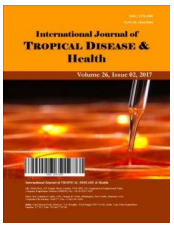

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Clinical Profile and Outcome of Paediatric Severe Malaria in a North-Eastern Nigerian Tertiary Hospital

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Authors' contributions

This work was carried out in collaboration between all authors. Author IAMI wrote the protocol, performed the statistical analysis and wrote the draft of the manuscript. Author HA designed the study and wrote the protocol. Authors MOY, TU and YYO collected the data. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The following cross-sectional study is performed to describe the clinical manifestations and outcome of severe malaria among children admitted into the Federal Medical Centre Azare, Nigeria.
Study Design: The study was a cross-sectional study.
Place and Duration of Study: The study was conducted at the Department of Paediatrics, Federal Medical Centre, Azare, Bauchi state, Nigeria from 1st August to 31st October 2013.
Methodology: Children aged 6 months to 12 years diagnosed with severe malaria were consecutively recruited from the Emergency Paediatric Unit. The information obtained included age, sex, weight, presenting complaints and associated symptoms. Elicited clinical signs, as well as the outcome were also documented. The data was analysed using SPSS version 16.0.
Results: Ninety- eight patients diagnosed with severe malaria were recruited into the study. There were 57 (58.2%) boys and 41 (41.8%) girls giving a male to female ratio of 1.4: 1. The mean age of

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the patients was 4.2± 2.8 years, with a median and modal age of 3 years. Ninety patients (91.8%) survived and were discharged home while 8 died, giving a case fatality rate of 8.2%. Cough (*P* = .04), breathlessness (*P* = .001), reduction in urine output (*P* = .003), loss of consciousness (*P* = .01) and abdominal swelling (*P* = .03) were significantly more common in children aged 3 years and below. There were also statistically significant relationships between age and nutritional status (*P* =.03), hepatomegaly (*P* =.02), coma (*P*<.001) as well as severe anaemia (*P* =.03). Six (6.1%) and 3 (3.1%) of the 8 deaths had convulsions and severe anaemia respectively. Nevertheless, binary logistics regression analysis showed that coma (*P* =.03) and dehydration (*P* =.02) were the most likely to predict death.

Conclusion: Prompt identification and management of fluid and electrolyte deficits may significantly reduce mortality in children with severe malaria managed at the Federal Medical Centre, Azare, Nigeria.

Keywords: Clinical profile; severe malaria; children; coma; dehydration; outcome, Azare.

1. INTRODUCTION

For over 4000 years humanity has experienced the ravages of malaria [1]. Notwithstanding that its incidence estimates have decreased globally in the last decade, malaria remains an important cause of mortality particularly in children younger than 5 years in sub-Saharan Africa [2]. Of the 429,000 malaria related deaths recorded in 2015, 92% occurred in sub-Saharan Africa with two countries; Nigeria and the Democratic Republic of Congo accounting for over a third of the total deaths [2].

Severe malaria remains the deadliest form of the disease and for the most part, affects children less than 5 years of age in endemic areas [2-4]. The clinical manifestations and prognostic factors of severe malaria have largely been described particularly in African children. However, disease pattern and the comparative impact on the outcome by the various symptoms and signs may vary with age, access to health care, endemicity, genetics and geographical location [5-9].

Understanding of the clinical spectrum and relative outcomes of severe malaria amongst children in our locale may aid in prompt diagnosis and appropriate treatment as well as identify gaps in knowledge requiring further research. Thus we carried out a cross-sectional study aimed at describing the clinical manifestations and outcome of severe malaria among children admitted into the Emergency Paediatric Unit (EPU) of the Federal Medical Centre (FMC) Azare in North-Eastern Nigeria. To our knowledge, this is the first of such studies to be conducted in this part of Nigeria.

2. METHODOLOGY

2.1 Study Area

The present study was conducted at the EPU of the Federal Medical Centre Azare, Bauchi state in North-Eastern Nigeria. The centre is a tertiary facility which serves as a referral hospital for the populations of Bauchi, Yobe and Jigawa states of Northern Nigeria. Prior approval was obtained from the research ethics committee of the hospital.

2.2 Study Design, Sampling and Duration

The study was a cross sectional study. Children aged 6 months to 12 years diagnosed with severe malaria were consecutively recruited from the EPU (excluding those who died on arrival) from 1st August to 31st October, 2013 corresponding to the peak of the rainy season and period of highest transmission.

Patients with evidence of other infectious diseases, namely typhoid fever, gastroenteritis, acute bacterial meningitis, upper respiratory tract infections or any other identified cause of anaemia other than malaria were excluded from the study.

Informed consent was obtained from the caregivers and information was obtained with the use of a structured questionnaire. The information included age, sex, weight, presenting complaints and associated symptoms. The duration of hospital stay, as well as the outcome was also documented.

The patients were examined by the admitting paediatrician and their vital signs were

documented. The axillary temperatures were measured with a mercury thermometer placed in the axillae for 3 minutes before reading and recording. Hypothermia was defined as axillary temperature < 35°C while hyperpyrexia was defined as axillary temperature > 38.5°C. Anthropometric measurements were taken and recorded. Other information obtained included hydration status (documented as no dehydration and presence of dehydration), nutritional status (using the modified Wellcome classification), liver span and splenic size in the presence of splenomegaly. Consciousness level was determined with the modified Glasgow Coma Scale and a score of less than ten (ie.< 10/15) was recorded as coma. Haemoglobinuria was defined as the presence of dark or brownish coloured urine. All the patients were managed using the WHO treatment guidelines [10,11].

2.3 Specimen Collection

Two millilitres of blood was collected from the patients into EDTA anticoagulated specimen bottles using aseptic techniques. Blood in the EDTA anticoagulated bottles were used to prepare thick and thin blood films for demonstration of asexual forms of Plasmodium *falciparum* as well as the rapid diagnostic test (RDT).

2.4 Performance of Haemoglobin Concentration

Haemoglobin concentration was obtained from full blood count results performed with a Sysmex KX 21N haematology analyzer (serial no. 060120920). Severe anaemia was defined as haemoglobin concentration < 5 g/dl [6].

2.5 Detection of Malaria Parasite

Confirmation of severe malaria diagnosis was done with microscopy (Plasmodium *f*alciparum (PF) parasitaemia confirmed with blood film microscopy) or rapid diagnostic tests (RDT) in the presence of any of the World Health Organization (WHO) case definitions for severe malaria [4,10]. The thin and thick films for malaria parasite were stained with Giemsa stain and read by medical laboratory scientists. The results were classified as (+) when 1-10 asexual forms of PF were seen per 100 thick fields, (2+) when 11-100 parasites were seen per 100 thick film fields, (3+) for 1-10 parasites per thick film field and (4+) for greater than 10 parasites per thick field [10].

The RDT was done using the paracheck Pf® rapid test kit for *P. falciparum* malaria (a rapid test for the detection of Plasmodium *f*alciparum specific histidine rich protein-2). Results were documented as positive or negative as indicated by the coloured bands on the control windows; test ('T') and control ('C') respectively.

2.6 Data Analysis

The collected data was entered into SPSS version 16.0. Categorical data were compared using the Chi-square test. A *P* value less than 0.05 was regarded as being statistically significant. The binary logistics regression analysis was applied to determine the most likely predictors of outcome utilizing 95% confidence interval.

3. RESULTS

Ninety-eight cases of severe malaria were recruited into the study. The patients were aged 6 months to 12 years. There were 57 (58.2%) boys and 41 (41.8%) girls giving a male to female ratio of 1.4:1. The mean age of the patients was 4.2± 2.8 years, with a median and modal age of 3 years. Fifty percent (50%) of the patients were less than 1 year of age while 2 % were between the ages of 10 years and 12 years. Of the 98 patients 90 (91.8%) survived and were discharged home while 8 died, amounting to a case fatality rate (CFR) of 8.2%. Table 1 displays the age and sex distribution of the patients.

Table 2 shows the distribution of presenting symptoms by age. All the patients had fever, 50 (51%) had presenting complaint of refusal to feed made by their caregivers. Twenty-five (25.5%) of these children were aged less than 1 year while none of them was between ages 10 and 12 years. The symptoms of cough (*P* = .04), breathlessness (*P* = .001), reduction in urine output (*P* = .003), loss of consciousness (*P* = .01) and abdominal swelling (*P* = .03) had statistically significant relationships with age.

The relationships between the clinical signs elicited in the patients and their ages are outlined in Table 3. Thirty-five (35.7%) patients had hyperpyrexia, while 3 (3.1%) had hypothermia. Twenty-eight (28.5%) patients were dehydrated

at presentation with the majority; 14(14.3%) being less than age 1 year. Of the 28 (28.5%) children who presented with features of dehydration, 14 (14.3%) were aged 6 months to 11 months whereas 1(1%) was aged 10 years-12 years.

Table 1. Age and sex distribution of children with severe malaria

Age (years)	Sex		Total (%)
	Male (%)	Female (%)	
< 1	27(27.6)	22(22.4)	49(50.0)
1-3	16(16.3)	12(12.2)	28(28.6)
4-6	10(10.2)	4(4.1)	14(14.3)
7-9	3 (3.1)	2 (2.0)	5(5.1)
10-12	1 (1.0)	1 (1.0)	2(2.0)
Total	57 (58.2)	41 (41.8)	98(100)

Table 2. Distribution of presenting symptoms by age

Symptoms	Age (years)					Total	*P*	X^2
	<1(%)	1-3(%)	4-6(%)	7-9(%)	10-12(%)			
Fever	49(50)	28(28.6)	14(14.3)	5(5.1)	2(2.0)	98(100)	-	-
Refusal to feed	25(25.5)	17(17.3)	5(5.1)	3(3.1)	0	50(51.0)	.39	4.61
Vomiting	23(23.5)	11(11.2)	6(6.1)	3(3.1)	2(2.0)	45(45.9)	.50	3.37
Diarrhoea	11(11.2)	11(11.2)	1(1.0)	1(1.0)	0	24(24.5)	.43	6.41
Cough	20(20.4)	10(10.2)	2(2.0)	1(1.0)	0	33(33.7)	.04	4.96
Breathlessness	20(20.4)	6(6.1)	0	0	0	26(26.5)	.001	13.09
Reduction in urine output	13(13.3)	1(1.0)	0	0	0	14(14.3)	.003	13.13
Coca-Cola coloured urine	5(5.1)	5(5.1)	2(2.0)	1(1.0)	0	13(13.3)	.65	1.43
Bloody urine	1(1.0)	1(1.0)	1(1.0)	0	0	3(3.1)	.73	1.20
Jaundice	11(11.2)	6(6.1)	2(2.0)	1(1.0)	0	20(20.4)	.43	.98
Convulsion	32(32.7)	17(17.3)	10(10.2)	3(3.1)	1(1.0)	63(64.3)	.87	.71
Loss of consciousness	14(14.3)	10(10.2)	8(8.2)	3(3.1)	2(2.0)	37(37.8)	.01	8.40
Abdominal swelling	10(10.2)	3(3.1)	0	0	0	13(13.3)	.03	5.54

Table 3. Distribution of clinical signs by age

Clinical signs	Age (years)					Total	*P*	X^2
	<1(%)	1-3(%)	4-6(%)	7-9(%)	10-12(%)			
Hypothermia	2(2)	0	1(1)	0	0	3(3.1)	.12	2.06
Hyperpyrexia	13(13.3)	13(13.3)	5(5.1)	2(2.0)	2(2.0)	35(35.7)	.12	6.84
Dehydration	14(14.3)	7(7.1)	3(3.1)	3(3.1)	1(1.0)	28(28.5)	.57	4.66
Oedema	4(4.1)	0	0	1(1.0)	0	5(5.1)	.64	5.61
Nutritional status								
Normal	13(13.3)	14(14.3)	8(8.2)	3(3.1)	2(2.0)	40(40.8)		
Underweight	31(31.6)	13(13.3)	6(6.1)	2(2.0)	0	52(53.1)		
Marasmus	2(2.0)	1(1.0)	0	0	0	3(3.1)		
Kwashiorkor	1(1.0)	0	0	0	0	1(1.0)		
Marasmic kwashiorkor	2(2.0)	0	0	0	0	2(2.0)	.03	12.63
Hepatomegaly	24(24.5)	11(11.2)	2(2.0)	2(2.0)	0	39(39.8)	.02	7.78
Splenomegaly	7(7.1)	2(2.0)	1(1.0)	0	0	10(10.2)	.18	2.12
Coma	7(7.1)	8(8.2)	7(7.1)	3(3.1)	2(2.0)	27(27.6)	<.001	15.77
Severe anaemia	18(18.4)	7(7.1)	1(1.0)	1(1.0)	0	27(27.6)	.03	5.99

There were statistically significant relationships between age and nutritional status (*P*=.03), hepatomegaly (*P* =.02), coma (*P*<.001) as well as severe anaemia (*P* =.03).

Table 4 relates outcome to the patients' symptoms. None of the symptoms studied reached statistical significance in their relationship with outcome. However, 6 (6.1%) of the 8 (8.2%) patients who died had convulsions. Table 5 shows the relationship between some clinical signs and outcome. Twenty – seven (27.6%) patients presented with severe anaemia and 3 (3.1%) died. Coma and dehydration had statistically significant relationships with outcome. The ability of the individual clinical signs to predict death from severe malaria was tested using the binary logistics regression model and as shown in Table 6, coma and dehydration (*P* = .03 and *P*= .02 respectively) were the most likely to independently predict death in this study.

Table 4. The association of outcome with clinical symptoms

Symptoms	Outcome		No of patients N=98(%)	X^2	*P*	ß	Exp(ß)	95% confidence interval
	Survived (%)	Died (%)						
Fever	90(91.8)	8(8.2)	98(100)	-	-	-	-	-
Jaundice	18(18.4)	2(2.0)	20(20.4)	.11	.74	.98	2.66	.18,39.41
Convulsion	57(58.2)	6(6.1)	63(64.3)	.43	.51	-1.07	.35	.01,10.08
Haematuria	2(2.0)	1(1.0)	3(3.1)	2.59	.11	2.67	14.49	.33,645.99
Cough	30(30.6)	3(3.1)	33(33.7)	.01	.81	-1.15	.32	.03,4.06
Vomiting	41(41.8)	4(4.1)	45(46.4)	.05	.83	-.26	.77	.09,6.71
Diarrhoea	20(20.4)	4(4.1)	24(24.5)	3.03	.08	3.15	23.33	1.40,390.24

Table 5. The association between outcome and clinical signs

Clinical signs	Outcome		No of patients N=98(%)	X^2	*P*
	Survived (%)	Died (%)			
Severe anaemia	24(24.5)	3(3.1)	27(27.6)	.43	.51
Haemoglobinuria	11(11.2)	2(2.0)	13(13.3)	1.03	.31
Hypothermia	2(2.0)	1(1.0)	3(3.1)	2.59	.11
Hyperpyrexia	33(33.7)	2(2.0)	35(35.7)	.43	.51
Coma	22(22.4)	5(5.1)	27(27.6)	5.28	.02
Splenomegaly	10(10.2)	0	10(10.2)	.98	.32
Hepatomegaly	37(37.8)	2(2.0)	39(39.8)	.98	.32
Severe malnutrition	5(5.1)	1(1.0)	6(6.1)	.03	.86
Dehydration	23(23.4)	5(5.1)	28(28.5)	6.71	.01
Oliguria	12(12.2)	2(2,0)	14(14.3)	.81	.37

Table 6. Binary logistics regression analysis of signs of severe malaria on outcome

Clinical signs	ß	Exp(ß)	X^2	*P*	95% confidence interval
Coma	-1.64	5.83	4.69	.03	.04, .88
Dehydration	1.48	3.49	5.52	.02	1.28, 15.16
Hyperpyrexia	-.55	.61	.46	.51	.11, 3.02
Hypothermia	1.84	36.49	1.62	.15	.51, 78.19
Severe anaemia	-.50	.24	.41	.51	.13, 2.73
Severe malnutrition	.08	1.50	.03	.86	.44, 2.70
Oliguria	.70	.56	.70	.38	.39, 12.00
Haemoglobinuria	.87	4.42	.88	.32	.43, 13.39
Splenomegaly	-18.90	.00	1.80	.18	.00
Hepatomegaly	-.76	.51	1.12	.33	.10, 2.16

4. DISCUSSION

Our study has demonstrated that severe malaria is more prevalent among preschool children (78.6% of all the study subjects were aged 3 years and below). This is in conformity with multiple studies done across sub-Saharan Africa [12-15]. However, what is at odds with findings from other studies is the observation that 50% of our patients were aged 6 - 11 months [8,12,16]. Several reasons have been adduced to justify the low prevalence of severe malaria in children younger than 1 year. These include; breast milk is low in para-aminobenzoic acid (PABA) which is vital for the replication of PF, high foetal haemoglobin levels impeding the growth of PF and acquired passive immunity from immune mothers in endemic areas [17,18]. The reasons for the contrary observation in the present study in unclear. Yet it has been demonstrated that in endemic areas children born during the low-transmission season possess significantly higher risk of being infected in comparison to those born during the high transmission season [19]. This may explain our finding given the fact that most of the patients less than age 1 year were born between the months of December and April which is part of the low transmission season in the Sahel region of sub-Saharan Africa [20]. Secondly, some authors have suggested that maternally acquired antibodies may be a marker for risk of infection instead of that of protective immunity [21,22].

Our case fatality rate (CFR) of 8.2% is lower than the estimated average for sub-Saharan Africa [13]. It is also lower than the 10.3% reported in parts of the Niger-delta region of Nigeria, [23] but higher than the 5.2% recorded in Osogbo, South West Nigeria [14]. The later study was done retrospectively and consisted of a small sample size (58) hence the findings are likely to be less representative than that of the present study - done prospectively with a larger sample size. Be that as it may, the fact that the patients who died on arrival were excluded from our study may have largely confounded the CFR.

There were notable age-related differences in the clinical features of our patients. Cough was a significantly frequent symptom in children less than age 5 years and non-existent in those older than 6 years. It was found at rates higher than that reported at Osogbo, South Western Nigeria but lower than that reported in Uganda [16,24]. Respiratory symptoms have long been known to be associated with malaria, furthermore, studies have recognized small airway obstruction, impaired gas exchange and increased pulmonary phagocytic activity in malaria patients exhibiting pulmonary symptoms [25-27]. These may explain the advent of respiratory symptoms in children with malaria.

Breathlessness, reduction in urine output, loss of consciousness and abdominal swelling were also more common in children aged 3 years and less, whereas hepatomegaly, severe anaemia and coma were more frequent in those aged 5 years and below. These are consistent with findings from previous studies [24]. No clear explanation has been given for the age-associated differences in the clinical presentation of severe malaria. However, there are indications that several factors may be responsible including; lower levels of complement regulatory proteins, significantly smaller red cell mass as well as differential organ sequestration of PF in younger children in comparison to older children putting them at greater risk of certain manifestations [28-30].

Coma and dehydration were independently associated with an increased risk of death in this study. This is in keeping with findings from multiple studies [5,12,31]. Nevertheless, it is inconsistent with the findings reported in Ado-Ekiti, South Western Nigeria [8]. The sequestration of parasitized erythrocytes in the microvasculature of the brain is fundamental to the aetiology of coma in severe malaria, deepening coma and subsequent affectation of the respiratory centre may lead to death [32]. The significant association of dehydration with death here may have stemmed from the cumulative prevalence of diarrhoea and vomiting (8.2%) among our patients and failure to promptly manage fluid and electrolyte deficits. Severe anaemia was not independently associated with an increased risk of death in our study. This may be largely due to the fact that blood transfusions were promptly administered to patients diagnosed with severe malarial anaemia. Blood transfusions have been shown to be effective at preventing death in severe malarial anaemia [33].

5. CONCLUSION

We have demonstrated that cough, breathlessness, reduction in urine output, abdominal swelling and loss of consciousness are common symptoms of severe malaria in preschool children. Severe anaemia,

hepatomegaly and coma are also frequent in this age group. The predictors of death as found in this study are coma and dehydration. However, severe anaemia and convulsions are also danger signs worthy of note. We recommend prompt identification and management of fluid and electrolyte deficits in children presenting with severe malaria to the Federal Medical Centre, Azare. In addition, parents should be continuously educated on the significance of uninterrupted feeding of their children when they are ill and the importance of home management of diarrhoea and vomiting with oral rehydration solution before presentation to the hospital.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

Approval was obtained from the research ethics committee of the Federal Medical Centre Azare, Bauchi state, Nigeria before commencement of the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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