Original Article

Pattern of malaria in hospitalized children in Khartoum state

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ABSTRACT

Malaria remains a major health problem in Sudan with significant morbidity and mortality particularly in children. We prospectively studied children with malaria admitted to an Emergency Department in Khartoum (August-November 2014). Malaria diagnosis was based on a positive blood smear and rapid diagnostic test. The aim was to study the clinical and laboratory features and short-term outcome of malaria among hospitalized children. Data collected from 112 children (males; 56.3%) who fulfilled the criteria for diagnosis of malaria of whom 72.3% had severe malaria and 27.7% uncomplicated malaria (UM). The mean age was 69.2 ± 54.5 months. Hyperparasitemia was detected in 53% of positive blood smears. *Plasmodium falciparum* was detected in 69.4%, *P. vivax* in 26.5%, and mixed species in 4.1%. The risk of severe malaria was significantly higher in patients with hyperparasitemia and *P. vivax* infection (P = 0.001 and P = 0.014 respectively). Severe malaria cases had significantly higher prevalence of thrombocytopenia and lower mean platelet count than those with UM, P = 0.001 each. Serious complications of severe malaria were cerebral malaria, severe malaria anaemia and acute kidney injury (AKI). The overall case fatality rate was 5.3% and that from severe disease was 4.9%. All deaths were among <60 months-olds and were due to *P. falciparum* infection with AKI being the only significant risk factor for death (P = 0.045). In Khartoum state, UM is still an important cause of morbidity in children. *P. vivax* has emerged as a causative species of severe malaria. The lower mortality rate of malaria probably reflects improvement in health care.

Keywords:

Malaria, Children, Severe malaria, Sudan.

INTRODUCTION

Malaria is one of the most infectious diseases worldwide with about 50% of the world's populations being at risk for its serious complications [1]. Malaria incidence in Sudan was estimated to be about 9 million episodes in 2002 with about 44,000 deaths. Moreover, 2,877,000 disability adjusted life year (DALYs), which is a measure of disease burden, lost in Sudan in 2002 due to malaria mortality, episodes, anaemia and neurological sequels [2]. In the same report under-five children had the highest burden with the highest incidence and mortality in males but more DALYs lost in

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females [2]. The spectrum of clinical presentation of malaria varies across various transmission zones from asymptomatic parasitemia, febrile illness, to severe potentially fatal disease [3,4]. This is due to factors like parasite species and patient's immune status. In areas with constant high-intensity malaria transmission most of mortalities occur in *Plasmodium falciparum* infection and in younger children [5,6]. Severe malaria in Sudan is usually due to *Plasmodium falciparum*, however, cases due to *Plasmodium vivax* have been described [7]. Despite the life threatening complications of malaria in children but available data about this problem in Sudan is limited. The aim of this study was to determine the clinical and laboratory features and outcome of malaria among a population of hospitalized Sudanese children in a single pediatric hospital in Khartoum State.

METHODS

This prospective cross-sectional hospital based study was conducted in Ahmad Gasim Children's Hospital, Khartoum state, Sudan. The hospital consists of a Pediatric Emergency Department, PICU and 10 wards with 154 beds. It receives referrals mainly from Khartoum North Provinces some of which have agricultural schemes. We included all children aged >2 months-15 years of both sexes who have been admitted with malaria in the period between August and November 2014. The sample was total coverage two times a week. The diagnosis of malaria was based on detection of parasite in 10% Giemsa-stained blood smears; thick for parasite detection and thin for count. Immuno-chromatographic test (ICT) as a rapid diagnostic test (RDT) was used when suspicion of malaria was high and the blood smear was negative. ICT detects circulating malaria antigens using antibodies against the parasite antigens targets (Histidine-rich protein of *P. falciparum* [PfHRP2] and the Plasmodium aldolase enzyme expressed by *P. falciparum* as well as non-falciparum species) and has specificity and sensitivity >95% for UM *P. falciparum* infection but lower sensitivity to *P. vivax* [8]. The diagnostic capacity of the laboratory technicians was certified and monitored by means of reading a slide bank; that is all positive blood films for malaria and 10% of negative films were rechecked in the reference laboratory in Federal Ministry of Health. Demographic data were recorded. Relevant symptoms obtained from parents or caregivers. Relevant clinical signs looked for by a Pediatric Registrar and double-checked by a Pediatrician were recorded. Hematological data (Hb, TWBCs, platelets) and biochemical data (glucose, urea, creatinine, Na+, K+) were recorded as low or high levels if below or above the age gender-specific values respectively. [9] Patients were classified as having severe malaria according to WHO definition [10] defined as the presence of *P. falciparum* asexual parasitemia with no other obvious cause of symptoms plus at least one of the followings:

- Clinical features: cerebral malaria (impaired consciousness or unrousable coma), prostration (weakness with inability to walk or sit up without assistance), failure to feed, multiple convulsions (>2 episodes in 24 h), deep breathing or respiratory distress (acidotic breathing), circulatory collapse or shock (systolic blood pressure < 50 mmHg), clinical jaundice plus evidence of other vital organ dysfunction.
- Laboratory features: hemoglobinuria, abnormal spontaneous bleeding, pulmonary edema (radiological), hypoglycemia (blood glucose < 2.2 mmol/l or <40 mg/dl), metabolic acidosis (plasma bicarbonate < 15 mmol/l), severe malaria anemia (Hb < 5 g/dl, PCV < 15%), hyperparasitaemia (> 2% or 100,000/µl in low intensity transmission areas or >5% or 250,000/µl in high stable malaria transmission intensity), hyper-lactatemia (lactate > 5 mmol/l), renal impairment (serum creatinine > 265 µmol/l). Treatment outcomes were complete recovery or death.

Ethical approval was obtained from the ethical committee in Sudan Medical Specialized Board and Hospitals Research Committees. An informed consent was taken from children's parents or guardians. We ensured confidentiality and serial numbers were recorded instead of names.

Statistics

Data entry and analysis were done using a software program statistical package for social science (SPSS) version 18. Descriptive statistics used comprised mean, standard deviation (SD) ± and percentages. Variables were compared using Students t-test. Chi-square test was used to examine the association

between risk factors and outcome. Statistical significance was defined as $P < 0.05$.

RESULTS

Baseline characteristics

The study included 112 children (males; 56.3%) with malaria. The mean age was 69.2 ± 54.5 months (range 3-204) with 57.2% being < 60 months and 24.1% < 24 months (Table 1). In 87.5% of patients diagnosis of malaria was based on positive blood smears and in 12.5% on positive ICT. Hyperparasitemia was detected in 53% of positive blood smears. *P. falciparum* was detected in 69.4%, *P. vivax* in 26.5%, and mixed species in 4.1%. Clinical presentation showed variable symptoms and signs (Table 2). Anemia (<8 gm/dl) was detected in 25.9% and thrombocytopenia in 44.6%. Other laboratory findings are shown in (Table 3). Anemia was significantly more common in those aged <60 months compared to ≥60 months (33.9%; versus 13% respectively, P = 0.010) but there was no statistically significant gender difference (24.6% versus 25.5% respectively, P = 1.000).

Uncomplicated malaria (UM)

Thirty-one patients (27.3%) had UM with a mean age of 57.84 ± 56.40 (range 3.96-192) months. The frequency of UM was similar across gender (21.9% in males versus 34.7% in females) and age (29.7% in <60 months versus 25% in ≥60 months), P = 0.201 and 0.672 respectively. All cases of UM were due to *P. falciparum*. Anemia was detected in 41.9% with a mean Hb of 6.76 ± 1.0 (range 5.2-7.9) gm/dl.

Severe malaria

Eighty-one patients (72.3%) had severe malaria (males; 60.4%). The mean age was 69.12 ± 54.48 (range 2-204) months with 55.5% being <5 years, 37% <3 and 14.8% <2years of age (Table 1). The prevalence of severe malaria was similar across age (55.6% in <60 months versus 54.8% in ≥60 months), P = 0.672 and gender (60.5% in males versus 45.2% in females), P = 0.201. Hyperparasitemia was detected in 72.2%. The species was *P. falciparum* in 62.5%, *P. vivax* in 31.9%, and mixed species in 5.6%. The risk of severe malaria was significantly higher in those with hyperparasitemia than with mild/moderate parasitemia (72.2% versus 37.8%, P = 0.001, RR = 2.30; 95% CI; 1.65-3.19) and in *P. vivax* infection than *P. falciparum* (76.2% versus 10%, P = 0.014, RR = 3.38; 95% CI; 1.09-10.40 respectively). Presenting symptoms and signs were variable (Table 2). Anemia and thrombocytopenia were the most common laboratory findings (55.6% and 44.6% respectively) (Table 3). Patients with severe malaria had a statistically significant higher prevalence of thrombocytopenia than UM (61% versus 19.2% respectively) and lower mean platelets count (166.843 ± 114.83 versus 322, 53 ± 211.273 respectively), P = 0.001 each.

Cerebral malaria (CM)

28% of cases with severe malaria had CM with a mean age of 50.4 ± 42.0 months. The prevalence of CM was higher in <60 months-olds than ≥60 months (25% versus 14.5% respectively) and in males than females (22.2% versus 18.4% respectively), but there was no statistically significant difference (P = 0.646; RR = 1.27. 95% CI; 0.498-3.237 and P = 0.230; RR = 1.952; 95% CI; 0.732-5.208 respectively). CM was not significantly associated with severe malarial anemia (SMA) (8.7% versus 10.1% respectively), P = 0.618, RR = 0.995, 95% CI; 0.367-3.696, respiratory distress (69.6% versus 69.7% respectively), P = 0.648, RR = 1.385, 95% CI; 0.118-16.227, hyperparasitemia (13.5% versus 21.7%), P = 0.300, RR = 0.560, 95% CI; 0.194-1.617 or parasite species (*P. falciparum*; 19.1% versus *P. vivax*; 13.3%), P = 0.574, RR = 1.53, 95% CI; 0.45-5.1.

Severe Malaria Anemia (SMA)

13.5% of patients with severe malaria had SMA with a mean age of 50.4 ± 41.6 months. Prevalence of SMA was similar across gender (11.1% in males; versus 8.5% in females) P = 0.756; RR = 1.34; 95% CI 0.36-4.88) and age (11.1% in <60 months versus 8.5% in ≥ 60 months), P = 0.756; RR = 1.34; 95% CI 0.36-4.88). SMA was not significantly associated with hyperparasitemia than mild/moderate parasitemia (11.5% versus 10.9% respectively), P = 0.446; RR = 1.11; 95% CI 0.28-4.43), or respiratory distress (6.4% versus 17.6% respectively), P = 0.083; RR = 0.31; 95% CI; 0.08-1.10).

Acute kidney injury (AKI)

7.4% of patients with severe malaria had AKI with a mean age of 23.2 ± 3.02 months. The prevalence of AKI was similar regarding gender (7.9% in males versus 2% in females), P = 0.186 and age (8.6% in <60 months versus 2.1% in ≥60 months), P = 0.72. All cases were due to *P. falciparum* infection and none of them had hyperparasitemia. There was no statistically significant association of AKI with anaemia or jaundice (P = 0.525 and 0.798 respectively).

Mortality

The overall case fatality rate of malaria was 5.3% and of severe malaria was 4.9% with a mean ± SD of 54 ± 42.3 months. AKI was the only significant risk factor for death (P = 0.045, RR = 7.50, 95% CI; 1.64-34.12). SMA and CM were not risk factors for mortality (P = 0.699, RR = 1.55, 95% CI; 0.16-14.20, P = 0.591, RR = 1.60, 95% CI; 0.29-8.83 respectively).

Treatment

Quinine therapy was given for 56.6% (46/81) of children with severe malaria, Artemether for 19.8% (16/81), Artemether followed by Quinine in 8.6% (7/81). The remaining 14.8% (12/81) received multiple drug therapies before presenting to hospital.

Table 1- Age distribution of hospitalized children with severe malaria in Khartoum State.

Age	Study group	Severe malaria	Uncomplicated malaria
<2 years	27 (24.1%)	12 (14.8%)	15 (48.3%)
2-3 years	20 (17.9%)	18 (22.2%)	2 (6.5%)
3-5 years	17 (15.2%)	15 (18.5%)	2 (6.5%)
5-10 years	24 (21.4%)	16 (19.8%)	8 (25.8%)
>10 years	24 (21.4%)	20 (24.7%)	4 (12.9%)
Total	112 (100%)	81 (100%)	31 (100%)

Table 2- Clinical features of malaria in hospitalized children in Khartoum State.

Clinical manifestations	Study group (n = 112)	Severe malaria (n = 81)	Uncomplicated malaria (n = 31)
Fever	112 (100%)	81 (100%)	31 (100%)
Vomiting ± Diarrhea	75 (66.9%)	48 (59.3%)	27 (87.1%)
Convulsions	30 (26.8%)	28 (34.6%)	2 (6.5%)
Disturbed level of Consciousness	10 (8.9%)	10 (11.1%)	-
Coma	4 (3.6%)	4 (4.9%)	-
Oliguria	7 (6.3%)	7 (8.6%)	-
Splenomegaly	37 (335)	30 (37.5%)	7 (22.6%)
Respiratory distress	34 (30.4%)	25 (31.0%)	9 (29%)
Hepatomegaly	32 (28.6%)	23 (28.4%)	9 (29%)
Prostration	7 (6.3%)	7 (8.6%	-
Jaundice	5 (4.5%)	5 (6.3%)	-

Table 3- Prevalence and profiles of haematological and biochemical abnormalities of malaria among hospitalized children in Khartoum State.

Laboratory findings	Study group		Severe malaria group	
	Prevalence	mean ± SD	Prevalence	mean ± SD
Anemia (Hb < 8 gm/dl)	60/108 (55.6%)	7.40 ± 0.77 gm/dl	47/77 (61%)	5.40 ± 1.56
Severe anemia (Hb < 5 gm/dl)	11/108 (10.2%)	3.56 ± 0.27 gm/dl	11/77 (14.2%)	10.12 ± 5.81
Thrombocytopenia	45/101 (44.6%)	85.72 ± 35.58 ×105	40/71 (56.3%)	166.8 ± 114.83 ×105
Leukocytosis	33/111 (29.7%)	17.76 ± 5.95 ×103	22/80 (27.5%)	120.47 ± 47.94 ×103
Leukopenia	8/111 (7.2%)	3.07 ± 0.6541 ×103	5/80 (6.3%)	36.98 ± 57.09 ×103
Mean high serum creatinine	6/81 (7.4%)	3.56 ± 2.18 mg/dl	5/81(6.3%)	0.78 ± 1.04 mg/dl
High blood urea	9/81 (11.1%)	129.77 ± 110.57 mg/dl	5/81 (6.2%)	129.09 ± 8.08
Hyponatremia	15/45 (33.3%)	125.5 ± 3.73 mmol/l	9/34 (26.5%)	4.4 ± 3.29 mmol/l

DISCUSSION

This study was designed to determine some clinical aspects and outcomes of malaria in a population of hospitalized children in Khartoum State where malaria transmission is unstable and epidemics occur. Severe malaria was common among our children admitted with malaria (72.7%). Different studies from other countries have shown variable rates; Cameroon (73.7%), Uganda (29.8%), Mozambique (13.2%), and North East India (49.1%) [11-14]. Factors influencing the severity of disease in malaria remained largely unexplained. However, age, genetics, malaria epidemiology, late presentation, medications before admission, co-morbidities and quality of local health care have been claimed [3-6]. In a previous report, rates of severe malaria vary in different areas (20%-8.4%) with different epidemiological contexts [3]. Age group < 3 years was the most affected age group (37%) in our series. This pattern is often seen where endemicity is stable causing partial immunity in older children [15,16]. However, similar age pattern was reported in a previous study and studies in other countries where malaria transmission is also low and unstable [3,11-14]. Our study was conducted in late rainy season and winter in which epidemics occur and this may explain our finding. In this study the risk of severe disease was significantly higher among patients with high compared to low-density parasitemia. This is consistent with reports in a previous study (72%), Uganda (67%) and India (61%) [3,12,14]. In some reports younger child had higher parasitemia, but we found no such age association. Infection with *P. vivax* was thought to be less common and benign [11]. However, recent reports showed severe *P. vivax* disease in Sudan and many other countries [7,17-19]. Our results showed a higher prevalence of *P. vivax* infection (31.9%) than in a previous report (22.8%) [7]. This may be due to influx of people from Ethiopia where *P. vivax* infection is increasing [20]. In this study, the risk of severe disease was higher in *P. vivax* than *P. falciparum* infection. This is consistent Similar with reports in North East India [14]. Symptoms and signs of malaria in our study were quite variable with convulsions and disturbed level of consciousness being the most common in severe disease which is comparable a previous and other reports [3,11,12]. Anemia (HB < 8 gm/dl) was detected in 55.6% of our children with malaria and in 61% of those with severe disease, which is similar to a previous report (62%) [3]. Higher figures were reported in Cameroon (87.9%) and Ghana; (81%) [11,21]. In this study, thrombocytopenia was detected in 44.6% that is comparable to reports in Ghana (52%) and India (70%) [21,22]. Severe malaria anaemia (SMA) was reported in 14.2% of our children with severe disease compared to variable rates (17%-55%) in other studies [3,11,13,17,21]. This variation may be due to the multifactorial aetiology of SMA that

could also be influenced by the nutritional status and helminths infestations [23]. SMA mean age was 50 months, which is similar to studies from both high and low transmission areas [11-13, 24]. Our results did not show significant association of SMA with hyperparasitemia as has been described in other areas [11,24]. Cerebral malaria (CM) was a common complication (28%) in our children compared to variable rates reported in a previous study (83%), Cameroon (9.2%), and India (50%) [3,11,22]. Our finding supports the evidence that the prevalence CM is more common at lower than higher transmission areas. In this study, the majority of children with CM were younger (<60 months) which is consistent with other studies [10]. This may be due to development of immunity in older children in areas where malaria is less prevalent. In this study, *P. falciparum* infection and low-density parasitemia were not statistically significantly associated with CM as has been reported in Cameroon, India, and Nigeria [11,14,25]. We recorded AKI in 7.4% of our children with severe disease. This finding is comparable to results of two studies from India (5.4% and 8.3%) [19,22]. All AKI cases in our study were due to *P. falciparum* infection and none had evidence of severe haemolysis. In this study, the overall case fatality rate of malaria was 5.3% (6/112) and of severe malaria was 4.9% (4/81) with a median age of 54 months. This result is comparable to reports in a previous study, other African counties, and India showing mortality less than 5% [3,14,18,23]. In contrast, other studies from Uganda and Nigeria reported higher mortality rates (14% and 13.6% respectively) [12,25]. This variation could be related to many factors including late presentation, co-morbidities and quality of local health care. Two of our patients died of CM complicated by AKI and one by SMA. All deaths were due to *P. falciparum* infection but none of them had hyperparasitemia. CM and *P. falciparum* were the main causes of mortality in many African countries and India [5,18,19]. However, in our study CM was not a predictor of mortality.

CONCLUSION

In Khartoum state, malaria among hospitalized children commonly affects young children with clinical and laboratory features comparable to those in tropical countries. UM remains an important cause of morbidity. Main complications of severe malaria were CM, SMA, and AKI and P. vivax has emerged as a causative species. Our children mortality rate is lower than in some African countries, which could be due to early treatment, less co-morbidities and/or improvement of our children health care. The low prevalence of severe malaria in infants suggests the need to increase population coverage with insecticide-treated beds rather than using preventive anti-malarial for children.

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