Dehydration	3	4.5
Meningeal syndrome	3	4.5
State of shock	2	3
Acute otitis media	1	1.5

Table 3. characteristics of infected sickle cell patients and the type of sample according to the micro-organism isolated during hospitalization

Micro-organisms		Patient characteristics				Type of sample
		Age (year)	Gender	MSCS*	Clinical picture	
Bacteria	*Streptococcus pneumoniae*	3.07	M	SS	Pneumonia	Blood
	Klebsiella pneumoniae	2	M	SS	Pneumonia	Blood
	Staphylococcus aureus	9	M	SS	AOM*	Urine
	Escherichia coli	10.05	M	SS	Sepsis	Urine
	Neisseria MeningitidisW135	0.08	F	SS	Meningitis	CSF*
	Salmonella spp	11	M	SS	AOM*	Urine
	Shigella spp	6.07	M	SS	AGE*	Saddle
	M. tuberculosis	2.04	M	SS	Pneumonia	Gastric fluid
Parasite	*Plasmodium*	6.11	M	SS	VOC*	Blood
	Falciparum	11.20	F	SS	Anemia	Blood
Virus	*SARS-CoV-2**	1.06	M	SS	Pneumonia	Nasal secretion
		15	M	SS	Pneumonia	Nasal secretion

SARS-CoV-2 : Severe acute respiratory syndrome coronavirus 2 ; MSCS : major sickle cell syndrome ; AOM : acute osteomyelitis ; AGE : acute gastroenteritis ; VOC : crise vaso-occlusive ; CSF : cerebrospinal fluid

Table 4. distribution of sickle cell patients infected according to the location of the infection during hospitalization

Infections		Frequency (n=66)	Percentage (%)
Otorhino-laryngological (n=21, or 31.8%)	Angina	13	19.7
	Nasopharyngitis	5	7.6
	Acute otitis media	3	4.5
Bronchopulmonary (n=21, or 31.8%)	Other bronchopneumonia	15	22.7
	Bronchiolitis	3	4.5
	*SARS-CoV-2** pneumonia	2	3
	Pulmonary tuberculosis	1	1.5
Osteoarticular (n=10, or 15,2%)	Acute osteomyelitis	6	9.1
	Chronic osteomyelitis chronique	2	3
	Osteoarthritis	1	1.5
	Osteitis	1	1.5
Other infections (n=13, or 19,7%)	Severe malaria	4	6.1
	Urinary tract infection	3	4.5
	Acute gastroenteritis	2	3
	Acute cholecystitis	2	3
	Bacterial meningitis bactérienne	1	1.5
	Sepsis	1	1.5

SARS-CoV-2 : Severe acute respiratory syndrome coronavirus 2

The immediate course was favorable for all patients. The mean length of patient hospitalization was 8.3 ± 1.8 days with extremes of 2 and 18 days. This duration was greater than 8 days in 56.4% of the children.

4. DISCUSSION

Infections are the leading cause of morbidity and mortality in children with sickle cell disease, especially before the age of 5. In our study population, the mean age of patients was 7.6 years and 45.4% of children were under 5 years old. In a study carried out in Dakar, at the Outpatient Care Unit for Sickle Cell Disease, a reference unit at the national level, the authors found an average age at the time of sickle cell infection, at 6 years and a peak of frequency between 1 and 5 years [9]. These results are also close to those found by other authors in Burkina Faso [10].

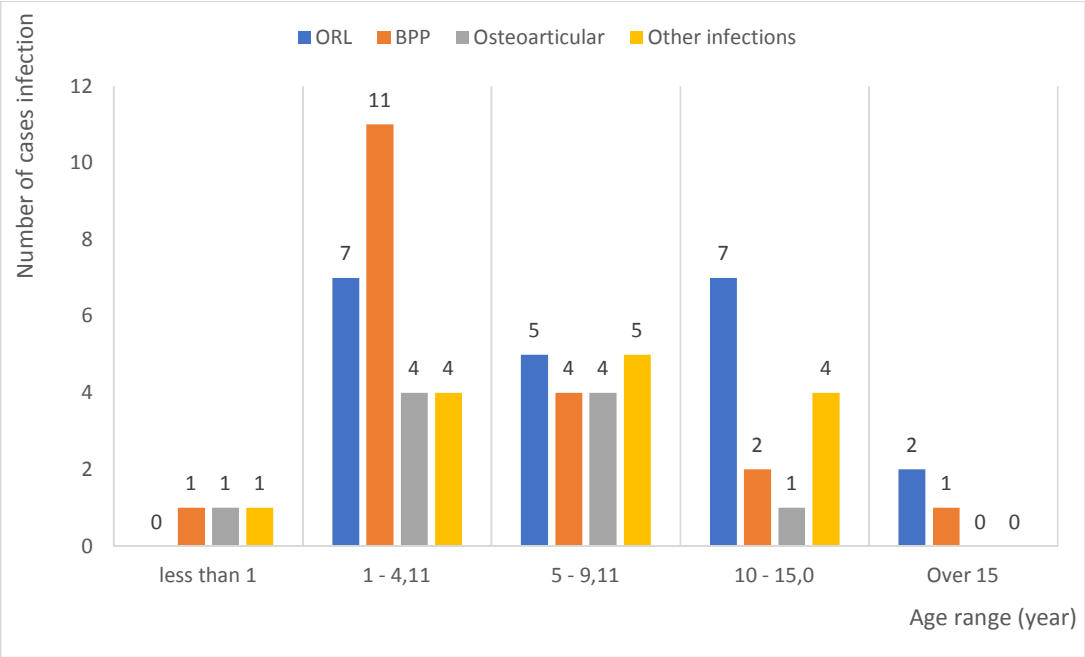

Fig. 1. Distribution of infections by age group

ORL: otorhinolaryngology ; BPP: bronchopneumonia; other infections: acute gastroenteritis; purulent meningitis; sepsis; urinary tract infection; malaria; acute cholecystitis

In general, the high susceptibility to infections in patients with sickle cell disease is well known and the risk of infection is greatest in young patients, in particular in the absence of vaccination against the encapsulated germs [11]. In our study, children were vaccinated up to 54.5% for pneumococcus; 33% for meningococcus and 33% for typhoid fever. These rates are comparable to those of *Douamba and colleagues* in Burkina Faso [10], but are lower compared to those found in Dakar [9]. But in all of these studies, vaccination coverage rates against encapsulated germs remain low. These underscores the need for pediatricians in the region, to create more awareness aimed at improving the vaccination coverage rate for sickle cell patients in Ziguinchor.

In our study, the functional signs associated with fever were dominated by abdominal pain, bone and joint pain, and cough. They do not differ from those usually described in the literature [12,13]. The cough could simply be a sign of the existence of a pulmonary infectious focus. As for osteoarticular pain with fever, it could be either the osteoarticular location of the infection or because of the fever as a factor triggering pain crises in sickle cell patients [12,13].

Faced with a clinical infectious syndrome in a sickle cell patient, the infectious assessment should be as broad as possible. It should include a chest x-ray, inflammatory workup, RDT for malaria, blood cultures, and CBEU, even if there is no warning sign. In our study, all patients received an RDT. But the performance rate of the other infectious assessment was low. This could be explained in part by the lack of resources for our patients and the insufficient technical platform in the region. HPZ has a microbiology unit with insufficient technical facilities. We recommend supporting the microbiology unit by recruiting qualified staff and making reagents and culture medium available. This will allow the systematic sampling (blood culture, CBEU) of sickle cell febrile patients.

In addition, the few paraclinical examinations carried out enabled *Streptococcus pneumoniae* to be isolated (1 cases); *Salmonella spp* (1 case); *Neisseria Meningitidis* serogroup W135 (1 case), *Staphylococcus aureus* (1 case), *Klebsiella pneumoniae* (1 case), *Escherichia coli* (1 case). The first three germs are frequently found in the literature, but our results do not allow us to comment on the bacteriological nature of the germs isolated in our study population [14]. In addition, antibiotic prophylaxis

and the generalization of vaccination against pneumococcus in our context since 2013 may modify the epidemiology of germs classically found in the literature.

Four children had presented with malaria with severe anemia. This shows that the sickle cell is prone to malaria infestation just like the normal person. None of the 4 children presented with neurological signs of severity. This is in line with the hypothesis of protection of hemoglobin S against certain severe forms of malaria, particularly neurological, supported by several authors [15-17].

The main infections recorded in our study are consistent with those found in the literature in sub-Saharan Africa, and globally; the difference sometimes residing in their order of frequency [10,13]. In our study, ear, nose and throat infections (31.8%) took first place, followed by bronchopulmonary infections (31.8%) and osteoarticular infections (15.2%). In the study by *Douamba and colleagues*, bronchopulmonary infections ranked first, followed by malaria and osteoarticular infections [10]. Unlike this study, malaria ranked fourth in our work. This difference could be explained in part by the fight against malaria in our country. In fact, since 2012, the national policy (RDT and syndromic management) has drastically reduced the incidence of malaria, especially of the severe forms.

Our patients received antibiotics in 100% of cases, represented by 3rd generation cephalosporins (100%), aminoglycosides (58.9%), oxacillin (26%). Other authors, had used the same antibiotics in Dakar in 2003 [18]. However, some authors have used ampicillin, amoxicillin and clavulanic acid. These antibiotics are more accessible in our structures and less expensive compared to other antibiotics. Indeed, *Douamba and co-authors* used the combination of amoxicillin and clavulanic acid in 16.5% [10]. For *Gbadoé and co-authors*, Ampicillin, amoxicillin-clavulanic acid, cephalosporins and aminoglycosides are the antibiotics of first choice depending on the site of infection, used alone or in combination [19].

The evolution of our patients was favorable in all cases. Unlike other studies where mortality varies between 1 and 8% [10,20]. This difference could be explained by the fact that our study concerns a population regularly followed in the service. Monitoring the sickle cell patient allows the prevention, detection and early treatment of any acute or chronic complications.

5. CONCLUSION

Otorhinolaryngological infections; Bronchopulmonary and osteoarticular cells are frequently associated with major sickle cell syndromes at the Ziguinchor Peace Hospital. We recommend the support of the structural microbiology unit to have easier bacteriological sampling in any child with febrile sickle cell disease.

CONSENT

In accordance with the international standard, the written consent of the parents was collected and retained by the authors.

ETHICAL APPROVAL

This study was carried out in accordance with the Declaration of Helsinki. To respect confidentiality, the hospitalization number of the file was used for each patient. This study was hospital-based research conducted under routine conditions.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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