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Clinical manifestations and outcomes of severe malaria among children admitted to Rungwe and Kyela district hospitals in south-western Tanzania

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Abstract: Malaria remains as an important public health and a major cause of childhood death and paediatric hospital admission in sub-Saharan Africa. This prospective hospital based cross sectional study was conducted from April 2007 to April 2008. The main objective was to assess clinical manifestations and outcomes of severe malaria in children admitted to district hospital in Rungwe and Kyela in south-western Tanzania. A total of 1371 children were selected as screening group of which 409 (29.8%) were tested positive for malaria. Mean age of the children was 2.7 (95%CI= 2.5, 2.8) years and the majority (86%) were under five years of age. The proportion of children severe malaria in Rungwe was significantly higher than that of Kyela by 21.3% (*P=0.002)*. The common symptoms of severe malaria during admission were convulsions (50.9%) compensated shock (30.6%), prostration (29.1%) and symptomatic severe anaemia (14.9%). The case fatality rate (CFR) was 4.6% and the cure rate (CR) was 95.4%. Children with suspected severe acidosis and symptomatic severe anemia were 4.8 (95%CI=1.6, 14.6) and 5.5 (95%CI 1.1, 28.2), respectively, more likely to die compared to those without these symptoms. The proportion of deaths among children presenting ≥5 symptoms was 32.1% higher than among those presenting one symptom (OR =0.50, 95%CI 0.125-2.000; *P*=0.000). Convulsions and compensated shock were the leading symptoms at admission. Suspected severe acidosis and symptomatic severe anemia were the predictors of mortality for children. In order to reduce mortality among admitted children with severe malaria there is a need for health providers to deploy strategic management of fatal prognostic factors. In conclusion, convulsion and compensated shock were the leading symptoms among children at admission and that suspected severe acidosis and symptomatic severe anemia were the predictors of mortality. It is therefore important to emphasis early diagnosis and prompt treatment of severe cases of malaria to minimize mortality among children.

Keywords: malaria, children, hospital, clinical, symptoms, outcome, Tanzania

Introduction

Malaria remains a leading cause of morbidity and mortality especially among children and pregnant women in sub-Saharan Africa where at least 90% of malaria deaths occur (WHO, 2005). The World Health Organization estimates that the number of malaria deaths in young children in sub-Saharan Africa in 2000 ranged from 710,000 to 896,000 (WHO & UNICEF, 2003). It is generally understood that malaria causes around 20% of

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all deaths in children under 5 years old in Africa and that it is now the most important cause of death in this group. In Tanzania there are an estimated 14-19 million cases of malaria annually and malaria is reportedly the cause of one third of all outpatient visits and hospital admissions. It is the main cause of admission for children (38%) and adults (32%) in health facilities (Rugemalila *et al.,* 2006). In Tanzania, malaria accounts for an estimated 16 million clinical episodes and 120,000 deaths occur per year and that of these deaths, over 58% are in children less than five years of age (Makundi *et al*., 2007).

Severe malaria is defined as history of fever plus at least one symptom of severe malaria and positive malaria test (WHO, 2010). Severe malaria mainly affects children under 5 years old, non-immune travellers, migrants to malarial areas, and people living in areas with unstable or seasonal malaria (Sheehy & Angus, 2011). In endemic countries with a high transmission of malaria, severe malaria is predominantly a disease of young children of 1 month to 5 years of age (Trampuz *et al*., 2003). Criteria for severe malaria have been established to assist clinical and epidemiological studies (WHO, 1990, 2000). The symptoms of severe malaria includes prostration, altered consciousness, lethargy or coma, respiratory distress, severe anaemia, convulsions, inability to swallow, persistent vomiting and dark or limited urine for adults only (http://archives.who.int/eml/expcom/expcom15/applications/formulations/artesunate.pdf). Studies in Ghana and Gabon reported that severe anemia, prostration, respiratory distress, convulsions, impaired consciousness and hyperlactaemia to be the major symptoms of severe malaria (Mockenhaupt *et al*., 2004; Dzeing-Ella *et al*., 2005).

The major complications of severe malaria include cerebral malaria, pulmonary oedema, acute renal failure, severe anemia, and/or bleeding. Acidosis and hypoglycemia are the most common metabolic complications. Any of these complications can develop rapidly and progress to death within hours or days (WHO, 2000). In clinical practice, patients must be assessed for any of these signs or symptoms that suggest an increased risk for developing complications and must be treated immediately.

Optimal care for severe malaria requires well-developed diagnostic facilities and intensive care. Centralizing these capabilities may be logical in a managerial sense but will not benefit the people at greatest risk. It is therefore, important to enable peripheral health services to provide emergency treatment by means of guidelines, training, and the regular supply of medicines and diagnostic supplies and equipment (FMoH, 2004). At the periphery, the priority requirement is the rapid recognition of the signs and symptoms of severe malaria that should lead to emergency care or referral to a higher level of care. It was therefore, the objective of this study to assess clinical manifestations and outcomes of severe malaria in children admitted to district hospital in Rungwe and Kyela in south-western Tanzania.

Methods and Materials

Study area

This hospital based study was done in Kyela and Rungwe districts in south-western Tanzania. Rungwe district has a highly variable terrain, while Kyela is mainly formed of

low-lying flood plains on the northern shores of Lake Malawi, at 475 m altitude. To its southern borders, Rungwe district shares a small strip of lowland with Kyela, but its altitude rises within a relatively short distance towards the north, northeast and northwest, to the volcanic summits of Mt. Rungwe and Kyejo, which rise to above 4,000m. The two districts have an estimated population of 500,000.

Study population and sampling technique

The study population was children with severe malaria admitted in the paediatric wards of the district hospitals in Kyela and Rungwe. Inclusion criteria were a child clinically diagnosed to have history of fever, at least one symptom of severe malaria, tested positive for malaria and aged 1 month to 12 years. The exclusion criteria were any child aged below one month and those above 12 years of age, clinically diagnosed to have no fever, not having any symptom of severe malaria and tested negative for malaria.

Paediatric wards in Kyela and Rungwe district hospitals were purposively selected. Although the target screening group of children was 1400, a total of 1371 children clinically diagnosed to have history of fever and at least one symptom of severe malaria were obtained out of 5,753 children admitted from April 2007 to April 2008. Of the children having history of fever and meeting at least one of the WHO 2000 malaria severity criteria, 440 children inclusive 10% for non-response were anticipated to be recruited for study upon being confirmed to have severe malaria from blood smear microscopy but the team recruited 409 in 24 hours every day.

Clinical procedures and laboratory tests

Children admitted to the paediatric wards were examined for symptoms or signs of malaria by either nurses, clinical officers, assistant medical officers or medical officers to ascertain if the child had history of fever and any of the symptoms of severe malaria. Indicators for hypoglycemia, shock were determined using WHO guidelines. The following are symptoms and their specifications as were considered for screening to participate in the study: Coma (Glasgow Coma Scale (GCS) ≤ 10, Blantyre Coma Scale (BCS) ≤2), prostration (not able to breastfed <6m, or able to sit >6m), convulsions (>30minutes), decompensated shock (children: systolic blood pressure<70mmHg), compensated shock (capillary refill ≥ 3sec. /temperature gradient) and severe respiratory distress (nasal flaring, lower chest in drawing/retractions). Other symptoms for qualification for enrolment group were either a child with suspected severe acidosis-deep breathing, hypoglycemia (BM-Stix<3mmol/L or clinical improvement after IV glucose), symptomatic severe anaemia (Hb<5g/dl) in combination with respiratory distress), black water fever, severe jaundice and anuria in older children.

Thick peripheral blood smears were performed to detect *Plasmodium falciparum* infection. Parasites were counted against 200 white blood cells. For recruited patients, absence of malaria after treatment was declared after 3 consecutive negative blood smears at 8 hourly intervals. Haemoglobin level was tested with a colorimeter using Drabkin's method and blood sugar glucose was tested using Glucometer machine.

Data analysis

Data was entered on Epidata version 3.1 and later exported to SPSS Version and analysed by Stata version 10. Chi-square test was performed to measure any association between independent and dependent variables. Unadjusted and logistics (adjusted) analysis was done to assess the relationships between the dependent and independent variables. The difference in means was tested using t-test. Statistical difference and associations between variables was tested at 5% significance level.

Ethical considerations

Ethical clearance was obtained from National Ethical Review Committee of the Medical Research Coordination Committee of the National Institute for Medical Research. Permission to conduct research in paediatric wards was sought from District Medical Officers, in charges of hospitals and matron of the respective wards. Oral consents were obtained from children's parents or caretakers.

Results

A total of 1371 children were included in the study. Of these, 409 (29.8%) children tested positive for malaria and hence confirmed to have severe malaria. Of the confirmed cases, 39.4% were from Kyela and 60.6% from Rungwe. Males constituted 53% while female accounted for 47% of the children. Mean age of the children was 2.7 (95%CI= 2.5, 2.8) years. Majority (86%) of the children were under five years of age (Kyela=91.9%; Rungwe= 82.3%). The proportion of children severe malaria in Rungwe was significantly higher than that of Kyela by 21.3% (*P=002)*.

Table 1: Common symptoms of severe malaria by confirmed patients (n=409)

Symptom	Overall cases	%	Kyela		Rungwe		P-value
			Freq	%	Freq	%	
Coma	40	9.8	18	45.0	22	55.0	0.273
Prostration	119	29.1	40	33.6	79	66.4	0.127
Convulsions	208	50.9	74	35.6	134	64.4	0.068
Decompensated shock	33	8.1	6	18.2	27	81.8	0.006
Compensated shock	125	30.6	92	42.0	125	57.6	0.109
Severe respiratory distress	23	5.6	13	56.5	10	43.5	0.066
Severe acidosis	14	3.4	8	57.1	6	42.9	0.135
Hypoglycemia	8	2.0	4	50.0	4	50.0	0.390
Severe anaemia	58	14.2	22	37.9	36	62.1	0.465
Black water fever	8	2.0	1	12.5	7	87.5	0.111
Severe jaundice	5	1.2	0	0.0	5	100.0	_
Anuria / oliguria	0	0.0	0	0.0	0	0.0	_
Hyperparasitaemia	25	6.1	2	7.4	25	92.6	0.000

Note: Multiple responses

During the period of study (390 days) the mean daily admission was 0.52 (0.46, 0.59) person per day. It was higher in Rungwe (95%CI= 0.54, 0.73) than in Kyela (95%CI=0.33, 0.49) (*P*=0.001). The common symptoms of severe malaria were convulsions (50.9%) compensated shock (30.6%), prostration (29.1%) and symptomatic severe anaemia (14.9%). There was significant variation in presentation of symptoms of severe malaria between the two hospitals. The frequency of hyperparasitaemia (92.6%) and decompasated shock (81.8%) were higher in Rungwe than Kyela (Table1). The majority (75- 92.6%) of symptoms of severe malaria were observed among <5 years children than in ≥5 years (7.4-25%). The overall case fatality rate (CFR) was 4.6% (Kyela=7.5%; Rungwe= 2.8%). The proportion of deaths among children in Kyela was higher than in Rungwe by 23.6%. There was no significance difference in death rates between <5 years and ≥5 years children or between females and males.

Table 2: Unadjusted odds ratio (or) for the symptoms of severe malaria on death

Symptom	**OR**	**X^2**	95%CI	P-value
Coma	4.830	10.700	1.700, 13.70	0.001
Prostration	1.450	0.580	0.550, 3.780	0.447
Convulsions	1.350	0.390	0.523,3.420	0.530
Decompensated shock	3.310	4.520	1.030, 10.740	0.033
Compensated shock	0.980	0.000	0.390, 2.470	0.970
Severe respiratory distress	2.067	0.900	0.446, 9.578	0.343
Suspected severe acidosis	6.460	9.200	1.611, 25.899	0.002
Hypoglycaemia	7.529	7.610	1.389, 40.818	0.006
Symptomatic severe anaemia	3.877	8.390	1.442, 10.424	0.004
Black water fever	3.040	1.130	0.352, 26.189	0.287
Hyperparasitaemia	1.717	0.500	0.374, 7.877	0.481

Note: Multiple responses

Table 3: Adjusted odds ratio (OR) analysis for the symptoms of severe malaria on death

Symptom	OR	Z	**95%CI**	**P-value**
Coma	2.74	1.48	0.72, 10.44	0.140
Prostration	0.95	-0.09	0.29, 3.14	0.929
Convulsions	1.92	1.17	0.64, 5.74	0.244
Decompensated shock	2.24	1.09	0.53, 9.51	0.275
Compensated shock	1.91	1.14	0.63, 5.76	0.253
Severe respiratory distress	1.64	0.56	0.28, 9.54	0.584
Suspected severe acidosis	5.47	2.03	1.06, 28.22	0.043
Hypoglycaemia	6.43	1.76	0.81, 51.13	0.078
Symptomatic severe anaemia	4.81	2.78	1.59, 14.55	0.005
Black water fever	1.95	0.51	0.15, 24.87	0.608
Hyperparasitaemia	1.39	0.39	0.27, 7.34	0.695

Note: Multiple responses

With unadjusted odds ratio analysis five out of 13 symptoms showed statistical significance on the odds of dying. At 95%CI, the risk of death was associated with coma (95%CI=1.7, 13.7), decompensated shock (95%CI= 1.0, 10.7), suspected severe acidosis (95%CI =1.6, 25.9), hypoglycaemia (1.4, 40.8) and symptomatic severe anaemia (95%CI =1.4, 10.4) (Table 3). However, using logistics analysis for adjusted odds ratio only severe acidosis (95%CI=1.1, 28.2) and symptomatic severe anaemia (95%CI=1.6, 14.6) were associated with high risk of death (Table 3). The probability of dying from severe malaria increased with an increase in the number severe symptoms the child presented at admission (Table 4). The proportion of deaths among children who presented five and more symptoms was 33.3% and those presented with four symptoms was 13.8% compared to those presented with one symptom (1.3%).

Table 4: Number of symptoms at admission on children' outcomes

No. of Symptoms	Admissions	Survived		Deaths		Odds	95% CI	P-value
		Freq	%	Freq	%			
1	156	154	98.7	2	1.3	0.013	0.003, 0.052	0.000
2	170	163	95.9	7	4.1	0.043	0.020, 0.091	
3	45	42	93.3	3	6.7	0.071	0.022, 0.230	
4	29	25	86.2	4	13.8	0.160	0.055, 0.459	
5+	9	6	66.7	3	33.3	0.500	0.125, 2.00	
Total	**409**	**390**	**95.6**	**19**	**4.6**	_	_	

Discussion

Findings from this study showed that about third of the screened children were diagnosed to have severe malaria. The proportion of children with severe malaria in Rungwe district was found to be significantly higher than that of Kyela by 21.3%. In our opinion, the difference can be due to the fact that children in Rungwe district which is located in high attitude (up to about 4000m a.s.l.) were not immune enough to malaria infection compared to those in Kyela which is endemic to malaria. Therefore, children in Rungwe district within area of unstable or seasonal malaria were likely to be severely ill from infection than those from Kyela district. The study also revealed that many children with severe malaria had either one or a combination of symptoms. Convulsion was observed to be the most common symptom of severe malaria among children. The frequency of convulsions among children in our study was higher than that reported in Ghana (Mockenhaupt *et al*, 2004) and Uganda (Idro & Aloyo, 2004). However, the proportion of children with convulsion in our study was similar to that found in a study done in Senegal (Camara *et al*, 2011).

Although in several studies (Maitland *et al*., 2003; Idro & Aloyo, 2004) anaemia has been reported as a common symptom of severe malaria, in this study only a small proportion of the children (14.2%) presented with severe anaemia. The reasons for low prevalence of anaemia among severe cases of malaria could not be established. This calls for further studies to ascertain the ambiguity.

The case fatality rate n this study is lower that reported elsewhere in Africa (Mockenhaupt *et al*., 2004; Dondorp *et al.*, 2010). However, the low CFR observed in our study is in agreement with studies carried out in Uganda (Idro & Aloyo, 2004) and in Gabon (Issifou *et al.*, 2007). Interestingly, in a study done among children admitted to Kumasi Hospital in Ghana, none of the children with severe malaria died (Gyapong *et al*., 2009). The low CFR in our study is likely be attributed to early treatment seeking behaviour among children care seekers and good management of severe malaria.

Although in this study, severe acidosis and symptomatic severe anaemia were major predictors of death, in Kenya, Gabon and Senegal, shock, hyperlactaemia, hypoglycaemia, respiratory distress, impaired consciousness, and jaundice were associated with larger proportions of all deaths (Marsh *et al.*, 1995; Maitland *et al*., 2003; Dzeing-Ella *et al*., 2005; Issifou *et al.*, 2007). In India, Tripathy *et al.* (2007) reported respiratory distress, coma, multiple organ dysfunctions, and hyperparasitemia as major predictors of death. Unlike in our study, a study in Ghana reported severe anaemia as the leading manifestation of severe malaria (Mockenhaupt *et al*., 2004). In a study in Senegal young age was also identified as one of the main death risk factors (Camara *et al*., 2011).

It has been observed that the number of symptoms the child present has a significant influence on the treatment outcomes. As the number of symptoms increases, the probability of a child to die also increases. That means the more the number of complications the child had, the difficult in its management. This finding is in agreement with the observations in Gabon (Dzeing-Ella *et al.*, 2005) and India (Tripathy *et al*., 2007)

In conclusion, convulsion and compensated shock were the leading symptoms among children at admission and that suspected severe acidosis and symptomatic severe anemia were the predictors of mortality. Moreover, the probability of a child to die increased with increased number of symptoms of severe malaria a child had during admission. In order to reduce mortality among children with severe malaria, it is important that health need to invest more efforts in promoting community early identification of malaria symptoms and presentation to health care facilities for appropriate management of severe malaria.

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