Short Communication

Malaria, clinical features and acute crisis in children suffering from sickle cell disease in resource-limited settings: a retrospective description of 90 cases

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Background: The prevalence of sickle cell disease (SCD) is extremely high in the Democratic Republic of Congo (DRC). Despite the high prevalence of this disease in our midst, there has been no report on the clinical features in the sickle cell pediatric population suffering from malaria in our midst.
Methods: A retrospective survey of records from the Department of Paediatrics of the University Hospital of Kinshasa, Kinshasa, Democratic Republic of Congo, was done for the period 1998–2008. For the 10 years studied, 108 children with SCD were reviewed and the data of those who developed malaria during admission were retrieved and analyzed.
Results: Of the 90 homozygous sickle cell children with malaria, fever, pallor, and jaundice were the commonly-found symptoms. Lethargy, severe anemia, respiratory distress, splenomegaly, hepatomegaly, digestive disorders, and prostration were common in children under 5 years, with significant difference ($P < 0.05$) to the older children. Transfusion because of to severe anemia was found necessary in 54.4% of cases. No case of cerebral malaria was found. Blackwater fever was a rare event. Hand–foot syndrome was present in 12.8% of patients, exclusively in those less than 5 years old. Pain crisis was associated in 46 cases (51.1%). Pain crisis was particularly present in SCD children less than 5 years of age (74.5% *vs* 25.6%, $P < 0.001$). No death was observed in this series.
Conclusion: We conclude that the acute crisis related to SCD is more common in children less than 5 years of age. High risk of a requirement for blood transfusion was found in young children. Anti-malarial prophylaxis is advocated in Kinshasa.

Keywords: Malaria, Sickle cell disease, Children, Kinshasa, Democratic Republic of Congo

Introduction

Sickle cell disease (SCD) is an autosomal recessive genetic condition due to a mutation in the beta-globin gene resulting in the replacement of glutamic acid in position 6 of the beta-globin chain by valine, resulting in an abnormal hemoglobin HbS molecule. Homozygous SCD occurs when people inherit abnormal genes from both parents responsible for hemoglobin production. SCD is the commonest genetic disease worldwide. The highest frequencies of homozygous SCD in the world occur in sub-Saharan Africa where 3–4% of the population is affected.[1] The sickle cell genes occur commonly in areas of the world with intense malarial transmission. The Democratic Republic of Congo (DRC) is located in equatorial Africa in the high transmission area for malaria.[2] The main vectors are *Anopheles gambiae* (92%) and *Anopheles funestus*.[2] The average inoculation rate varies between 2.8 and 620.5 bites/person/year in Kinshasa, and the sporozoite rate is up to 7.2% in urban areas.[2]

In the DRC the first cases of SCD were described in the 1950s.[3] The DRC has the highest population of SCD patients in the whole world, after Nigeria. The prevalence of SCD is extremely high, with 25–30% of sickle cell trait carriers in the gene among the general population. Recent population-based studies have calculated the prevalence to be 1.4% in Congolese newborns, and the incidence to be approximately 50 000 newborns per year.[4] Despite the high prevalence of this disease in our midst, there has been no

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report on the clinical features in the sickle cell pediatric population suffering from malaria in DRC; probably this is a result of the cost and logistics involved in obtaining it. As such, hospital-based disease frequency often offers the second best alternative.

Our ultimate goals are to develop the basis for designing and implementating effective preventive interventions in sickle cell patients. These researches also seek to inform clinical practice, education, and counseling guidelines. In this first report, we retrospectively describe clinical characteristics of malaria in children suffering from homozygous SCD in the University Hospital of Kinshasa in Kinshasa, DRC.

Population and Methods

The study was conducted at the emergency unit of the Department of Paediatrics of the University Hospital of Kinshasa, Kinshasa, DRC. Kinshasa is located in the holoendemic zone of malaria in the tropical rainforest belt, with two distinct weather conditions of wet and dry seasons.[2] The prevalence of SCD in this area is 1.4% in newborns.[4]

Patients who were diagnosed with SCD, proved by positive results of hemoglobin electrophoresis, from 1998 to 2008 were included in this study. For patients whose hemoglobin status was unknown, 5 ml blood samples were collected and were screened for hemoglobin phenotypes and confirmed using cellulose acetate hemoglobin electrophoresis at pH 8.6 at the Laboratory of Haematology of the University Hospital of Kinshasa or at the Institut National de Recherche Biologique (INRB) of Kinshasa.

We used hospital-based data from the records because there is no population-based sickle cell registry in DRC. Patient charts were reviewed retrospectively. The following clinical and laboratory information was collected and analyzed: (i) demographic characteristics, age, and gender; (ii) signs and symptoms; (iii) routine hemoglobin at admission, and (iv) outcome; and the clinical presentation report of what the physician had seen when examining the patient at admission.

Severe anemia was defined as a hemoglobin concentration of $\leq$5g/dl.

Parasitological diagnosis was done by thick smear and light microscopic observation. Thick blood films were stained with Giemsa and read for malarial parasites by trained microscopists. Children were eligible for inclusion if they had fever $>38.0^{\circ}$C, symptoms suggestive of clinical malaria, and positive *Plasmodium falciparum* parasites in the peripheral blood. Patients with incomplete records were excluded. All children were treated for severe malaria with quinine (30 mg/kg/day for seven days). The cases were classified according to different malarial problems known to be found in the following age groups: children $\leq$5 years and children $>$5 years.

Statistical analysis was performed using the statistics software SPSS for windows (15.0 SPSS, Chicago, USA). Data are represented as means$\pm$SD when the distribution was normal and median with range when the distribution was not normal. Categorical variables were compared using Fischer's exact test. A P value of <0.05 was considered significant.

Results

A total of 108 patients were identified as having SCD during the period of study. Some children were known to be SCD patients in our institution. By contrast, others were discovered during their admission by performing the hemoglobin electrophoresis. Eighteen were excluded because of insufficient information. Ninety sickle cell patients met the inclusion criteria for malaria, and the prevalence of malaria was 63.3% in this cohort. There were 37 girls (41.1%) and 53 boys (58.9%) with a male:female ratio of 1.4:1. All children were homozygous (Hb-SS). The median age was 5.4 years (range: 6 months–13 years). Forty-seven (52.2%) children were aged less than 5 years and 43 (47.8%) were aged more than 5 years.

No child received anti-malarial prophylaxis in their regular follow-up for SCD. Fifty-one (56.7%) patients in our series received anti-malarial treatment prior to hospital admission.

During diagnosis in our institution (Table 1), the most frequent symptoms found were fever (100%), loud systolic murmur $>$2/6 (94.4%), pallor (91.1%), and jaundice (90.0%). Other clinical manifestations are shown in Table 1. Lethargy, severe anemia, respiratory distress, splenomegaly, hepatomegaly, digestive disorders, and prostration were common in children under 5 years with significant difference ($P < 0.05$) than the older children (Table 1). No cases of convulsions and/or coma, abnormal bleeding, and circulatory collapse were found in this series. Severe anemia with Hb $\leq$5g/dl was present in 49 cases (54.4%).

No case of cerebral malaria was found. Blackwater fever was a rare event and was found in one case (1.1%).

Hyperhemolytic crises defined as precipitous fall in the hemoglobin levels associated with jaundice, marked reticulocytosis, and increased unconjugated hyperbilirubinemia were present in 49 cases (54.4%). Overall, hyperhemolytic crisis was more common in children under 5 years than in older children (78.7% *vs* 27.9%, $P < 0.001$). All cases with severe anemia were transfused and represented 54.4% of patients. Hand–foot syndrome was associated in 12.8% ($n = 90$) of patients and was exclusively found in children under 5 years (Table 1). Pain crisis was frequently present in SCD children with malaria, particularly among children less than 5 years of age (74.5% *vs* 25.6%, $P < 0.001$). No death was observed in this series.

Table 1 Spectrum of clinical manifestations in the 90 sickle cell study patients according to age

Clinical findings	All children (n = 90)		Children <5 years (n = 47)		Children ≥5 years (n = 43)	
	Frequency (n)	Percent (%)	Frequency (n)	Percent (%)	Frequency (n)	Percent (%)
Fever	90	100	47	100	43	100
loud systolic murmur >2/6	85	94.4	45	95.7	40	93.0
Pallor	82	91.1	43	91.5	39	90.7
Jaundice	81	90.0	41	87.2	40	93.0
Lethargy***	64	71.1	44	93.6	20	46.5
Severe anemia*** (Hb ≤5g/dl)	49	54.4	37	78.7	12	27.9
Respiratory distress***	39	43.3	32	68.1	7	16.3
Splenomegaly***	34	37.8	29	61.7	5	11.6
Hepatomegaly**	26	28.9	20	42.6	6	14.0
Digestive disorders**	24	26.7	18	38.3	6	14.0
Headache***	22	24.4	3	6.4	19	44.2
Abdominal pain	21	23.3	14	29.8	7	16.3
Prostration*	13	14.6	11	23.4	2	4.7
Hemoglobinuria	1	1.1	0	0	1	2.3
Seizures	0	0	0	0	0	0
Abnormal bleeding	0	0	0	0	0	0
Circulatory collapse	0	0	0	0	0	0
Acute crisis related to sickle cell disease (SCD)						
Hyperhemolytic*** crisis	49	54.4	37	78.7	12	27.9
Pain crisis***	46	51.1	35	74.5	11	25.6
Hand–foot*** syndrome	11	12.2	11	23.4	0	0
Spleen sequestration	0	0	0	0	0	0

*<0.05; **<0.01; ***<0.001 (χ^2 test).

Discussion

Our study is the first to look at the clinical profile and the outcome of malaria in children with SCD in DRC. The study spanned 10 years in a region of 7 million with 2% of sickle cell patients, and 90 cases of SCD with malarial infection were identified during that time. This is an extremely small number. The total number of children in this study indicates that only a tiny fraction of children with SCD suffering from malaria benefited from treatment in our tertiary referral center. This may be explained by some obstacles outside the University Hospital of Kinshasa, such as lack of pediatricians, or in population education to consult a pediatrician directly. It is common for some children with SCD to be taken to the primary and secondary level in the health care system of DRC, but also to herbalists or prayer houses instead of a hospital. This last situation is due to cultural beliefs, poverty, and ignorance.[5] In addition, many patients had started anti-malarial treatment at home before their admission to our institution.

Malaria as a cause for transfusion and hospitalization in this population is found to be important. The prevalence found in this study was 63.4%. This is not surprising, as severe malaria has been reported to be a leading cause of sickle cell morbidity and high rates of transfusion in a previous study in DRC.[6] In our series, malaria was the most common precipitating cause of pain and hyperhemolytic crises that required blood transfusion. In DRC, there is no recommendation of life-long malarial prophylaxis in people with homozygous SCD. It is a possible explanation for the increased numbers of malaria sufferers with severe anemic attacks observed in our series. A similar observation was noted by McAuley in Kenya.[7]

The highest incidence of malaria was found in the age group 0–5 years. This is the age group most susceptible to the effect of the malarial parasite associated with severe anemia. No case of cerebral malaria was found in our series. It is possible that cerebral malaria is very rare, or undiagnosed in our poor-resource settings. Non-availability of appropriate diagnostic tools remains a formidable hindrance to be surmounted in the establishment of the true prevalence of this severe form of malaria in our pediatric population suffering from SCD. However, our observation was similar to those reported by Diagne *et al.* in Senegal.[8]

It has been postulated that the development of *Plasmodium falciparum* is partially inhibited by the Hb-SS red cells. More recently, this theory has been challenged. Molecular mechanisms may inhibit the aetiology of cerebral malaria as it occurs in the general population and confers SCD patient tolerance to cerebral malaria.[9,10] Our study supports this relationship since, among the 90 SCD children, no case of cerebral malaria was found. In addition, a majority of patients in our series received anti-malarial treatment prior to hospital admission.

Still, the protection is not complete, as is evident with our 90 patients with SCD having complicated malaria that necessitated transfusion in half of them, particularly in children less than 5 years. In addition, acute crisis related to SCD is more common in children less than 5 years. Provide data that can be used for advocacy as well as for the further development of

strategies for the prevention and treatment of severe malaria in sickle cell disease. This situation should draw the attention of all partners involved in the fight against malaria in DRC. Sickle cell patients should be a priority target for the further development of strategies for the prevention of severe malaria in sickle cell children, particularly in children less than 5 years of age.

Limitations

Although this study was done in the largest tertiary hospital in DRC, findings cannot be assumed to be representative of the whole country, due to differences which may exist in the patient profile and the spectrum of clinical activity of SCD and malaria. In this retrospective study, no control group (e.g. SCD children without malaria, heterozygotes and/or children with normal Hb) are included because of lack of information about the hemoglobin status of other children admitted to our institution during the period of study; therefore, it is difficult to interpret this information. In addition, the status of G6PD of these children was unknown. During the period of this study, in the DRC there were no technical possibilities to assess G6PD activity in our laboratories. Better data, to estimate the number of child deaths due to malaria and to compare with (i) SCD children admitted without malaria and (ii) normal Hb (Hb-AA) and carriers of S-trait (Hb-AS), are needed in the second step of this project with a prospective study. Is the disease more or less severe in sicklers? The future prospective studies will answer the question.

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