

Health care related factors associated with severe malaria in children in Kampala, Uganda

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Abstract

Background: Severe malaria is responsible for the high load of malaria mortality. It is not clearly understood why some malaria episodes progress to severe malaria.

Objective: To determine factors associated with severe malaria in children aged 6 months to 5 years living in Kampala.

Methods: Over a 6-month period, 100 children with severe malaria were matched by age and place of residence with 100 children with non-severe malaria. We collected health care information from care takers.

Results: Mean duration of illness before getting antimalarial treatment was shorter for controls than cases (8hours vs. 20hours, $p=0.015$). Children with severe malaria were less likely to have been treated with sulphadoxine-pyrimethamine in the preceding 2 weeks (OR 0.2, 95% CI 0.04-0.85, $p=0.016$). Odds of severe malaria were higher in those who reported lack of protective measures (mosquito coils (OR = 20.63, 95% CI 1.5-283.3, $p=0.02$ and insecticide sprays OR 10.93, 95% CI 1.13-105.64, $p=0.03$), although few reported their use.

Conclusions: Early anti-malarial treatment and use of barriers against mosquitoes prevent severe malaria in children. There is need to increase the use of barriers against mosquito bites and to scale up prompt treatment and community-based interventions to reduce the incidence of severe malaria in children.

Keywords: health care, severe malaria, children, Uganda

Running head: Factors associated with severe malaria in children

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Introduction

It is estimated that in sub-Saharan Africa, between 1.5 – 2.7 million people die annually due to malaria of whom about 1 million are children below five years of age¹. Severe malaria occurs in one in every 100 clinical cases of malaria among African children, often within 48 hours of the onset of fever². Previous studies identified parasite, host genetic, and immunologic factors, associated with development of severe malaria³⁻⁹, however, there is limited data on health care related factors associated with severe malaria in resource limited settings.

Inaccessibility to basic health facilities because of geographical or economic reasons often presents major challenges preventing prompt access to early diagnosis and effective antimalarial treatment. Home based management of malaria in the form of self-

treatment is often opted for after self-diagnosis based on presumptive symptoms of malaria. We performed a case control study to determine health care related factors associated with severe malaria in children.

Materials and Methods

Study site

The study was conducted in Mulago Hospital, the national referral and teaching hospital of Uganda. An area within 20km radius of the hospital was defined as the catchment community for both cases and controls. Malaria is meso-endemic in this area, occurring perennially with peaks during the 2 rainy seasons.

Population

A case of severe malaria was defined as a child aged 6 months to 5 years, with *P. falciparum* asexual parasitaemia, plus either cerebral malaria (*P.falciparum* malaria with manifestations of cerebral dysfunction including any degree of impaired consciousness, delirium, abnormal neurological signs, and focal or generalized convulsions), prostration or severe

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malarial anemia (*P.falciparum* malaria with hemoglobin less than 5mg/dl) with no other confirmed cause of the symptoms. All children with cerebral malaria had lumbar puncture and cerebro-spinal fluid analyzed to exclude meningitis.

A control was defined as a child aged 6 months to 5 years, who presented with fever or history of fever in the preceding 24 hours, with a positive blood smear for *P.falciparum*, a parasite count of at least 2000/ul with no other cause for the fever as well as not satisfying the criteria for severe malaria. Following recruitment of each case, a control from the same residential area and having a birth date within 6 months of the case' birth date was recruited. All the children were from areas surrounding Mulago Hospital and were all recruited during the same study period.

Calculation of sample size was done using data from a previous study done in Jinja hospital¹². Substitution into the formula for comparative studies (Schlesselman, 1974); yielded a sample size of 100 cases and 100 controls.

Study procedures

The caretakers were interviewed to establish symptom history, health seeking behavior, number of fever episodes in the past one year period, and use of protective measures against mosquito bites. A finger prick blood sample was taken for parasitological and hematological examinations and each child had a physical examination performed by the study physician. All children were treated according to the Uganda National Treatment guidelines.

Laboratory Tests

Thin and thick blood smears were stained with 2% Giemsa stain for thirty minutes, and parasite densities were calculated by counting the number of asexual parasites per 200 white blood cells (WBC) assuming a WBC count of 8,000/ul of blood. Complete blood counts and hemoglobin estimation were done using the Coulter method.

Statistical analysis

Data were recorded on standardized case report forms, reviewed daily for accuracy and completeness, and entered into EpiInfo version 6.04® (Centers for Disease Control and Prevention, Atlanta, GA) and analysis was done using SPSS 10.0 statistical software. Odds ratios (OR) with 95% confidence intervals were calculated. Categorical variables were analyzed

using Chi square test and Fisher's exact test was used where cell numbers were expected to be less than 5. The Independent T test was used for comparison of continuous variables that were normally distributed. Non-normally distributed variables were log transformed before applying the Independent T test and multiple regression analysis. Only variables found to have a statistically significant association with severe malaria at bivariate analysis were entered into the multiple regression model using Conditional Logistic Regression to identify independent predictors for severe malaria controlling for other factors. The Cox Regression procedure was used to fit a Conditional logit model. This was done by creating a failure time variable and a censoring indicator variable. A strata variable was created to specify the variable that determined the stratification. The Enter method was used to get the final model of independent risk factors for severe malaria using a p value of 0.05 as the cut off level for significance.

Ethical considerations

The study was approved by the Makerere University Faculty Research and Ethics Committee and was conducted according to Good Clinical Practice standards²¹. All parents/guardians of the children gave written informed consent.

Results

Between January and March 2002, 130 children with severe malaria were screened, of these, 100 children were enrolled consecutively and matched with 100 children with non severe malaria. Thirty children with severe malaria were not enrolled because they either lived outside the catchment community for this study, had malaria with meningitis, or their guardians did not consent to participate.

Among the children with severe malaria 44 (44%) had severe anaemia, (13, 13%) had cerebral malaria and (17, 17%) had prostration. Some children had more than one complication; 11 had cerebral malaria with severe anaemia, 8 had cerebral malaria with prostration, 4 had severe anaemia with prostration, and 3 had severe anaemia, cerebral malaria with prostration. Mean age of participants was 24 (SD 15.9) months and over 30% of the participants were in the age group 6-12 months. Ninety six percent and 97% of the cases and controls were female. Mean (range) number of episodes of fever per child within the previous year was 3 for both cases and controls. Most children (93% cases and 92% controls) had normal haemoglobin type

(haemoglobin AA). Two percent of the cases and 5% of the controls were carriers of the sickle cell gene (haemoglobin AS). None of the controls had hemoglobin SS compared to 3% of cases who had

sickle cell anaemia. Mean malaria parasite density was significantly higher among cases, (175,514/ul vs. 73,052/ul $p=0.002$) as indicated in table 1.

Table 1: Comparison of characteristics of cases and controls

Variable	Cases N=100	Controls N=100	P value
Mean age in months (SD)	25 (15.9)	24 (15)	0.49
% female	39	45	0.39
Mean age of caretaker in years (SD)	25.6 (6.8)	24.8 (6.7)	0.44
% with a mother as caretaker of child	91	91	1.0
Caretaker's marital status	72	81	0.13
% of caretakers with at least primary level education	89	86	0.36
Mean number of malaria episodes in previous year (range)	3 (0-10)	3 (0-20)	0.60
Haemoglobin AA	93 (93%)	92 (92%)	0.213
Haemoglobin AS	2 (2%)	5 (5%)	
Haemoglobin SS	3 (3%)	0	
Mean parasite density	175,514	73,052	0.002

Sociodemographic characteristics of caretakers of cases and controls were comparable as shown in table 1. Most caretakers (132, 66%) administered some form of medicine to the children at home before visiting hospital. Chloroquine was the commonest antimalarial taken at home; (51% cases and 52% controls). Other drugs administered included quinine, sulphadoxine-pyrimethamine (SP), amodiaquine, herbal medication, antibiotics and antipyretics. Duration of illness before receiving antimalarial treatment was significantly shorter for the controls (8 vs. 20 hours, $p=0.015$). Children with severe malaria were less likely to have been treated with SP in the proceeding two weeks (OR 0.2 95% CI 0.04-0.85 $p=0.016$).

Most caretakers (89, 89%) knew that mosquitoes transmit malaria although not all of them used protective measures against mosquito bites. Bed nets were the most frequently used protective measure (80, 40%) however, the majority of caretakers did not know if their nets were insecticide treated. Insecticide sprays and mosquito coils were the other methods used, however, very few caretakers reported their use (insecticide sprays; 17, 8.5% and mosquito coils; 10, 5%). Adjusted odds ratios of having severe malaria were higher in those who did not use any protection against mosquito bites (mosquito coils; OR=20.6, 95% CI 1.5-283.3, $P=0.02$, insecticide sprays; OR 10.9, 95% CI 1.1-105.6, $p=0.03$, bednets OR 2.27, 95%CI 0.95-5.36 $p = 0.06$) (table 2).

Table 2: Factors associated with severe malaria after multiple regression analysis

Factor	OR	CI	P value
Log (duration of illness prior to getting antimalarial treatment in hours)	2.23	1.07-4.65	0.03
Log (duration of illness prior to presentation at the hospital in days)	0.51	0.09-2.7	0.43
Lack of use of insecticide sprays	10.93	1.13-105.64	0.03
Lack of use of bed nets	2.27	0.95-5.36	0.06
Lack of use of mosquito coils	20.63	1.50-283.3	0.02
Log (parasite density/ul of blood)	2.0	1.04-3.87	0.03

Discussion

We performed a case control study to determine factors associated with development of severe malaria in children. Our findings show that high

parasite density and longer duration of illness before administering antimalarial treatment plus lack of use of protective measures against mosquito bites

significantly increased risks for severe malaria in children.

Our findings are consistent with findings from previous studies performed in malaria endemic areas¹⁰⁻¹³. We found very limited use of barriers against mosquito bites in our study population. This could be explained by low socio-economic status of our study population although information to determine socio-economic status was not collected. Although two previous studies concluded that socio-economic factors were not the major determinants for severe malaria in children^{3,5}, socio-economic status determines access to insecticide treated nets, insecticide coils and access to health facilities.

Sixty six percent of all the children in our study received some form of treatment within 24 hours of recognition of illness as either herbal medication or monotherapy like chloroquine or amodiaquine which is inappropriate for malaria treatment. This reflects insufficient knowledge of diagnosis and treatment of malaria in the community. Indeed Nsungwa-Sabiti et al in a study in Uganda found a number of fever illness classifications in the community all of which could be biomedical malaria¹⁴ but were defined otherwise. A study done in 4 districts of Uganda found high rates of self-medication as first action when the children fell sick¹⁵. In another study in Kabarole district, Uganda, many mothers gave local herbs which they thought were effective against malaria and so delayed taking their children to health facilities¹⁶. One study found that although treatment initiation was promptly done, over half the times it was inappropriate¹⁷.

Uganda was the first country to scale up Home Based Management of Fever/Malaria (HBMF) in 2002¹⁸. This HBMF strategy in rural Uganda was evaluated and revealed an improvement in the accumulated proportions of patients treated¹⁹. Our finding of reduced risk of severe malaria among children treated with SP in the preceding two weeks suggests that use of a longer acting effective antimalarial reduces risk for severe malaria. Use of artemisinin based combination therapy (ACT) as part of HBMF could reduce the incidence of severe malaria in children. Ajayi et al showed that ACTs can be successfully integrated into the HBMF strategy in a study conducted in Ghana, Nigeria and Uganda²⁰. This could be combined with appropriate training of mothers on recognition of symptoms and prompt treatment of malaria.

The case control study design is prone to information and selection bias as well as bias resulting

from confounding factors. However, we minimised bias by training the interviewers how to administer the questionnaire. Blinding of interviewers was not possible because the clinical picture of the cases was evidently different from that of the controls. Selection bias was minimised by restricting both cases and controls to individuals living within a 20 Km radius of the hospital. Confounding was minimised by matching cases and controls by age and area of residence. It is possible that some of the controls later on developed severe malaria; however, we were unable to identify these because we did not follow them up.

In conclusion, our results demonstrate the need for scale up of health education to promote use of barriers against mosquito bites, prompt anti-malarial treatment and community-based interventions against malaria as part of a national program to reduce the incidence of severe malaria in children.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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