Characterization and Treatment of Severe Malaria in Hospitalized Children at a Ghanaian District Hospital

R.N.K. Gyapong[1], M. Duwiejua[*,1], F.Y. Bio[2], E. Woode[3], C. Ansah[3], F.T. Owusu-Daaku[1] and K.O. Buabeng[1]

[1]*Department of Clinical and Social Pharmacy, Faculty of Pharmacy & Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science & Technology (KNUST), Kumasi, Ghana*

[2]*Department of Community Health, School of Medical Sciences, College of Health Sciences, KNUST, Kumasi, Ghana*

[3]*Department of Pharmacology, Faculty of Pharmacy & Pharmaceutical Sciences, College of Health Sciences, KNUST, Kumasi, Ghana*

Abstract: *Objective*: To document the demography of paediatric admissions due to severe malaria, presentation and determinants of clinical symptoms and treatment for the condition at the KNUST Hospital, Ghana.

Methods: A prospective, non-randomized, observational study was undertaken at the Children's Ward of the KNUST Hospital, in Kumasi. During a one month period, the symptoms on admission, treatment and treatment outcome of included children were documented. Inclusion criteria were age 0-144 months, verbal informed consent and severe malaria defined by presence of asexual *Plasmodium falciparum* parasitaemia coupled with at least one criterion suggestive of severe malaria as defined by WHO.

Results: Overall, there were 82 malaria admissions with 69 cases being enrolled. On admission, mean haemoglobin levels were consistent for both males and females. Mean body weight was higher for females. Main presentations were anaemia of moderate to severe form (56); fever (52) and convulsions (24). Prostration was observed in all cases. Children under 5 years of age were associated with anaemia (p=0.018) and neurological symptoms (p=0.003). Clinical presentation of severe malaria was found to be independent of patients' sex. Quinine was used as treatment in 17 cases; monotherapy with artemisinin derivatives in 26 cases and artemisinin-amodiaquine combinations in 19 of the cases. No deaths were recorded.

Conclusions: Children under 5 years of age presented more often with severe malaria. Prostration, anaemia and neurological symptoms were the most frequent manifestations.

Key Words: Severe malaria, anaemia; convulsions; prostration, quinine, artemisinin.

INTRODUCTION

Globally, malaria-attributable death rates have been estimated to be as high as 75 % of all deaths in children under the age of five years in Africa [1]. In Ghana, malaria accounts for approximately 44% of reported outpatient cases and an estimated 22% of mortality in children under-5 years of age at primary health care facilities [2]. Complications of malaria in children include metabolic acidosis (often caused by hypovolaemia), hypoglycaemia, hyperlacticacidaemia, severe anaemia, seizures and raised intracranial pressure [3].

The clinical presentation of severe malaria is affected by a number of factors including the genetic characteristics of the population, malaria epidemiology, health-seeking behaviour and non-malaria co-morbidity [4-8]. Other determinants of malaria severity are age, geographic location and level of transmission [9-11].

Prompt early recognition of the signs and symptoms, followed by administration of appropriate parenteral antimalarial agents is crucial to the successful management of severe malaria.

Since knowledge of the local clinical and epidemiological spectrum of severe malaria is critical for early diagnosis and successful treatment of the disease, we sought in this study to describe the presentation of severe malaria at the time of admission, the prevalence and determinants of clinical symptoms, and to assess appropriateness of pharmacotherapy for the condition at the Kwame Nkrumah University of Science and Technology (KNUST) Hospital, Ghana.

SUBJECTS AND METHOD

Study Site

The study was conducted at the KNUST Hospital. The hospital is situated approximately eight miles to the east of

*Address correspondence to this author at the Office of the Dean, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, KNUST, Kumasi, Ghana; Tel: +233 51 60 359 / +233 20 815 0189 (mobile); Fax: +233-51-60137; E-mails: mahama_duwiejua@yahoo.com, mduwiejua.pharm@knust.edu.gh

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Kumasi, the capital of the Ashanti region of Ghana. It is classified as a district hospital by the Ministry of Health of Ghana – a hospital that serves as the main referral point for surrounding health facilities. The hospital serves a catchment area population of approximately 300,000 including the University community (with an estimated population of 150,000 as at June, 2008) and surrounding localities. Malaria is holoendemic in this area with an entomological inoculation rate (EIR) of about 400 infective bites per individual per year. The average annual attendance is estimated at 112,000 with approximately 4,397 admissions per year. Malaria in all ages accounts for an annual average of 45,762 attendances, constituting 40.9% of average annual attendances. Paediatric attendance accounts for 9.8% (11,028/112,000) with annual average of 1150 admissions. The Children's Ward of the hospital is a 24-bed ward.

Study Design

A prospective, non-randomized, observational study, spanning a one-month period (May, 2008) was undertaken at the Children's Ward of the KNUST Hospital, in Kumasi. All new paediatric admissions over the stipulated study period were captured. Included in this study were patients who showed a positive blood film for asexual forms of *Plasmodium falciparum,* were aged 0-144 months (inclusive), expressed at least one symptom suggestive of severe malaria (Table **1**) and whose parents/care-givers gave verbal informed consent.

Patients already on admission with either severe malaria or some other medical condition, on commencement of the study were not enrolled. Patients admitted during the study period but whose clinical presentation, on admission, was due to a cause other than severe malaria were also excluded.

All data were captured on structured case report forms bearing patient demographic information and identification numbers to ensure confidentiality. The symptoms on admission, treatment and treatment outcome for each patient were recorded.

Definitions

Severe malaria was defined by an asexual *Plasmodium falciparum* parasitaemia, with at least one of the following criteria, and no apparent, non-malarious cause of these symptoms [11]:

Fever was defined as axillary temperature > 37.5^{o}C. Parasitaemia was determined by Giemsa-stained thick blood films. High parasitaemia was defined by 11-100 parasites per 100 thick film fields (++), 1-10 parasites per single thick film field (+++), or >10 parasites per single thick field film (++++). Low parasitaemia (+) referred to 1-10 parasites per 100 thick film fields. Dosages of anti-malarial agents were deemed incorrect if the drug dose, frequency of administration or duration of therapy did not conform with recommended guidelines, either individually or collectively.

Guidelines on Treatment for Severe Malaria

At the time of this study, the national recommended treatment for severe malaria was as follows: Quinine (10mg/kg body weight of dihydrochloride salt, maximum 600mg, 8 hourly given intravenously over 4 hours until patient can tolerate oral quinine to complete a full 7-day course. In previously untreated patients, a loading dose of 20mg/kg body weight is given. Alternatively, intramuscular injections of 10mg/kg of quinine dihydrochloride may be given 8 hourly until oral therapy can be tolerated) *or* Artemisinin derivatives (artemether - 3.2 mg/kg body weight intramuscularly on the first day, followed by 1.6 mg/kg body weight daily for a minimum of 3 days until the patient can take oral treatment or another effective antimalarial; artesunate – 2.4 mg/kg body weight on the first day, followed by 1.2 mg/kg body weight daily for a minimum of

Table 1. WHO Definition Criteria for Severe Malaria

Sign/Symptom	Definition
Severe anaemia	Hb < 5g/dL or PCV< 15%
Prostration	Inability to sit or drink/eat, although normally able to do so
Respiratory distress	Sustained nasal flaring, subcostal recessions or Kussmaul breathing
Hyperpyrexia	Axillary temperature > 40^{o}C
Multiple convulsions	History of convulsions within preceding 24 hours, and one directly observed convulsion
Impaired consciousness	Blantyre score ≤ 4
Coma	Blantyre score ≤ 2
Hypoglycaemia	Whole blood glucose <2.2mmol/L
Circulatory collapse	Systolic blood pressure <60 and <80 mm of Hg in children ≤5 and >5 years of age, respectively, with cool limbs, or weak or absent peripheral pulses
Hyperlactataemia	Lactate ≥5mmol/L
Haemoglobinuria	Dark red or black urine and positive urinalysis dipstick test for Hb, with absence of microscopic haematuria

*Hb – haemoglobin, PCV – packed cell volume.

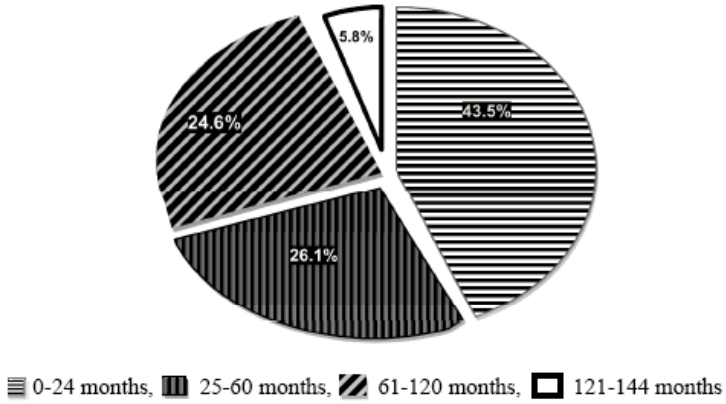

Fig. (1). Age distribution of severe malaria cases.

3 days until the patient can take oral treatment or another effective antimalarial) [12].

Ethical Clearance

The study protocol was approved by the Committee on Human Research, Publications and Ethics (CHRPE), of the School of Medical Sciences, College of Health Sciences, KNUST.

Data Analysis

Data analysis was done using SPSS for Windows statistical software, version 16. Basic statistics (proportions and means) were calculated for baseline characteristics (weight, temperature, parasitaemia and haemoglobin levels). Standard deviations were determined for means and 95% confidence intervals calculated for proportions. Prevalence of clinical and laboratory features were determined by age group and sex. Pearson's chi-square test, with Yates' continuity correction was used to determine association between the occurrence of clinical symptoms and age, sex and level of parasitaemia. Comparisons between groups were made also by chi-square. Odds ratio for the association of risk of anaemia, fever and neurological symptoms in high parasitaemia, were determined. Statistical significance was set at $p < 0.05$.

RESULTS

Demography

Out of 96 children admitted over the study period, 82 cases (85.4%) were due to malaria. Severe malaria represented 84.2% (69/82) of the cases. There was one case of neonatal malaria.

Fig. (**1**) describes the age distribution of enrolled patients. Forty-three percent (30/69) of children who satisfied criteria for severe malaria were aged less than 2 years (Fig. **1**). Males accounted for 62.3% (43/69, p = 0.002) of severe malaria admissions. The median age for enrollees was 36 months.

Baseline Characteristics

Majority (67/69) of the children admitted with severe malaria had experienced at least one previous episode of

Table 2. Baseline Characteristics of Enrolled Children, by Age and Sex

Age (months)	Parasitaemia n(%)				Hb(g/dL) mean±SD	Weight(kg) mean±SD
	1+	2+	3+	4+		
0-24 [n=30]	10(33.3)	6(20.0)	10(33.3)	4(13.3)	8.0 ± 2.4	9.6 ± 2.3
25-60 [n=18]	6(27.8)	9(50.0)	2(11.1)	2(11.1)	8.7 ± 2.8	15.3 ± 4.2
61-120 [n=17]	6(35.3)	5(29.4)	6(35.3)	0	12.0 ± 7.4	24.6 ± 4.2
121-144 [n=4]	2(50.0)	1(25.0)	1(25.0)	0	11.0 ± 1.5	27.3 ± 2.9
Sex						
Male [n=43]	14(32.6)	14(32.6)	12(27.9)	3(7.0)	8.9 ± 2.4	15.2 ± 7.3
Female [n=26]	9(34.6)	7(26.9)	7(26.9)	3(11.5)	8.9 ± 2.6	16.9 ± 7.7

*Hb- haemoglobin; SD=standard deviation.

Table 3. Prevalence of Clinical Observations by Compressed Ages and Sex

Clinical Manifestation	0-60 Months (N=48) n(%)[95%CI]	61-144 Months (N=21) n(%)[95%CI]	Males (N=43) n(%)[95%CI]	Females (N=26) n(%)[95%CI]
Mild/moderate anaemia	33(68.75%) [57.99-83.67]	13(61.90%) [35.97-78.31]	33(76.74%) [64.11-89.37]	13(50%) [30.78–69.22]
Severe anaemia	10(20.83%) [9.34-32.32]	0	5(11.63%) [2.05–21.21]	5(19.23%) [4.09–34.38]
Fever	37(77.08%) [65.19-88.97]	15(71.43%) [46.5-86.84]	31(72.09%) [58.68–85.5]	21(80.76%) [60.72–93.12]
Neurological Symptoms And Prostration				
Prostration only	24(50.00%) [35.85-64.15]	19(90.48%) [77.93-103.03]	28(65.12%) [50.87–79.37]	15(57.69) [38.7-76.68]
Prostration+ Convulsions	22(45.83%) [31.73–59.93]	1(4.76%) [-4.35–13.87]	13(30.22%) [16.49–43.95]	10(38.46%) [19.76–57.16]
Prostration + Impaired consciousness	1(2.08%) [-1.96–6.12]	1(4.76%) [-4.35–13.87]	1(2.33%) [-2.18–6.84]	1(3.85%) [-3.55–11.25]
Prostration + Convulsion + Impaired consciousness	1(2.08%) [-1.96–6.12]	0	1(2.33%) [-2.18–6.84]	0

malaria within the preceding 12 months. High parasitaemia was detected in 66% (46/69) of all severe malaria cases (Table **2**). Mean haemoglobin levels and body weights were higher in older children, at time of admission. Female children presented with a higher mean body weight. Baseline falciparum parasitaemia of 4+ was observed only in children under 5 years of age (Table **2**).

Characteristics of Severe Malaria

Overall, 91% (63/69) of enrolled patients presented with gastrointestinal symptoms – vomiting (31); diarrhoea (24); vomiting and diarrhoea (8).

Table **3** shows the prevalence of clinical manifestations of severe malaria in the cases under review. Whereas mild to moderate anaemia was common in all patients, children under 60 months were more likely to develop severe anaemia and a combination of neurological symptoms - prostration, convulsions, impaired consciousness; ($\chi^2_{(corrected)}$ = 5.621; p=0.018 and $\chi^2_{(corrected)}$ = 8.541; p=0.003**,** respectively; Table **3**). Proportions of both clinical features were significantly higher in the under 5-year group (anaemia-χ^2=0.31; p= 0.007; neurological symptoms- χ^2 = 0.359; p=0.001). The presentation of neither anaemia nor the neurological symptoms was influenced by sex of the patient ($\chi^2_{(corrected)}$ = 2.732; p=0.098 and $\chi^2_{(corrected)}$ = 0.130; p=0.719, respectively; Table **3**). Fever was independent of both age ($\chi^2_{(corrected)}$ = 0.039; p=0.843) and sex of the patient ($\chi^2_{(corrected)}$ = 0.273; p=0.602) (Table **3**).

Prevalence of fever was however predictably significantly higher in patients with higher levels of parasitaemia (χ^2= 0.309; p=0.023; Table **4**). Differences in prevalence of anaemia and neurological symptoms were observed between patients with low and high levels of parasitaemia (Table **4**), albeit not significant (anaemia - χ^2= 0.21; p=0.082; neurological symptoms - χ^2= 0.213; p=0.077). The risk of developing fever was increased by a factor of 4.29 in high parasitaemia (Table **4**). Prostration was observed in all cases.

Treatment

Table **5** indicates the medications used. A total of 62 (89.9%) cases were given the right choice of medication (Artemisin derivative:26, Artemisin+Amodiaquine:19, Quinine:17). The dosage regimen used for either Artemsinin derivative alone or Quinine were according to recommendations from the National Treatment Guidelines

Table 4. Parasitaemia in Relation to Anaemia, Fever and Neurological Symptoms

Variables	Low Parasitaemia N=23	High Parasitaemia N=46	High Parasitaemia Odds Ratio (95%CI)
Anaemia [n (%)]	16 (69.6)	40 (87.0)	2.92 (0.85 to 10.03)
Fever	13 (56.5)	39 (84.8)	4.29*(1.35 to 13.56)
Neurological symptoms	5 (21.7)	21 (45.7)	2.77 (0.88 to 8.74)

*p = 0.01

Table 5. Antimalarial Chemotherapy

Medication Prescribed [encounters]	Number of Encounters (%) in Compliance with National Treatment Guidelines
Chloroquine [n=5]	Not a recommended medicine
Artemisinin derivative only [n=26]	22 (84.6)
Amodiaquine only [n=1]	Monotherapy not recommended
Artemisinin + Amodiaquine [n=19]	12 (63.2)
Artemisinin + Lumefantrine [n=1]	1 (100)
Quinine [n=17]	14 (82.4)

[12] in over 80% of the encounters (Artemisinin derivative: 84.6%, Quinine: 82.4%). However, compliance with dosage recommendations of Artesunate+Amodiaquine was appropriate in only 63.2% of the cases. Chloroquine (obsolete) was used in five cases and Amodiaquine alone was used in one case. One case was treated with Artemisinin + Lumefantrine combination.

Treatment Outcome

After an average bed stay of three days, all enrolled patients showed improvement in clinical state and were discharged accordingly. Minimum and maximum duration of hospitalization were 1 and 7 days respectively. No deaths were recorded.

DISCUSSION

We have described the presentation, prevalence and treatment of severe *Plasmodium falciparum* infection in children on admission at a district hospital, within the Kumasi metropolis. Although results gathered may indeed be a fair index of the prevalence of severe malaria among children with malaria attending the hospital, the figure does not reflect the prevalence of all malaria cases in the study area as most cases of malaria infections are treated at either the household or community pharmacy level without ever getting to the hospital.

The proportion of male children admitted with malaria was significantly higher than females. This observation is consistent with reports from Tanzania [13], northern Ghana [8] and Gabon [5]. Although males may indeed be more liable to develop severe malaria, sociological reasons often suggest that this trend is indicative of household-level gender bias in treatment-seeking behaviour for male children. In our view, a more plausible explanation may be that older male children, by default, tend to spend longer periods outdoors, thereby increasing their exposure to the vector.

A greater part of the morbidity burden was borne by the under 5 age group; with children aged under 2 years accounting for nearly half of all cases enrolled. This finding is in consonance with a report by Snow and others [14] that in highly endemic zones, severe malaria mainly affects younger children. This predominance in younger children could be attributed to a lack of adequate clinical immunity against the disease.

Ninety-seven percent of enrollees had experienced at least one previous malaria episode within the 12 months preceding the study. Treatment for majority of these had been effected outside of the hospital setting. Consequently, questions regarding the appropriateness of any previous therapy come up prominently. Current illness could therefore have resulted from either failure of previous inadequate home-based treatments or from post-treatment re-infection.

Anaemia was a common clinical feature, presenting in over 80% of cases. Severe anaemia (Hb< 5g/dL or PCV< 15%) was however less frequently observed (14% of all cases). Association of anaemia with malaria is expected from the effect of the life cycle of the plasmodium parasite in humans. The low prevalence of severe anaemia in our subjects may be explained by factors like patients Hb level before infection, duration of infection and self medication with haematinics before admission. At the time of admission, a good proportion of patients presented with gastroenteritis manifested by diarrhoea and vomiting. Dehydration-induced haemoconcentration could have caused an underestimation of severe anaemia prevalence by spuriously increasing haemoglobin concentrations. Similar to previous reports [10, 14], severe anaemia was associated with age, showing a significant inverse correlation. In contrast with this, sex did not influence the pattern of expression of severe anaemia.

Contrary to earlier reports of neurological involvement being more common in low transmission zones and in older children [15], the symptoms, particularly convulsions, were common in younger children in our study. Here also, neurological symptoms were independent of sex of the patient.

Fever, a characteristic feature of *falciparum* infection, was seen in about 75% of all eligible cases. As with anaemia and neurological symptoms, fever was also independent of sex. Malaria infections are complicated syndromes involving many inflammatory host-derived factors such as cytokines. Parasite antigenic products stimulate the overproduction of tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and interleukin-1 (IL-1), which adversely affect disease progression [16]. These cytokines, among other effects, cause changes in the host such as fever, suppression of bone marrow and erythrocyte production, coupled with direct destruction of host erythrocytes [17]. It is reasonable to expect, therefore, that high levels of parasitaemia would correlate directly with incidence of fever and anaemia. Fever was indeed significantly higher in the high parasitaemia

group. A sizeable proportion of severe malaria reports were however afebrile on admission. Some reports [5] have attributed this observation to self-medication with antipyretics or anti-malarial medicines before reporting at the hospital. Considering the high mortality associated with the first hours of admission [4], all malaria-related paediatric admissions should receive prompt parenteral treatment, regardless of parasitaemia level. In this study, the majority of cases received appropriate medication therapy. However, though patient weights were recorded in all cases, doses were based on the age-dose relation rather than being calculated according to a uniform body weight protocol. This consequently led to some discrepancies in dosing. The deviant dosing however did not cause clinically important untoward effects in the patients as judged by morbidity and duration of hospitalization. The change of policy in malaria treatment from chloroquine to combination therapy with artemisin derivatives and amodiaquine (for uncomplicated malaria) was not well received by many prescribers and the public because of the frequency of persistent unpleasant (but not life-threatening) effects including distressing dystonic reactions associated with amodiaquine use. This probably accounted for the use of unapproved medicines like chloroquine and arthemeter-lumefantrine (this medicine is now included in the guidelines).

In conclusion, children under 5 years are more vulnerable to the pathological effects of malaria. Prostration, anaemia, fever and convulsions make up the clinical spectrum of severe paediatric malaria, in the study area. Clinical presentation of severe malaria was independent of patients' sex. We recommend that any child presenting at the KNUST hospital with the spectrum of clinical symptoms described above should be investigated for malaria. Case treatment of severe malaria at the KNUST hospital revolved around the use of quinine and the artemisinin derivatives, either alone or in combination with amodiaquine. We reiterate the need to convince prescribers to comply with evidenced based national treatment guidelines. Mothers and care takers should be educated on the signs and dangers of severe malaria and the benefits to be gained from seeking early appropriate care.

DISCLOSURE

F.Y.B is the Director of Health Services of the KNUST and doubles as Medical Director of the KNUST hospital. The other authors declared no conflict of interest. Funding for this study was provided by the Kwame Nkrumah University of Science and Technology.

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