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Bacterial Etiologies of Fever in Sickle Cell Children followed up at "Centre de Recherche et de Lutte Contre la Dr é panocytose" – Mali

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Abstract

Fever is a common symptom in sickle cell patients, and may be a sign of a bacterial or non-bacterial infection. **Objective:** Describe the bacterial aetiologies of fever in Sickle Cell Disease (SCD) children consulted or hospitalized, and the extent of confection with other pathogens in children at "Centre for Sickle Cell Disease Research and Control" (CRLD) in Bamako, Mali.

Patients and methods: From April 2014 to January 2016, a bacteriological study was conducted on nasal swabs, blood cultures, urine cultures and malaria diagnosis by Rapid Diagnosis Test (RDT) and Thick smear. All febrile SCD children aged 0.5-15 years seen at CRLD. All morbidity events related to fever were systematically recorded.

Results: Two hundred and thirty one SCD children were enrolled in this study. Urinary tract infections accounted for 14.28%; they were mainly caused by *Escherichia coli*, *Klebsiella pneumonia*, and *Enterococcus faecalis*. Blood cultures were positive for 10 patients (4.32%), and the isolated bacteria were dominated by *Salmonella* spp. *Streptococcus pneumonia* was the cause in 2 cases of pneumopathies confirmed by chest X-ray. *Klebsiella pneumonia*, isolated in naso-pharyngeal specimens, was the cause in a meningoencephalitis case which was gradually cured with antibiotic therapy. Fever was associated with malaria in 6.92% of the cases. Coinfections were frequent. Hospitalization was required for 62.3% of the children. Clinical progress was favourable in 99.2% of the cases; we noted 2 cases of death associated with HIV infection.

Conclusion: Fever in sickle-cell children in Mali is frequently associated with a urinary or invasive infection due to enterobacteria other than *Salmonella*. However, malaria and viral infections also play a key role in its occurrence, as well as coinfections. This study calls for exploration of immunological characteristics that contribute to the occurrence of bacterial infections in sickle cell children.

Keywords: Bacterial aetiologies; Fever; Sickle cell children; CRLD; Mali

Introduction

Sickle cell anaemia is the most severe form of haemoglobin diseases [1]. Africa is the most affected region, with sickle cell prevalence ranging from 2 to 30% depending on the geographical areas [1-4]. In Mali, sickle cell anaemia is very widespread, and its ethnic and geographical distribution varies between 4% and 15% from the North to the South [5]. The natural history of sickle cell anaemia is characterized by chronic anaemia, which appears early in life and is accompanied by simple or complicated Vaso-Occlusive Crises (VOCs), which may sometimes involve the patient's vital prognosis as well as chronic life-threatening and/or functional complications [6-9]. Under certain conditions, sickle haemoglobin (HbS) gelation is the cause of these VOCs [10,11]. Fever is one of the triggers of this sickle haemoglobin gelation; it is most often due to bacterial, viral or parasitic infections. In the tropics, studies have shown that fever was observed in sickle cell children in varying proportions. According to these studies, the fever was most often associated with urinary or invasive infections with a high risk of morbidity and mortality [12-16]. These studies are, however, essentially cross-sectional hospital studies which do not concern sickle cell cohorts enrolled in a regular monitoring programme. The extent of association of fever with bacterial infections in sickle cell children is not known in Mali where 5,000 to 6,000 sickle cell children are born each year [5]. Our study describes the bacterial aetiologies of fevers and the extent of coinfection with other pathogens among sickle cell children followed at the CRLD of Bamako, Mali.

Patients and Methods

The study was conducted at "Centre for Sickle Cell Disease Research and Control" (CRLD). Since it was opened to the public in March 2010, the CRLD has offered, to all sickle cell patients, a preventive medicine programme consisting of regular quarterly or semi-annual medical follow-up depending on the expressiveness of sickle cell anaemia, during

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which the WHO expanded programme on immunization vaccines, as well as anti-typhoid (Typhim vi), meningococcal (Meningo A + C) and anti-pneumococcal (Pneumonia 23) vaccines are administered systematically, and oral penicillin V is prescribed for children under 6 years. The Centre provides also systematic malaria prophylaxis with sulfadoxine-pyrimethamine.

Study population

It was a cross-sectional descriptive study conducted from April 2014 and January 2016. To be included in the study, patients were supposed to be between 6 months and 15 years of age and come for consultation or be hospitalized with fever (Temperature ≥38°C). Two hundred and thirty one sickle cell patients (SS, SC, S/ß°, S/ß+) was enrolled in this study. The consent of parent and assent for children had to be obtained in advance. The study was approved by the National Health Sciences Ethics Committee.

Study design

A detailed medical history and a clinical examination were performed for each patient during the screening visit; this information was recorded in the case report form along with socio-demographic information, clinical and therapeutic history and physical examination data (including axillary temperature, respiratory and heart rates, and oxygen saturation). A chest x-ray was requested in case of suspected pneumonia or acute chest syndrome. A venous blood sample was collected from each patient included in the study. Nasal swab and urine were also routinely collected during the screening visit. Blood was also collected in Serum Separation Tube (SST) for Procalcitonin (PCT). Blood collected in EDTA tube allowed for a Complete Blood Cell Count (CBC) and reticulocyte dosage. The nasal swab helped us to determine the nasal carriage of pathogenic bacteria. Finally, the blood collection in a blood culture tube and the urine collection were used to diagnose bacteraemia or bacteriuria respectively. The haemoglobin phenotype of the patients was determined before their inclusion in the study.

Cytobacteriological examination of nasal swab

The nasal carriage for each child was determined using two swabs carefully and deeply inserted into each nostril (2.5 cm) and gently turned on itself a few times per nostril. Two Select and Columbia CNA + 5% Sheep Blood agar plates were immediately cultured after treating the swab in physiological water. The cultured plates were incubated for 24 h to 48 h at 37°C. The Slidex STAPH-Kit and Slidex STREPT biochemical agglutination tests supplemented as needed by the Vitek® 2 system (bioMérieux) were used for bacteria determination.

Cytobacteriological examination of urine

After careful cleaning of the urinary meatus or vulva and parametric space for children able to control their urination, mid-stream urine was collected in a sterile bottle. For children unable to control their urination, urine collector tubes were used to collect their urine. Urine samples collected outside the Centre were quickly sent to the Centre's laboratory. The urine samples were cultured on UriSelect™ 4 and CandiSelect™ 4 media (CANDI 4) and incubated for 24 h at 37°C. Prior to culturing, the macroscopic appearance of the urine was assessed. Examination of fresh urine before and after centrifugation was intended to look for the following elements: leucocytes, red cells, bacteria, parasites, yeast epithelial cells, cylinders and crystals. Gram staining identified the bacteria and yeast present in urine samples. Biochemical agglutination tests and conventional identification methods were also used. The results were confirmed using the Vitek*II device (BioMérieux).

Blood culture

Blood culture sampling consisted in collecting blood aseptically during the same puncture in 2 vials, one aerobic and the other anaerobic. The vials were incubated in an automatic BacT/Alert system for 5 days at 37°C, the principle being to incorporate in each vial a green colorimetric detector "CO_2 sensor". This method allowed for the detection of positive vials. Gram staining was then performed, and a subculture of the blood culture sample on Horse Blood Gelose, Chocolate Agar and MacConkey Agar areas was made. The cultured boxes were incubated for 24 h to 48 h at 37°C. The bacteria were identified using biochemical agglutination tests and conventional identification methods, and then confirmed with the Vitek® 2 device (bioMérieux).Complete Blood Cell Count (CBC) and Reticulocyte Count (RC): The complete blood cell count was done using an ABX Micros 60 automatic counter (18 parameters). The leukocyte count was done on a blood stained smear using the May Grunwald Giemsa (MGG) technique; the reticulocyte count was done on a smear stained with bright creasy blue.

Diagnosis of malaria

Malaria diagnosis was initially done using the SD BIOLINE Malaria Ag Pf/Pan test for a differential diagnosis between a Plasmodium falciparum infection and other Plasmodium species. A thick drop and a thin smear were subsequently performed to confirm the diagnosis and species.

Case definitions

Fever was defined as a body temperature ≥38°C. Bacteremia was defined by the presence of bacteria in the circulating blood, confirmed by positive blood cultures. Urinary tract infection was defined by the presence of bacteria or yeast in urine. Nasal carriage of pathogenic bacteria was defined by the identification of bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae* and *Hemophylus influenzae*), which is a major risk factor for bacteremia and which plays a key role in the occurrence of morbidity. Biological product culture was considered to be contaminated if it was mono-microbial or polymicrobial, with the following bacterial species: negative coagulase staphylococci, *Corynebacterium*, alpha or gamma haemolytic streptococci, Micrococci, Bacillus, and *Propionibacterium* for blood culture. Malaria was defined by the presence of asexual forms of parasites (Plasmodium) in the blood.

Statistical analysis

Data analysis was conducted using Stata and SPSS version 20 software. A $p<0.05$ value was considered statistically significant.

Results

The 231 sickle cell patients with fever included in our study were 6 months to 15 years old. They comprised 183 SS homozygotes (79.2%), 26 SC (11.3%), 12 S/β-thalassemics (5.2%) and 10 S/β+ thalassemics (4.3%). The 231 sickle cells patients accounted for 36.6% of the Centre's paediatric population during our recruitment period. Bacterial exploration during the fever documented positive blood cultures in 10 sickle cell patients, i.e., 4.32% of blood cultures, and positive urine cultures in 33 patients, i.e., 14.28% of urine cultures. The bacteria isolated by blood culture or urine culture are listed in Table 1. It shows that the most frequent micro-organism in blood culture was the *Salmonella* spp. (4 out of 10). The biological characteristics of bacteraemia are described in Table 2. They were mostly found in SS homozygous patients, and they were constantly associated with

Bacteria isolated	Number of bacteria isolated (n)	Origin of the bacteria isolated	
		Blood (Percentage 100 × n/10)	Urine (Percentage 100 × n/33)
E. coli	15	1 (10)	14 (43.75)
Klebsiella pneumoniae	5	1 (10)	4 (12.5)
Enterococcus faecalis	3	-	3 (9.03)
***Enterobacter* spp.**	2	-	2 (6.25)
Salmonella group	4	4 (40)	-
***Staphylococcus* spp.**	3	2 (20)	1 (3.03)
***Pantoea* spp.**	1	-	1 (3.03)
Pseudomonas aeruginosa	1	-	1 (3.03)
Candidaalbicans	3	-	3 (9.03)
***Burkholderia cepacia* group**	1	1 (10)	-
Serratia ficaria	1	-	1 (3.03)
Raoultella ornithinolytica	1	-	1 (3.03)
Acinobacter iwoffii	1	-	1 (3.03)
Chromobacterium violaceum	1	-	1 (3.03)
Corynebacterium	1	1 (10)	-
Total	**43**	**10 (100)**	**33 (100)**

E. coli: *Escherichia coli*; n: Number

Table 1: Bacteria isolated in urine and blood cultures during fever in our study population.

Sex	Age	Hb Type	No. of plates/mm³	No. WBC/mm³	No. of Reticulocytes /mm³	Hb g/dl	LDH UI/L	PCT J0 ng/ml	PCT J1 ng/ml	PCT J2 ng/ml	PCT J7 ng/ml
M	5	SS	458000	20700	380000	7.8	872	0.36	0.60	ND	ND
F	7	SS	422000	26200	250000	8.2	1552	37.35	30.0	17.48	2.71
M	1	SS	508000	190000	198940	9.4	85	0.71	ND	0.04	0.04
M	12	SS	573000	47000	80400	3.9[a]	810	0.24	ND	0.12	ND
F	12	SB0	398000	17200	30060	7.7	810	0.85	ND	1.27	0.15
F	2	SS	591000	17100	48720	8.4	1350	0.06	ND	1.13	0.12
M	15	SS	268000	20100	8400	5.7	170	57.34	ND	68.75	ND
F	12	SS	461000	19000	75600	6.6	702	0.17	ND	0.39	0.04
M	10	SS	199000	30900	84150	7.1	420	6.70	ND	9.50	ND
M	7	SS	1244000	12800	177840	7.2	1680	0.26	ND	7.31	ND

No.: Number; WBC: White Blood Cells; Hb: Hemoglobin; LDH: Lactico Deshydrogenase; PCT: Procalcitonin; [a]Coinfection associating bacteremia and AgHBs+; ND: Not Determined

Table 2: Clinical and biological characteristics of ten sickle cell patients who had bacteremia.

leucocytosis (more than 10,000/mm³) and increased PCT level. In the urine, three bacteria were most frequently found, in descending order of frequency as follows: *E. coli*, *K. pneumonia* and *Enterobacter faecalis*. In the nasal swab, *Streptococcus pneumonia* was found to be the cause in two cases of pneumonia documented by x-ray of the lung, and *K. pneumonia* was the cause in one meningoencephalitis case which was gradually cured with antibiotic therapy. Malaria was found in 16 patients, i.e., 6.92%. The malaria cases were classified as severe when the haemoglobin level was <5g/dl [17] in 3 patients, i.e., 19% of the malaria sickle cell patients and 1.30% of those who consulted for fever (Table 3). Table 4 shows the cases of coinfections, namely two cases of bacteraemia, one of which was associated with hepatitis B virus seropositivity and the other with a urinary infection with *Candida's albicans*, and two cases of urinary tract infections, one of which was associated with malaria infection and the other with hepatitis B virus seropositivity. These coinfections were observed in 4 homozygous SS sickle cell patients and 1 S/ß-thalassemia sickle cell patient. Sickle cell complications associated with fever episodes were Vaso Occlusive Crisis (VOC) in 138 patients (59.7%), acute chest syndrome in 45 patients (19.5%), severe anaemia in 13 patients (5.6%), splenic sequestration in 3 patients (1.3%) and osteomyelitis in 3 patients (1.3%). Table 5 shows that these complications were associated with invasive or urinary bacterial infection in the respective proportions of 18.8% (26 cases out of 138), 15.5% (7 cases out of 45), 15.4% (2 cases out of 13), 30% (1 case out of 3), and 30% (1 out of 3 cases).

Discussion

Fever is recognized as a natural defence of the human body; however, it may results in discomfort and is sometimes life-threatening for Sickle Cell Disease (SCD) children because it is the most frequent factor that can initiate and maintain haemoglobin S gelation responsible for sickle cell complications that are sometimes fatal. From this point of view, its diagnosis and management which, above all, implies the identification of its cause, must be among the main concerns of practitioners in charge of sickle cell disease. This study is, to our knowledge, the first study that has prospectively and systematically investigated bacterial aetiologies of fever in children with SCD in sub-Saharan Africa. An assessment of the scope of the results obtained must, however, take into account some limitations: The fact that patients were taken only from the hospital, only children were considered, and certain infections, particularly those caused by oro-pharyngeal tropic viruses common in children, by mycobacteria or mycoplasmas, have not been investigated. Among the 231 sickle cell children with fever, 4.32% were caused by bacteraemia, 14.28% by urinary bacterial infections, and 6.92% by *P. falciparum* infections. A study conducted in Tanzania, reported 4.8% positive blood cultures in 648 patients out of 890 admitted in a tertiary

Sex	Age	Hospitalized	TBS	Hb Type	Hb Rate g/dl	No. of Reticulocytes / mm³	No. of RBC/ mm³	No. of plates/mm³	PCT J0 ng/ml	PCT J2 ng/ml	PCT J7 ng/ml	LDH UI/L
F	10	YES	Positive	SS	7.8	120000	15000	332000	0.06	0.15	0.17	576
M	15	YES	Positive	SS	6.3	141980	20300	470000	0.47	1.06	1.20	1206
M	11	NO	Positive	SB+	10.4	119600	9100	100000	7.62	35.71	0,83	60
M	12	YES	Positive	SS	6.7	853710	17800	284000	0.86	ND	ND	1035
M	15	YES	Positive	SS	6.9	391280	42100	438100	1.06	ND	ND	1431
M	11	YES	Positive	SS	3.4[b]	322050	19400	158000	1.52	ND	ND	195
M	15	NO	Positive	SB+	10.1	90960	7700	164000	0.70	2.36	0.04	675
M	10	YES	Positive	SC	8.6	68770	16300	559000	0.04	0.04	ND	640
M	6	YES	Positive	SC	9.6	371700	11500	450000	0.05	0.08	ND	860
F	11	YES	Positive	SS	9.4	21120	14300	322000	0.06	ND	ND	1370
M	5	YES	Positive	SB0	6.8	585550	20254	207000	1.11	ND	ND	4560
M	9	YES	Positive	SS	5.2	787720	13148	460000	0.48	1.14	0.26	3430
M	7	NO	Positive	SS	4.8[b]	35040	18200	207000	2.08	ND	ND	1730
F	8	YES	Positive	SS	4.6[b]	953440	13600	179000	21.12	15.30	ND	350
M	7	YES	Positive	SS	7.2	177840	12800	1244000	0.26	7.31	ND	1680
M	11	YES	Positive	SS	6.7	877800	14900	426000	0.43	0.17	ND	390

No.: Number; WBC: White Blood Cells; Hb: Hemoglobin; LDH: Lactico Deshydrogenase; PCT: Procalcitonin; [b]Hemoglobin rate requiring blood transfusion; ND: Not Determined; TBS: Thick Blood Smear

Table 3: Clinical and biological characteristics of sickle cell patients who had a positive thick smear.

Sex	Age Years	Temperature T°C	Hb Type	Hb Rate g/dl	No. of Reticulocytes / mm³	No. of WBC/ mm³	No. of plates/m³	Coinfection (type of association of infections)
M	13	38.4	SS	3.9[b]	80400	47000	573000	Bacteremia + Viral infection (AgHbS)
M	2	38	SS	9.4	198940	190000	50800	Bacteremia + Urine infection (bacteria)
F	2	39.4	SS	8.4	48720	17100	591000	Bacteremia + Urine infection (*C. albicans*)
M	5	38	S/ß^0	6.8	585550	20254	207000	Urine infection + malaria
F	11	39.9	SS	10.3	240960	20300	520000	Urine infection + Viral infection (AgHBs).

No.: Number; WBC: White Blood Cells; Hb: Hemoglobin; [b]Hemoglobin rate requiring blood transfusion

Table 4: Clinical and biological characteristics of sickle cell patients who had a coinfection.

Bacteria isolated		Complications						
		VOC (N=138)	Severe Anemia (N=13)	Splenic Sequestration (N=3	STA (N=45)	Osteomyelitis (N=3)	Others	None
E. coli	Urine culture	08 (24.24%)	-	-	03 (9.09%)	-	02 (6.06%)	01 (3.03%)
Klebsiella pneumoniae		02 (6.06%)	-	-	01 (3.03%)	-	01 (3.03%)	-
Enterococcus faecalis		01 (3.03%)		01 (3.03%)	01 (3.03%)	-	-	-
***Enterobacter* spp.**		-	01 (3.03%)	-	-	-	-	01 (3.03%)
Candida albicans		03 (9.03)	-	-	-	-	-	-
Others		06 (18.18)	-	-	01 (3.03)	-	-	-
***Salmonella* group**	Blood culture	04 (40%)	-	-	-	-	-	-
***Staphylococcus* spp.**		-	-	-	-	01 (10%)	-	01 (10%)
Klebsiella pneumoniae		-	01 (10%)	-	-	-	-	-
E. coli		-	-	-	01 (10%)	-	-	-
Burkholdéria cepacia		01 (10%)	-	-	-	-	-	-
Others		01 (10%)	-	-	-	-	-	-
Total (%)		26 (18.8)	2 (15.4)	1 (30)	7 (15.5)			

Table 5: Sickle cell complications and results of bacteria tests.

hospital [15]. Studies in Gabon in 2014, in Kenya in 2009, and Jamaica in 2001 reported higher bacteraemia rates [18-20]. These differences reflect the different methodologies adopted in the studies. Unlike these studies, our study involved a population of sickle cell children enrolled in a regular follow-up and benefiting from preventive medicine. A Study conducted in New York, was focus on bacteraemia in sickle cell children and using the same methodology we have adopted, reported a proportion of 3.8% in a sickle cell population followed-up in New York in 2011 [21]. This relatively low prevalence of bacteraemia in sickle cell children underscore the importance of adherence to medical follow-up, as well as current recommendations regarding empirical antibiotic therapy in cases of sickle-cell fever introduced into the preventive medicine programmes of the Recruitment Centre of our patients [22-26]. The bacteria isolated from the blood cultures were in descending order of frequency as follows: *Salmonella* group, *Staphylococcus* spp., *Echerichia coli*, *Klebseilla pneumonia*, *Burkholderia cepacia*, and *Corynebacterium*. This distribution pattern of the bacterial germs is close to that reported by Studies conducted

in New York and Boston [21,27] and underscores the predominance of bacteria other than *Streptococcus pneumonia*. The prevalence of urinary tract infections estimated at 14.28% in this study is lower than that reported by some authors in Africa [14,28]. The infection is dominant in girls probably because of their special anatomical configuration consisting in a short urethra close to the anal and vaginal orifices, as well as inadequate hygiene practices. The involvement of these bacterial urinary infections in the occurrence of fever in sickle cell patients is documented in several studies [26-30], and result in increased sickle cell morbidity and mortality [4,22-25,31,32]. At the end of this study, we recorded the association of urinary or invasive infection in large proportions with simple VOC cases, as well as with life-threatening complications such as acute chest syndrome, severe anaemia, and splenic sequestration. The bacteria isolated in urine among our patients are mostly enterobacteria dominated by *E. coli* and *K. pneumonia*. This distribution profile of the bacterial agents found in the urine of our patients is that reported in Maiduguri (Nigeria) in 2011 [14]. Some authors have reported that enterobacteria other than salmonella were found with an abnormally high frequency in sickle cell patients during urinary tract infections [33], sepsis or bone infection [34]. In our study, we found 40% infections by salmonella and 20% by enterobacteria in case of bacteraemia. Bacterial cultures are the most reliable way to diagnose bacterial infections, sometimes supplemented by molecular diagnosis. These laboratory tests are quite expensive and require, for some, a relatively long running time. They raise the issue of making them systematic for low-income population. Lastly, our results raise the crucial issue of making bacteriological examinations systematic in case of fever among sickle cell children in Mali. They also raise the issue of other bacterial infection markers that allow for a therapeutic decision within a short time. Some authors have proposed Procalcitonin (PCT) as a bacterial infection marker. In this study, we observed that the level of this marker was high (>0.05 ng/ml) in all cases of bacteraemia or HBV infection, as well as in most patients with malaria. There is very little literature in Africa on the dosage of this marker. Our results encourage us to consider it also for the diagnosis of malaria and viral infections. The rate of malaria infection found in this study is similar to that reported by a study conducted in Cotonou in 1999, i.e., 6.7% [35]. However lower, rates were reported for the paediatric population in rural areas in Mali and a retrospective study on sickle cell patients in Gabon in 2014 [18,36]. The biological aspects associated with malaria show that cases of severe malaria are not unusual. All these data on malaria raises doubts on the effectiveness of malaria prevention with sulfadoxine-pyrimethamine routinely prescribed for all sickle cell patients followed up by the Centre. In this study, we observed four cases of coinfections most often involving a bacterial and viral agent, particularly the hepatitis B virus. It is possible that coinfections involving HIV were underestimated since HIV tests were not systematically performed for our patients. The number of patients is low to draw any conclusion from the results, but it has been reported that malaria infection can contribute to bacterial infection [37,38]. The sickle cell phenotypes among our patients allows us to conclude that fever is most often associated with bacterial infections in SS homozygotes among the 6 months to 5 years age group, whether the bacterial infection is urinary track or invasive. The asplenia condition does not alone account for this epidemiological situation. This work paves the way for further research so as to better understand the immune system of sickle cell patients.

Conclusion

This study shows that fever is a frequent reason for outpatient consultation and hospitalization of sickle cell children in Mali. It also shows a high frequency of bacterial infection in this context, mainly related to enterobacteria other than salmonella. However, malaria and viral infections are important in the aetiologies of fevers and life-threatening complications. The immunological features that contribute to the occurrence of these infections among sickle cell patients should be explored in our context.

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