Pattern and Outcome of Severe Malaria among Children in Sokoto, North Western Nigeria

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ABSTRACT

Malaria still remains the leading cause of morbidity and mortality in Nigerian children. Despite the fact that it is a preventable and curable illness, its high incidence and prevalence continue unabated especially in the tropical sub-Saharan Africa. The objectives of this study was to determine the pattern of severe malaria with reference to the clinical and laboratory criteria and its outcome in children aged 1month - 15years. It was a prospective study conducted in children aged 1month 15 years with diagnosis of severe malaria admitted consecutively into the Emergency Paediatrics Unit (EPU), Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria. Information of the patients with regards to their age, gender, date of admission, presenting clinical features, results of laboratory investigations, and outcome were entered into a study pro-forma sheet and analysed. A total of 1,715 children aged 1month - 15years were admitted into EPU, UDUTH, Sokoto. Of this number, 508 (29.6%) had clinical and parasitological case defining features of severe malaria. Males were 308 (60.6%) while the females were 200(39.4%) with M: F ratio of 1.5:1. The mean age of the children was 3.5 years (±3.44) with those aged 5years and below accounting for 78% of the patients. The most frequent criteria of severe malaria were prostration (38%), persistent vomiting (35%), hyperpyrexia (31%) and multiple convulsions (25%). There were 33 deaths which gave a case-fatality rate of 6.5 %. Fatal outcome was significantly affected by the occurrence of unconsciousness (cerebral malaria) (p=0.001), prostration (p=0.04), severe anaemia (p=0.04) and respiratory distress (p=0.01). Prostration, persistent vomiting, hyperpyrexia and multiple convulsions were the most common features of severe malaria in this study. However, fatal outcome was significantly associated with occurrence of unconsciousness (cerebral malaria), prostration, respiratory distress and severe anaemia. Hence, children with either of these features should be managed with utmost care and urgency.

Keywords: Pattern, Severe Malaria, Criteria, Children, Outcome

INTRODUCTION

Malaria continues to be a major global health problem with over 40% of the world's population (3.3 billion people) being at risk[1]. It still remains the leading cause of morbidity and mortality in Nigerian children. In Nigeria, malaria is responsible for 60% of outpatient visits, 30% of childhood mortality, 25% of infant mortality and 11% of maternal deaths[2-4]. It is also responsible for 300,000 deaths in children annually, mostly between the ages of 1 and 5 years[3]. Most of these deaths occur from severe malaria due to non-recognition of its features and failure to institute prompt and adequate treatment[1,3]. Nigeria loses as much as N132 billion ($825 million) annually; in terms of treatment costs, prevention, school absenteeism, loss of man hours, and other indirect costs[2,4]. These present significant obstacles to socio-economic development.

In 1990, the World Health Organization (WHO) developed criteria for diagnosis of severe malaria. These criteria were revised in 2000 and 2014 to include other clinical and laboratory manifestations, which may indicate poor prognosis and risk of death[1,5]. In a patient with *Plasmodium falciparum* asexual parasitaemia and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as having severe malaria: impaired consciousness or unarousable coma, prostration (i.e. generalized weakness so that the patient is unable to walk or sit up without assistance), multiple convulsions (>two episodes in 24 hours), deep breathing, respiratory distress (acidotic breathing), circulatory collapse or shock, jaundice plus evidence of other vital organ dysfunction. Other features are haemoglobinuria, abnormal spontaneous bleeding, pulmonary oedema (radiological), hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl), metabolic acidosis

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(plasma bicarbonate < 15 mmol/l), severe anaemia (haemoglobin< 5 g/dl, packed cell volume < 15%), hyperparasitaemia (> 5% or 250 000/µl in areas of high stable malaria transmission intensity), hyperlactataemia (lactate > 5 mmol/l), and renal impairment (serum creatinine> 265 µmol/l)[1] and persistent vomiting (two or more in 24 hours) as modified by the Federal Ministry of Health, Abuja, Nigeria in 2005[4].

Studies have demonstrated the existence of regional variations in the pattern and epidemiologic profile of severe malaria, largely due to differences in the level of malaria transmission[6,7]. Even within the same geographic location, there may be subtle differences in the relative frequencies of specific manifestations and their resultant outcome[6]. No data is currently available on the pattern of severe malaria in children from our centre. This information is needed for comparison with findings of other studies and in the management of children with severe malaria in the study area. Hence, this study was undertaken to determine the pattern of severe malaria with particular reference to clinical and laboratory criteria for its diagnosis and to determine the factors associated with fatal outcome in children aged 1month- 15 years.

PATIENTS AND METHODS

This study was conducted at the Paediatrics Department of Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto. Sokoto is located in the extreme North-western Nigeria and has characteristic climatic factors that favours intense malaria transmission as previously highlighted by Jiya *et al*.[8]

The study was a descriptive prospective study conducted over a one-year period between 1st July 2010 and 30th June 2011.

Consecutive ***c***hildren aged 1month-15 years with diagnosis of severe malaria that presented to the Emergency Paediatrics Unit (EPU) of the hospital were recruited for the study. Those with other obvious clinical co- morbidities such as confirmed septicaemia, meningitis and sickle cell cerebrovascular accident were excluded so that outcome of the studied subjects will not be affected by them.

At the time of the study, severe malaria was defined using the WHO 2000 diagnostic criteria that was modified by Federal Ministry of health in 2005[1,4].

For each of the selected subject**,** *relevant* information with regards to age, gender, date of admission, presenting clinical features and duration of illness was obtained and entered into a study pro-forma sheet. Each of the patients also had detailed general and systemic physical examination.

Parasitological diagnosis of malaria was done by thick and thin smears microscopy using 3% Giemsa stain. A test was considered positive when asexual forms of *Plasmodium falciparum* were seen. A slide was considered negative only after 100 microscopy fields were examined without an asexual form of the parasite seen[9]. Other laboratory investigations including random plasma glucose, serum urea and creatinine, packed cell volume and blood culture were done for each patient. Additional investigations such as serum bilirubin, cerebrospinal fluid analysis, urinalysis and urine microscopy and culture, and blood culture were done where indicated.

All patients with positive malaria test on light microscopy were treated with intravenous Quinine which was recommended first line antimalarial drug at the time of the study. Alternatively, intramuscular Arthemeter and Sulphadoxime/pyrimethamine (Fansidar) were used especially where clinical and parasitological response to Quinine therapy was not satisfactory. Supportive measures such as blood transfusion, correction for hypoglycaemia and fluid therapy were instituted as necessary. The clinical outcome of each patient while on admission, at discharge and during follow up was documented.

Data Analysis

Data of all the patients with clinical and parasitological features of severe malaria were entered and analysed using statistical package for social sciences (SPSS) version 20. Quantitative data was expressed as means and standard deviations while categorical variables were expressed as proportions. Chi-square test or, where figures were small, Fisher's exact test, was used for comparison of proportions. Multiple regression analysis was used to determine factors that are independently associated with mortality. A p-value of less than 0.05 was considered statistically significant.

Ethical consideration

Ethical approval for the study was obtained from UDUTH Health Research and Ethics Committee. Informed verbal and written consent were obtained from parents or guardians of the study subjects while assent was obtained from children older than 8years where practicable. The informed consent forms were kept by the principal investigator together with the study proforma data sheets. Full confidentiality was followed regarding all recorded patients' data during and after the study.

RESULTS

A total of 1,715 children were admitted into EPU of UDUTH, Sokoto during the study period. Of this number, 508 (29.6%) had clinical and parasitological features of severe malaria. Males were 308 (60.6%) while the females were 200(39.4%) with M: F ratio of 1.5:1(Table 1). Their mean age was 3.5 ±3.44years. Children aged 5years and below accounted for 78% of the patients.

The Presenting Symptoms

Table 1: Age and Gender Distribution of Children with Severe Malaria

Age (Years)	Male	Females	Total (%)
0-1.0	89	66	155 (30.5)
1.1-5.0	155	86	241 (47.4)
5.1-10.0	43	33	76 (15.0)
10.1-15.0	21	15	36 (7.1)
Total	**308**	**200**	**508 (100.0)**

χ^2=2.643; df= 3 p=0.45

The main presenting symptoms were fever 473(93.1%), vomiting 281 (55.3%), convulsions 198 (39.0%), diarrhoea 153 (30.1%), and cough 101 (19.9%) as displayed in Table 2. The mean duration of illness among the patients with severe malaria was 2 days (SD± 1.02) with a range of 1 to 6 days.

Pattern of Diagnostic Criteria for Severe Malaria

Table 2: Presenting Symptoms among 508 Children Admitted with Severe Malaria

*Presenting symptoms	Frequency (%)
Fever	473 (93.1)
Vomiting	281 (55.3)
Convulsion	198 (39.0)
Diarrhoea	153 (30.1)
Cough	101 (19.9)
Difficulty in breathing	7 (1.4)
Poor appetite	7 (1.4)
Other symptoms	30 (5.9)

*A patient may have more than one symptom

The most frequent diagnostic criteria in the 508 children with severe malaria were prostration seen in 195(38.4%) patients; persistent vomiting in 180(35.4%); hyperpyrexia (=39.5°C) in 156(30.7%) and multiple convulsions in 128 (25.2%) patients. Less frequent manifestations included hyperparasitaemia in 87(17.1%), severe anaemia in 42(8.3%) and unconsciousness (cerebral malaria) in 36(7.1%) patients as shown in Table 3. Mean age of children with severe anaemia was 3.8

Table 3: Pattern of Severe Malaria among 508 Children

*Pattern of severe malaria	Number (%)
Prostration	195(38.4)
Persistent vomiting	180(35.4)
Hyperpyrexia	156(30.7)
Multiple convulsions	128(25.2)
Hyperparasitaemia	87(17.1)
Severe anaemia	42(8.3)
Unconsciousness (Cerebral malaria)	36(7.1)
Hypoglycaemia	19(3.7)
Respiratory distress	17(3.3)
Jaundice	4(0.8)
Disseminated intravascular coagulation	2(0.4)

*A patient may have more than one criterion

(± 3.2) years as against 4.94 (± 3.4) years for those with cerebral malaria. The difference in the mean age of the children with severe anaemia and cerebral malaria was statistically significant (t-test = 19.078, p= 0.04).

Outcome

Of the 508 children who had parasitologic diagnosis of severe malaria, 489(96.3%) were treated with IV Quinine while the remaining 19(3.7%) patients were given combination of intramuscular Arthemeter and Sulphadoxime/pyrimethamine (Fansidar). The duration of hospitalisation was = 6 days in 428(84.3%) patients and = 7 days in the remaining 80(15.7%) patients. Four hundred and seventy five patients recovered while 33 died, giving a case-fatality rate of 6.5 %. The mean age of patients that died was 3.5 (±3.1 SD) years compared to 4.98 (± 3.5 SD) among survivors. The difference in age between those that survived and those that died was statistically significant (t-test = 19.078; p =0.04). Outcome was significantly affected by the following criteria: Unconsciousness (cerebral malaria) (p = 0.001), prostration (p= 0.04), severe anaemia (p= 0. 04), and respiratory distress (p= 0.01). After logistic regression analysis, only cerebral malaria and respiratory distress were found to be independent predictors of death.

Cerebral malaria accounted for 9/33 (27.3%) of the deaths, severe malaria anaemia 8/33(24.2%), prostration 4/33(12.1%), multiple convulsions 4/33(12.1%) and respiratory distress 3/33(9.1%) patients. Of the 27 survivors of cerebral malaria, 7(25.9%) had neurologic sequelae such as generalized spasticity, seizure disorder, cortical blindness and attention deficit hyperactivity disorder. These sequelae resolved completely in all the patients within 6 weeks of outpatient follow - up.

DISCUSSION

The present study shows that severe malaria is a significant cause of morbidity and mortality in hospitalized children in our Emergency Paediatrics Unit (EPU). The high proportion of children with this condition in this study is consistent with what has been previously described by many studies,[6, 10-14] including that of Modiano *et al.* in Burkina Faso[6] and Dzeing-Ella *et al* in Gabon[13]. The result further highlights the fact that malaria still remains a major public health problem[4,10].

Like other studies,[6,11-14] majority of patients that had severe malaria in this study were children aged 5 years and below. The increased susceptibility of under-fives to malaria infection is related to the pattern of malaria transmission and immunity in a population[11]. In areas with stable malaria transmission (hyper endemicity), such as sub-Saharan Africa, there is a well-recognized change in immunological status of the indigenous population, from passive immunity in the early post- natal-period, through the susceptibility of infancy and early childhood, and to the relatively strong immunity in later childhood and adult life[11]. Consequently, severe and potentially life-threatening malaria is confined to children within the first five years of life, whereas older children and adults suffer mild clinical attacks with asymptomatic parasitaemia reaching as high as 75% in primary school children[11]. In areas with intermittent malaria transmission or low endemicity on the other hand, severe infections occur in all age groups including adults due to their relatively low immunity[12].

Several studies have reported relative male preponderance in malaria prevalence[15]. This was also observed in this study. Suggested reasons for this difference include relatively better immunity to parasitic infections in females, probably due to genetic and hormonal factors.[16] In addition, boys tend to have more contact with the vector as a result of the clothing they wear and the time they spend outdoors while a female is more likely to cover herself due to cultural and religious values[17].

The spectrum of diagnostic criteria for severe malaria in the study cohort is broad. The most frequently observed manifestations were prostration, persistent vomiting, hyperpyrexia and multiple convulsions while other features such as cerebral malaria and severe anaemia remained relatively uncommon. This pattern is similar to what has been previously described by previous studies in high malaria transmission areas[6,12,18]. The present study was also consistent with a previous study in Uganda,[18] which reported prostration as the commonest manifestation. There appears to be differences in the pattern of severe malaria between low and high malaria transmission areas[19]. Generally, cerebral symptoms are more common in areas with low transmission intensity than in those with high transmission intensity[6,20-22]. In Gondar, an area of

low malaria transmission, cerebral malaria, hypoglycaemia and severe anaemia were observed to be the three most common manifestations of severe malaria,[20] whereas Giha[19] in Sudan, an equally low transmission area, found cerebral malaria, convulsions and severe anaemia to be the most common features among their study cohort. These findings suggest that considerable differences between individual complications of severe malaria do occur.

Less than 1% of the study cohort presented with jaundice and disseminated intravascular coagulopathy (DIC) while no case of renal impairment was observed. The rarity of renal involvement in children with severe malaria, unlike adults, has been consistently demonstrated by many studies, [1, 6, 13, 20] though the reason(s) for this is not clear. Banzal *et al* [21] in Saudi Arabia has reported a relatively high prevalence of acute renal failure (6.1%), but this may be due to the fact that the study subjects included both children and adults.

The mortality from untreated severe malaria can be up to 100%, but with anti-malarial treatment, the overall mortality falls to 15-20%[5]. Case-fatality rate in the present study was 6.5 %, which was lower than 15.2% reported by Desta in Ethiopia[20] and 11.2% reported in Ghana.[23] Studies have reported variable factors that may be associated with risk of death in children with severe malaria.[6, 13,17,24] In the present study, prostration, severe anaemia, respiratory distress and cerebral malaria were associated with death. Except for prostration, these factors were similarly reported by earlier studies[6,20]. Tripathy *et al*[24] in India had also noted respiratory distress, coma, multiple organ dysfunction and hyperparasitemia as significant predictors of death while Dzeing-Ella *et al*[13] in Gabon found coma, hyperlactataemia, respiratory distress and hypoglycaemia as independent predictors of a fatal outcome. Unlike aforementioned studies, respiratory distress was not found to be associated with poor prognosis from a study in Yemen[17]. Our study and that of others[6,20] found severe anaemia to be associated with risk of death. However, this association was not demonstrated in many other studies.[13,17,23,24] This observation supports the assertion that the pattern of severe malaria and the relative contribution of individual symptoms to mortality differ with endemicity, geographic location, access to health services, and age.[25] It is of note that27.3% of the mortality was attributable to cerebral malaria. Many studies have shown cerebral malaria to be associated with significant mortality, reaching as high as 80 %.[8, 26, 27]

The presence of any of the afore-mentioned life threatening features of severe malaria in a child should prompt urgent treatment. This is because severe malaria can be rapidly fatal especially in children below the age of five years.[1, 4] Health care workers, particularly at the primary health facilities, must be adequately trained on how to recognize features of severe malaria and offer timely pre-referral intervention, which has been shown to significantly reduce the risk of death and morbidity from severe malaria.[1] Intravenous quinine was the first line anti malarial drug used for the treatment of most of our patients at the time of the study. However, the current WHO recommendation for treatment of severe malaria is intravenous artesunate.[5] High quality evidence has shown reduced mortality and less side effects with artesunate compared to quinine, which is now reserved as an alternative to artesunate and intramuscularartemether.[5] This new treatment policy has already been adopted in our institution.

Though few patients had neurologic sequelae, all of them recovered on subsequent follow up. This is in keeping with findings in many studies, [8, 26] which showed excellent and usually full neurologic recovery following cerebral malaria.

CONCLUSION

The pattern of severe malaria in this series is similar to other studies from hyper endemic areas, with prostration, persistent vomiting, hyperpyrexia and multiple convulsions being the most common features. Cerebral malaria and respiratory distress were the independent predictors of mortality. Therefore, any child presenting with either of these features should be managed with utmost care and urgency. This is because early detection, prompt and effective treatment has been shown to reduce case-fatality rates particularly among children less than 5 years

REFERENCES

1. WHO. Management of severe malaria. A practical handbook. 3rd edition Geneva, world Health Organization. 2012; p.1-83.
2. Ogun SA. Management of malaria. Nig Med Pract 2006;49:94-01.
3. Federal Ministry of Health. A 5 year

strategic plan: 2006-2010. A road map for impact on malaria in Nigeria. National malaria control program, Federal Ministry of Health, Abuja, Nigeria. 2005; p.1-36.

4. Federal Republic of Nigeria. National Antimalarial Treatment Policy. Federal Ministry of Health, Abuja, Nigeria; May 2005;p. 13-19
5. *WHO. Guidelines* for the treatment of malaria. 3rd edn. Geneva, World Health Organization. *2015; p.1-313.*
6. Modiano D, Sirima BS, Sawadogo A, Sanou I, Pare J, Konate A, *et al.* Severe Malaria in Burkina Faso: Influence of age and transmission level on clinical presentation. *Am. J. Trop. Med. Hyg* 1998;59:539-42
7. Snow R, Bastos de AI, Lowe BS, Kabiru EW, Nevill CG, Mwanskusye S *et al.* Severe childhood malaria in two areas of markedly different *falciparum* transmission in East Africa. *Acta Trop* 1994;*57:*289-300.
8. Jiya NM, Airede KI, Ahmed H. Cerebral Malaria: Presentation and Outcome in Children in Sokoto. Nig Med Pract2006; 50:55-61
9. Cheesbrough M. Examination of blood for malaria parasites. In: District Laboratory practice in tropical countries (part 1). Cambridge University press, UK. 1998; p.239 -58
10. Runsewe-Abiodun T.I., Olanrewaju D.M. Management of Malaria in Nigerian Children Recent Advances. Nig Hospital Practice 2007;1:89-95.
11. Hendrickse, R.G. Parasitic Diseases. In: Hendrickse R.G., Barr, D.G.D., and Mathews, T.S. (ed). Paediatrics in the Tropics. Philadelphia, Blackwell Scientific Publication, 1991; p. 695-710
12. World Health Organization: Malaria Control today; Current WHO Recommendation Working Document. WHO: Geneva, 2005; p. 8-22
13. Dzeing-Ella A, Obiang PCN, Tchoua R, Planche T, Mboza B,Mbounja M *et al.* Severe falciparum malaria in Gabonese children: clinical and laboratory features. *Malaria Journal* 2005;4:1
14. Federal Ministry of Health: National Malaria and Vector Control Programme. Training Manual for Management of Malaria in Nigeria. September 2008; p.13-26
15. Ekepenyong EA, Oyo JE. Malaria control and treatment strategies among school children in semi urban tropical communities. West Indian Med J. 2008;57:1-5
16. Zuk M, Mckean KA. Sex differences in parasite infection: patterns and processes. Inter J. Parasitol. 1996;26:1009-23
17. *Al-Taiar A, Jaffar S, Assabri A, Al-Habori M, Azazy A, Al-Mahdi N et al.* Severe malaria in children in Yemen: two sites observational study *BMJ* 2006; 333:827
18. Idro R, Bitarakwate E, Tumwasgire S, John CC. Clinical manifestations of severe malaria in the highlands of southwestern Uganda. Am J Trop Med Hyg May 2005;72: 561-67
19. Giha HA, ElGhazali G, A-Elgadir TME, Al basit IE, Eltahir EM, Baraka OZ *et al*. Clinical pattern of severe *Plasmodium falciparum* malaria in Sudan in an area characterized by seasonal and unstable malaria transmission. Trans Roy Soc Trop Med Hyg. 2005; 99:243-51
20. Desta KM. Pattern of severe and complicated malaria in children Admitted to Gondar Medical College hospital during 1995-2000. Ethiop .J. Health Dev.2002;16:53-9
21. Banzal S, Ayoola E.A, El Sammani E.E, Rahim S.I, Subramaniam P, Gadour M.O.E *et al.* The clinical pattern and complications of severe malaria in the Gizan region of Saudi Arabia. Annals of Saudi Medicine19 1999;4:378-380
22. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. Lancet 1990; 336:1039-43.
23. M,ockenhaupt FP, Ehrhardt S, Burkhardt J, Bosomtwe SY, Laryea S, Anemana SD *et al.* Manifestation and outcome of severe malaria in children in northern Ghana. Am J Trop Med Hyg 2004;71:167-72
24. Tripathy R, Parida S,Das L, Mishra DP,Tripathy D, Das MC *et al*. Clinical

Manifestations and Predictors of Severe Malaria in Indian Children. Pediatrics. 2007; 120:454-60

25. Snow RW, Bastos de AI, Lowe BS, Kabiru EW, Nevill CG, Mwankusye S, *et al.* Severe childhood malaria in two areas of markedly different falciparum transmission in east Africa.; Acta Trop, 1994;57:289-00.

26. Ikpatt, NW, Ekanem, IA, Kalil, MI. and Asindi AA. Preliminary observations on cerebral malaria in Nigerian children. Medicare Journal,1992,5:3-7.

27. Trampuz A, Jereb M, Muzlovic I, Prabhu RM. Clinical review: Severe malaria. Crit Care. 2003;7:315-23.