SEVERE MALARIA IN SUDANESE CHILDREN: CLINICAL ASPECTS AND PROGNOSIS IN HOSPITALIZED PATIENTS

Zeidan A. Zeidan, MD,* Elkhir M. Kojal H,MD† Ali B. Habour,MD‡ Kamal A. Nowary,MD§ Fatih H. Mohammed,MD†† Mohammed A. Awadelkareem, PhD*

*University of Khartoum, †University of Islamia, ‡University of Gazera, §Gadarif Hospital, ††Sennar Hospital, Sudan

Objective: To assess the epidemiology, clinical presentations, disease management, outcome and risk factors associated with severe malaria in children in four hospitals in Sudan.

Methods: Follow-up prospective design was used to fulfil the objectives of the study in four hospitals: Omdurman paediatrics hospital, located in the capital (Khartoum) compared to Madani, Gadarif and Sennar hospitals located in other states.

The results: Total admission of severe malaria was 543 children representing 21% of all paediatric admissions, and 12% of malaria outpatient cases. Median age of children with severe malaria was 48 months. 93% of children with severe malaria died before the age of 9 years.

Case fatality rate was 2.6%. The risk of dying because of delay was four times more than when there was no delay, 95% CI (1.5 – 14.3). Other risks of death were severe malaria associated with coma, inability to sit or eat and hyperpyrexia. Omdurman hospital in Khartoum State in the capital, had the highest case management performance percentage compared to other regional hospitals.

Conclusions: In view of this, it can be argued that deaths due to severe malaria could be reduced by improving health management and planning with the redistribution of resources (including consultants) at the central and regional levels and the conduct of proper training.

Correspondence to:
Dr. Zeidan Abdu Zeidan, Associate Professor, University of Khartoum, Community Medicine Department, P.O. Box 102, Khartoum, Sudan E-mail: drziedan61@hotmail.com
programs on the management of severe malaria at all levels. Raising the awareness of parents about seeking treatment for malaria early in order to avoid unnecessary deaths is vital.

Key words: Severe malaria. Case fatality rate. Severe malaria management scoring system.

INTRODUCTION
A severe malaria patient is defined by WHO as a febrile patient of *falciparum malaria* with some complications of no other obvious causes who requires emergency treatment in hospital. Out of 1.5 to 2.7 million deaths that occur in the world every year, one million are children. In Africa, malaria kills one child in twenty before age of five; it causes 59% of reported deaths among children in the Volta Region of Ghana and 49.0 per 1000 children admitted in hospitals in Zimbabwe.

In Sudan, malaria still remains a major public health problem, where an estimated seven million new cases are registered annually with estimated 3500000 deaths in 1997.

Although severe malaria is life threatening to children, information available on the severity of disease, management, deaths and associated factors in Sudan is limited. There is, therefore, an urgent need for reliable clinico-epidemiological information on severe malaria as a killer disease in children.

The objective of the study was to assess the clinical and the epidemiological features of the disease before admission, management in hospital, outcome of the disease and factors associated with death.

METHODOLOGY
A cross-sectional study was carried out in four hospitals, Omdurman in Khartoum state, Madani and Sinnar in central Sudan and Gadrif in eastern Sudan. Children below 15 years of age of both sexes admitted to the above hospitals and diagnosed as severe malaria cases based on WHO definition for severe malaria were included. WHO defined children with severe malaria as those patients who have asexual forms of *plasmodium falciparum* in blood film and presented with any or combined complications of change of behaviour, confusion or drowsiness, altered consciousness or coma, convulsions, hypoglycaemia, acidosis, difficulty in breathing, pulmonary edema, oliguria, acute renal failure, severe anaemia (haematocrit <20%, Hb<6g/dl), haemoglobinuria, jaundice, the tendency to bleed, and generalized weakness rendering the patient unable to walk or sit up without assistance.

The study was performed in a period of five months, between August and December 2000. Daily records of paediatric admissions to hospitals and of children admitted because of malaria in four selected hospitals and children diagnosed with severe malaria based on WHO criteria and were reviewed and checked by trained medical officers and verified by a senior pediatrician in each hospital.

Interviews for background information (name, age, gender, symptoms, duration of illness, accessibility to hospital, and time taken to reach the hospitals) using a questionnaire, were performed with mothers or co-patients of children admitted and diagnosed as severe malaria during the study period by trained social workers. Research assistants and field supervisors checked the completion of questionnaires and answers immediately after the interviews in the hospitals on a daily basis.

A checklist with clinical information and procedures relevant to the cases and case management of severe malaria in children were reported for each case by medical officers and checked by the senior paediatricians in the hospitals. This information included the age of the children; gender; previous attack; duration of illness; early symptoms and signs; treatment before and on admission; diagnostic tests and results for blood film, parasite count, Hb count, blood glucose, white blood count, haemoglobin in urine, cerebrospinal fluid analysis and outcome (hospital case fatality rate of severe malaria in children); management; complications developed. Laboratory tests for malaria were checked in the Malaria Reference Laboratory of Federal Ministry of Health and based on these results, the cases were included in the study.

Reliability and internal validity were certified through a pilot test for the data collection tools (questionnaires and checklist) done in Khartoum
teaching hospital. A scoring system for hospital management performance was developed with six criteria which were considered essential for the care of severe malaria in children. A consensus on those six criteria was reached by all senior pediatricians working in these hospitals. These criteria were: performance of thick and thin blood film for malaria, white blood count, haemoglobin count, blood glucose, lumbar puncture and the introduction of intravenous quinine. The score system was developed according to the percentage of performance as following: Performance of 90–100% got 10; 80 to less than 90% was 8; 60% to less than 80% got 6; 50% to less than 60% got 5 and less than 50% got 1 (one). The study hospitals were then compared.

Data were analyzed using computer statistical software package (SPSS). Mean, standard deviation, median, percentiles, percentages, tables and figures were used to summarize the data. Relative Risk and Rate Ratio (RR) were used to assess the risk factors, 95% confidence interval was used to assess the significant difference.

RESULTS

Epidemiological findings

Total malaria load compared to total paediatric admissions was 21% (4462/20944). Malaria load in Sennar compared to the total malaria in our area was 2008/4462. Severe malaria load from total malaria outpatient attendance children was 12% (543/4462). However, most of the severe malaria cases in children were reported in Sennar which had 304 cases (56%) followed by Madani 99 cases (18.2%) and Gadarif 65 cases (12%). Severe malaria rate i.e severe malaria cases from the total malaria cases seen during the study period in the target hospitals was highest in Omdurman hospital in the north of Sudan 20% (75/357), followed by Sennar 12% 304/2526, Madani 12% (99/821) and Gadarif 8.4% (65/776) (Table 1).

The median age of children with severe malaria was 48 months and the 75 percentile for age was 72 months. The disease affected male and female equally. The median age of children who died from severe malaria was 66 months. Thirteen out of fourteen (93%) deaths occurred below 9 years (before adolescence). Only one child of 12 years old died of severe malaria with coma.

Ninety-seven percent of the children with severe malaria had the normal weight for age. Mean duration of severe malaria in children before admission was 4.46 days (SD 2.57).

Table 1: Severe malaria rate in children by hospitals, Sudan 2000

| Hospital      | Total malaria load | Severe malaria cases | Severe malaria rate | Severe malaria cases | Case fatality rate (%) |
|---------------|--------------------|----------------------|---------------------|----------------------|------------------------|
| Omdurman      | 375                | 75                   | 20.0                | 0                    | 0.0                     |
| Sennar        | 2526               | 304                  | 12.0                | 4                    | 1.3                     |
| Madani        | 821                | 99                   | 12.0                | 3                    | 3.0                     |
| Gadarif       | 776                | 65                   | 8.4                 | 7                    | 10.8                    |
| Total         | 4462               | 543                  | -                   | 12                   | -                       |

Clinical findings

History of fever was commonly stated in 528/543 (97.5%) of the cases, 16/480 (3%), developed hyperpyrexia, i.e body temperature more than 40 degree centigrade). Majority of children 95.7% had a normal weight for age. Convulsions were reported in 255 (47%), anaemia (Hb count <7 g/dl) was found in 337out of 543 (62%). Severe anaemia (Hb < 5 g/L was found in 90 (17 %). Parasite count was done for 302 patients (56%). Heavy parasitemia (number of parasites > 10 000 per µl) was found in 218 cases (72%), 95% CI was (67%-72%). Heavy parasitemia was the cause of anaemia for 131/187 cases (70%), 95% CI was (63%-77%). Children who presented with severe malaria with coma were 198 (36.5%); cerebral malaria, the commonest complication was in 453/543 (83%) cases. Spleenomegaly was found in 199 (36.6%), hepatomegaly in 1222 (22.8). Children who received quinine and had hemolysis were 25 out of 310 (8%, 95% CI 5-13%), i.e children with G6PD (Glucose 6 Phospate dehydrogenase deficiency were, between 5%-13%; Eleven of them (developed jaundice) and only one of them (4%) with very dark urine died. Test for thrombocytoppenia was not done. Leucocytosis was found in 33/133, 23% (95% CI =17% - 30%) of cases (Table 2).

Different clinical complications were observed in different states. Sennar had the highest number presenting with convulsions 148/255 (58%), followed by Omdurman hospital 42/255 (16.5%). Also Sennar had the majority of cases presenting with severe malaria and coma 133/198 (67%), followed by Gadarif 30/198 (15%). Severe malaria with anemia was
commonest in Sennar 200/337 (59%) followed by Madani 79/337 (23%) (Table 3).

Table 2: Symptoms, signs and laboratory data in 543 children with severe malaria from four states in Sudan 2000

| Symptoms, Signs and Lab abnormalities | No. (%) |
|--------------------------------------|---------|
| **Symptoms:**                        |         |
| Fever                                | 528 (97.2) |
| Vomiting                             | 222 (23.6) |
| **Signs:**                            |         |
| Anaemia (Hb <7.5 g/dl)               | 337 (62.0) |
| Jaundice                             | 11 (2.0) |
| Hepatomegaly                         | 122 (22.8) |
| Splenomegaly                         | 199 (36.6) |
| Coma                                 | 198 (36.5) |
| Convulsion                           | 255 (47.0) |
| **Laboratory abnormalities:**         |         |
| Haemoglobinuria (<5 g/dl)            | 90 (16.6) |
| WBC >1100/mm3 (n=144)                | 31 (22.0)* |
| Haemoglobinuria                      | 14 (6.0) |
| Blood sugar <60 g/ml (hypoglycemia)  | 113 (21.0) |

Management plan and performance

Omdurman hospital had the highest management performance percentage (75%) followed by Sennar (47%), Gadarif (38%) and Madani (25%) (Table 4). Thick blood film for malaria got the highest performance in all hospitals (89 – 98%), whereas lumbar puncture was poorly done in all hospitals (range from 1% to 2% of patients). The critical management differences, needing urgent action was the use of an initial dose of parenteral intravenous quinine on the first day in hospital. Omdurman hospital had the highest performance in the use of parenteral quinine as initial dose for 70/75 patients (93.3 %), followed by Sennar 174 patients (57.2 %), Gadarif 30 patients (46.2 %) and Madani 36 (36.4 %).

Unavailability of I.V Glucose was the reason for not giving parenteral quinine by most doctors (all of them were from Sennar) 51/90 (55.7 %), followed by presence of anaemia (quinine is contraindicated for anaemic cases in severe malaria) 20/90 (22.2 %) and difficulty in finding the veins 19/90 (21.1 %).

Disease outcome

The total number of children who died from severe malaria was 14 out of 543 children giving a total case fatality rate of 2.6%. No deaths occurred in Omdurman hospital, whereas the fatality rate in Gadarif was 10.8% (7/65), followed by 3% (3/99) in Madani hospital and 1.3% (3/304) in Sennar (Table 1).

Cerebral malaria was the commonest cause of death. The majority of children (93%) who died were under 9 years old, making the risk of dying for children below the age of nine twice as much as those above nine. Relative risk of mortality due to delay in seeking treatment for children with severe malaria was 13.7, 95% CI was 9.1–20.6 and attributable risk was 87.9%.

The risk of dying of severe malaria in patients who go into coma was significantly five

Table 3: Distribution of the commonest clinical presentation of severe malaria in children by hospitals in four states, Sudan, 2000

| Clinical presentation | Sennar No. (%) | Madani No. (%) | Gadarif No. (%) | Omdurman No. (%) | Total No. (%) |
|-----------------------|----------------|---------------|----------------|-----------------|---------------|
| **Convulsions**       | 148 (58.0)    | 36 (14.0)     | 29 (11.0)      | 42 (17.0)       | 255 (100)     |
| **Coma**              | 133 (67.2)    | 16 (8.0)      | 30 (15.2)      | 20 (10.1)       | 198 (100)     |
| **Anaemia**           | 200 (59.3)    | 76 (22.6)     | 27 (8.0)       | 34 (10.1)       | 337 (100)     |

Table 4: Management performance index for optimum care of severe malaria in children by hospitals, Sudan 2000

| Hospitals | BF | WBC | Hb | Blood glucose | Lumbar puncture | IV Quinine | Total Score | MP % |
|-----------|----|-----|----|--------------|-----------------|-----------|-------------|------|
| Maximum score | 10 | 10  | 10 | 10           | 10              | 10        | 10          | 100  |
| Hospital A - % (Score) | 95.0 (10) | 95.0 (10) | 57.0 (5) | 97.0 (10) | 1.0 (1) | 93.0 (10) | 46 | 77.0 |
| Hospital B - % (Score) | 98.0 (10) | 11.0 (1) | 14.0 (1) | 95.0 (10) | 2.0 (1) | 57.0 (5) | 28 | 47.0 |
| Hospital C - % (Score) | 89.0 (8) | 40.0 (1) | 78.0 (6) | 72.0 (6) | 2.0 (1) | 46.0 (1) | 23 | 38.0 |
| Hospital D - % (Score) | 96.0 (10) | 40.0 (1) | 1.0 (1) | 40.0 (1) | 2.0 (1) | 36.0 (1) | 15 | 25.0 |

Hospital A=Omdurman, B=Sennar, C=Gadarif, D=Madani
BF=Performance of blood film for malaria, thick and thin; WBC=Performance of White Blood Count; Hb=Performance of Haemoglobin count; IV Quinine=Performance of intravenous Quinine; MP=Management performance
Table 5: Risk of dying from severe malaria in Sudanese children, 2000

| Risk               | Died | Recovered | Total | Case fatality rate % | Relative risk 95% CI | Attributable risk % |
|--------------------|------|-----------|-------|----------------------|----------------------|---------------------|
| Coma:              |      |           |       |                      |                      |                     |
| Yes                | 10   | 188       | 198   | 5.1                  | 4.3 (1.2-13.3)       | 76.0                |
| No                 | 4    | 341       | 345   |                      |                      |                     |
| Cannot sit:        |      |           |       |                      |                      |                     |
| Yes                | 13   | 197       | 210   | 6.2                  | 20.6 (2.7-157.6)     | 95.0                |
| No                 | 1    | 332       | 333   |                      |                      |                     |
| Cannot eat:        |      |           |       |                      |                      |                     |
| Yes                | 13   | 196       | 209   | 6.2                  | 20.8 (2.7-157.7)     | 95.0                |
| No                 | 1    | 333       | 334   |                      |                      |                     |
| Age in months:     |      |           |       |                      |                      |                     |
| 1-108              | 13   | 382       | 395   | 3.3                  | 4.9 (3.4-14.8)       | 91.0                |
| >108               | 1    | 144       | 145   |                      |                      |                     |
| Delays:            |      |           |       |                      |                      |                     |
| Yes                | 12   | 46        | 56    | 21.4                 | 13.7 (9.1-20.6)      | 88.0                |
| No                 | 2    | 128       | 130   |                      |                      |                     |
| Hyperpyrexia:      |      |           |       |                      |                      |                     |
| <40°C              | 460  | 4         | 464   | 1.0                  | 20.8 (16.7-91.6)     | 95.0                |
| >40°C              | 13   | 3         | 16    |                      |                      |                     |
| Convulsions:       |      |           |       |                      |                      |                     |
| Yes                | 5    | 250       | 255   | 2.0                  | 0.63 (0.2-1.8)       | 33.0                |
| No                 | 9    | 279       | 288   |                      |                      |                     |
| Leucocytosis:      |      |           |       |                      |                      |                     |
| <11000/mm³        | 4    | 98        | 102   | 3.9                  | 2.5 (-1.9-11.2)      | 60.0                |
| ≥11000/mm³        | 3    | 28        | 31    |                      |                      |                     |

CI=95% confidence interval

times more than those who did not go into coma. The 95% confidence interval was (1.5 – 14.3). The risk of children dying with severe malaria and hyperpyrexia was high; it was more than 20 times for those who had severe malaria without hyperpyrexia, (95% CI 16.7 – 91.6). Children with severe malaria with leucocytosis had two times risk of dying compared to those with normal total white blood count. However, the difference was not significant, 95% CI was ( -1.9 – 11.2). Also children with severe malaria and convulsions had a relative risk of 0.63, though the difference from children without convulsions (95% CI = 0.2–1.8) was not significant (Table 5).

DISSCUSION

The rates of severe malaria were different in the different hospitals, the highest being obtained in Omdurman hospital in the north of Sudan. This rate decreased from north to south, 12% in a Madani and Sennar, and 8% in Gadarif. Also clinical presentations of severe malaria, were different when compared in different hospitals (Table 3). This result revealed that the epidemiological context of the different state influences the occurrence, presentation and mortality associated with severe malaria. The same results were also obtained by Sodiomon, who analysed severe malaria presentation in Ouagadougou University Hospital and compared them to the Sourou and Nayala district hospitals located in different areas with different endemicity.6

Based on the results of this study, severe malaria in children was a disease of young children with a median age of 4 years; 75% of the children were below 6 years of age. The majority of mortalities (93%) occurred below the age of nine. This result agreed with a previous study by Imbert and Luxerborg,7,8 who reported that severe malaria cases and deaths decreased with increasing age.

The results of this study showed a normal nutritional status of children with severe malaria. Similar results were obtained by Esamai F. et al in western Kenya9 who reported that a majority of children with severe malaria (95.7%) had a normal weight for age.

No death occurred in Omdurman (which is in the capital) where there was better management performance. Omdurman hospital had high management performance (93.3%) in prescribing
initial parenteral quinine treatment which reflects good training and proper management. This was absent in other regional hospitals which faced two problems, the first being a resource problem, the unavailability of quinine in some of the state regional hospitals (not in Omdurman), and the second the simple skill of finding veins. This reflects the lack of technical training in the regional hospitals as well as inappropriate central health planning and distribution of resources (including health personnel). As indicated by WHO, proper disease management cannot be expected if the formal proper health services are absent. One of the priorities of government should be to improve the accessibility to good quality care for malarial patients.\textsuperscript{10}

The study revealed that deaths resulting from severe malaria was higher in younger children (less than 9 years). This means it is necessary to pay greater attention to those children belonging to the high risk group. Delay was one of the risk factors leading to death as a result of severe malaria. It is a non-medical factor that can easily be avoided by raising the awareness of parents through health education. Deaths could be reduced by 88\% if delays were avoided (population attributable risk was 88\%) (Table 7). The same results were obtained by Ejov et al, from Myanmar. In his hospital-based study of severe malaria, he reported that the proportion of deaths increased with highest duration of illness before admission.\textsuperscript{11}

\textbf{CONCLUSION}

The severity of malaria is affected by seasonality in the different areas in different epidemiological contexts. Malaria control strategies should, therefore, take into consideration the different epidemiological contexts in the different states in Sudan.

Children below 9 years, delay in seeking treatment and severity of the illness at admission are the major risk factors of disease mortality that could be easily avoided. Better management performance was found in the central hospitals compared to regional hospitals. In view of this, it is argued that the incidence of malaria could be reduced by improving the planning, resource distribution (including health personnel) and provision of proper training to medical staff.

Raising the awareness of parents, and health education on avoidance of delay in seeking treatment will reduce mortality resulting from severe malaria.

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