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Relationship between Serum C-reactive Protein Levels and Severity of *Plasmodium falciparum* Malaria in Children Seen in South-South Nigeria

Utuk Eno-Obong Edet^{1*}, Ikpeme Enobong Emmanuel¹,
Udo Jacob Jackson² and Okpokowuruk Frances Samuel¹

¹Department of Paediatrics, University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria.

²Department of Paediatrics, University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria.

Authors' contributions

Authors UEE and IEE conceived and designed the study. They were involved in the drafting and writing of the manuscript. Authors UJJ and OFS were responsible for the acquisition, analysis and interpretation of the data. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: To determine the relationship between serum C-reactive protein levels and severity of malaria infection in children aged six months to five years in a malaria endemic setting.
Study Design: A prospective cross-sectional study.
Place and Duration of Study: This study was carried out in the Children Out-patient (CHOP) Clinic, Children Emergency Unit (CHEU), Child Welfare/Growth Monitoring Clinic, Immunization Centre and main Paediatric Ward of the University of Uyo Teaching Hospital (UUTH), Uyo in Akwa-Ibom State. It was conducted over a six month period.
Methodology: We studied three hundred and sixty (360) children with microscopically confirmed *Plasmodium falciparum* malaria and three hundred and sixty (360) healthy controls matched for age and gender. Their serum C-reactive protein levels were measured using the highly sensitive Enzyme Linked Immunosorbent assay (ELISA). Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 17.0.

*Corresponding author: Email: utukenoobong@yahoo.com;

Results: The serum C-reactive protein levels showed a positive correlation with the malaria parasite count ($r = 0.55$; $p < 0.001$). Children presenting with severe manifestations of malaria had significantly higher mean serum C-reactive protein levels (33.3 ± 6.88 mg/l) than the 8.12 ± 9.09 mg/l obtained in those with uncomplicated malaria ($t = -15.57$; $p = 0.001$).

Conclusion: This study shows that C-reactive protein levels are increased in children with malaria, especially in severe malaria. Its estimation therefore holds potential usefulness as an adjunct for assessment of malarial severity.

Keywords: Malaria; severity; C-reactive protein; children; Nigerian.

1. INTRODUCTION

Malaria remains a major cause of morbidity and mortality worldwide and more than 90% of these deaths, occur in sub-Saharan Africa [1,2]. All cases of *falciparum* malaria are potentially severe and life-threatening, especially when treated inappropriately. A major reason for progression from mild to complicated or severe disease is missed or delayed diagnosis especially when initial test was negative [3,4]. Measurements of parasitaemia have drawbacks as markers of severity as the intensity of parasitaemia does not always correlate with disease severity [1,5,6]. Hyper-parasitaemia in itself does not necessarily have major prognostic significance in semi-immune individuals (individuals living in an endemic area and exposed to malaria several times), as they often tolerate high parasite counts without signs of disease or severe effects [7].

The burden of malaria disease and its complications during childhood still constitutes a major public health problem that warrants more integrated and collaborative interventions towards its control [5,7,8]. Though microscopy is helpful, it is laborious, requires experienced technicians and is an imperfect 'gold standard' [7,8]. Prompt and accurate diagnosis is essential for proper case management. Efforts are being made to develop new procedures for malaria diagnosis, treatment and control [2,5,6]. The severity of an episode can be assessed by evaluating and combining a panel of criteria including fever, parasite load with *in vivo* measures of host factors which have rarely been assessed before as markers of malarial severity [9-11]. C-reactive protein is synthesized in the liver and is secreted in increased amounts within six hours of an acute inflammatory stimulus. Interleukin-6 (IL-6) plays a critical role in CRP induction. After effective treatment or removal of the inflammatory stimulus, levels can also fall. The only condition that interferes with the normal CRP response is severe hepato-cellular impairment [11,13,14].

Kremsner et al. [12] reported high plasma levels of C-reactive protein (CRP) in patients with severe malaria than uncomplicated cases. Some researchers believe that CRP or its toxic effects may contribute to the pathology of severe forms of malaria, and that many of the malarial symptoms may be due to excessive CRP induction [6,13,14]. This was suggested because the control of *P. falciparum* parasitaemia is dependent on a pro-inflammatory response, and an uncontrolled inflammation is thought to cause severe symptoms. It is postulated that higher levels of circulating CRP could affect the delicate balance between pro- and anti-inflammatory responses, leading to a reduced control of parasitaemia [14,15].

Host immune markers of inflammation, like CRP has been found to play an important role in the immune responses to malaria. Its measurement has physiological relevance as an indirect measure of inflammatory events. In hyperendemic or holoendemic malarial areas like

the sub-Saharan Africa, including Nigeria, these immunological markers may serve as useful indicators for active malarial episodes [6,13,16]. A prospective characterization of its level during malaria infection could provide additional insight to its response in the disease. This study sought to determine the importance of measuring C-reactive protein (CRP) levels in *falciparum* malaria in an area where it is endemic, and if this would prove valuable in the assessment of malarial severity.

2. MATERIALS AND METHODS

This study was carried out in the Children Out-patient (CHOP) Clinic, Children Emergency Unit (CHEU), Child Welfare/Growth Monitoring Clinic, Immunization Centre and main Paediatric Ward of the University of Uyo Teaching Hospital (UUTH), Uyo in Akwa-Ibom State. It was conducted over a six month period. Uyo, the capital city of Akwa-Ibom State, is located in the south-south region of Nigeria. All children with features of severe malaria were admitted into the children emergency unit for treatment, and were there after transferred to the Paediatric ward when their clinical condition was stable.

The study populations were children aged six months to five years, and were made up of two groups, the patients and the controls. Children with fever or a history of fever in the previous 48 hours prior to presentation in the hospital with a parasitological proof of *P. falciparum* malaria, and those with one or more features of severe malaria such as prostration, repeated convulsions, hyperpyrexia, impaired consciousness, severe anaemia, respiratory distress, jaundice, haemoglobinuria were included [2,17]. Children with history of anti-malarial use in the preceding three days of presentation and those with any obvious foci of infection and/or a positive blood culture examination were excluded. Also, excluded were children with evidence of chronic illnesses, chronic liver disease, inflammatory diseases, viral exanthema and those receiving anti-inflammatory drugs.

Every consecutive patient, aged six to sixty months, who presented with fever, (axillary temperature $\geq 37.5^{\circ}\text{C}$) or a history of fever had a detailed history and physical examination, including examination of the ears and throat. Those with a positive smear for *Plasmodium falciparum* who met other inclusion criteria were ultimately studied.

Severe malaria was defined as the presence of life threatening features in a patient with peripheral malaria parasitaemia. These features include any of the following: Unarousable coma (cerebral malaria), severe anaemia (haemoglobin less than 5g/dl), acidosis (arterial pH less than 7.5 or plasma bicarbonate level less than 15 mmol/l), haemoglobinuria, acute renal failure (urinary output less than 1ml/kg/hour), hypotension/shock (systolic blood pressure less than 50mmHg in children aged one to five years), bleeding manifestations, respiratory distress, hypoglycaemia (plasma glucose less than 2.2mmol/l), jaundice, hyperparasitaemia (greater than 250,000 parasites/ μl), prostration and hyperpyrexia (axillary temperature greater than 39.5°C). Severe malaria is a major cause of hospital admissions, morbidity and deaths in children especially in the first five years of life [1,4,5].

Uncomplicated malaria was defined as malaria parasitaemia with no life threatening features. The characteristic symptom of uncomplicated malaria is fever. Most cases of malaria in children in the tropics belong to this group [1,4,5].

The controls were afebrile, apparently healthy children aged six to sixty months, matched for age and gender with no clinically identifiable foci of infection after a detailed clinical examination. They were selected from children attending child welfare clinic for growth

monitoring and those presenting for immunization. A malaria parasite test was done in all the control children to exclude those with asymptomatic parasitaemia.

Serum C-reactive protein assay was done by the quantitative method using the highly sensitive Enzyme Linked Immunosorbent Assay (ELISA) method [18]. Two millilitres each of the patient's serum and control serum were diluted 100-fold prior to use and 10ul of CRP standards, diluted specimens and diluted controls were dispensed into the appropriate wells. The absorbance value (OD450) for each set of reference standards, controls and samples were obtained using the micro-plate reader. The obtained values of the patient samples and control sera were multiplied by the dilution factor of 100 to obtain CRP results in mg/l. Other investigations done in every patient presenting with severe malaria included random blood glucose and a full blood count. Electrolytes/urea and creatinine was done only in children with signs of renal impairment, urine output less than 1ml/kg/hour [17].

Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 17.0. Data were summarized into Tables and Graphs as appropriate. Discreet variables were expressed as numbers and percentages, while continuous variables expressed as mean and standard deviation. Normally distributed continuous variables were compared using the student's t-test. The Wilcoxon rank sum test was used for non-normally distributed continuous variables. Proportions were compared using the Chi-square (χ^2) test. Univariate and multivariate models were built. These helped to adjust for possible associations between malarial infection and the C-reactive protein response. P-value less than 0.05 ($p < 0.05$) was considered statistically significant.

Ethical approval was obtained from the University of Uyo hospital's ethics committee while a verbal informed consent was obtained from parents/guardian of children to be included in the study after initial assessment.

3. RESULTS

Three hundred and sixty (360) patients, and three hundred and sixty (360) controls were studied. Of these, 200 (55.6%) each were males and 160 (44.4%) each were females with a male to female ratio of 1.25: 1. The mean age of the male and female patients and that of the control group were similar (six months to five years). The duration of fever in the patients was one to four days (mean 1.9 ± 0.8) and mean temperature $37.83 \pm 0.89^\circ\text{Celsius}$ (range $36.5 - 40.1^\circ\text{Celsius}$). No child in the control group had fever (Table 1).

Table 1. General characteristics of the study population

Characteristics	Patients		T (p-value)	Controls		T (p-value)
	Male	Female		Male	Female	
Age (months)	24.24±16.77	25.48±17.97	-0.67 (0.50)	24.92±17.24	24.71±17.20	0.12 (0.91)
Weight (kg)	11.50±3.01	11.58±3.04	-0.25 (0.80)	11.59±3.07	11.40±2.97	0.59 (0.52)
Height (cm)	82.2±13.91	83.44±14.49	-0.83 (0.40)	82.48±14.09	83.14±14.23	-0.44 (0.65)
*MUAC (cm)	13.42±0.47	13.40±0.45	0.31 (0.76)	13.43±0.46	13.43±0.43	0.09 (0.92)
#OFC (cm)	50.02±3.09	49.87±3.25	0.45 (0.66)	50.12±2.97	49.82±3.28	0.92 (0.36)
Temperature (°C)	37.84±0.94	37.79±0.85	0.53 (0.59)	36.96±0.22	36.94±0.91	0.92 (0.36)

*MUAC - Mid Upper Arm Circumference

#OFC - Occipito-frontal circumference

The clinical characteristics of all the patients at presentation showed fever as the most common clinical feature in 217 (60.28%) of patients. Others in order of frequency were poor appetite, in 118 (32.8%) of patients, hyperpyrexia 54 (15.0%), splenomegaly 52 (14.4%), hepatomegaly 16 (4.4%), severe pallor 15 (4.2%), convulsions 10 (2.8%), altered sensorium in seven (1.9%) of the patients. Only three (0.8%) of the patients had jaundice.

Five of the fifteen patients who presented with severe pallor, also had signs of congestive cardiac failure – tachycardia (with a gallop rhythm), dyspnoea and tachypnoea (*respiratory distress) and tender hepatomegaly. Of the seven patients who presented with altered sensorium, three were deeply comatose (Blantyre’s score of 0-2), with a diagnosis of cerebral malaria, while four had light coma (Blantyre’s score of 3 - 4) from hypoglycemia. The mean packed cell volume (%) in patients with uncomplicated malaria was 30.7±2.40 greater than the 25±9.03 obtained in those with severe malaria (t = 8.84; p = 0.001). The mean random blood sugar (mmol/l) in the patients with severe malaria was 3.09±0.75 (range 1.60 to 4.80) Table 2. The relative frequency of the characteristics in patients presenting with severe malaria showed prostration as the most common sign in 31 (53.4%), and jaundice the least, in three (5.5%) of the patients (Table 3).

Table 2a. Clinical symptoms of the patients at presentation

Symptoms#	N	(%)
Fever	217	60.28
Poor appetite	118	32.8
Vomiting	94	26.1
Convulsions	10	2.8

#Most children had more than one clinical symptom at presentation.

Table 2b. Clinical signs of the patients at presentation

Signs#	N	(%)
Hyperpyrexia	54	15
Splenomegaly	52	14.4
Prostration	31	8.6
Hepatomegaly	16	4.4
Severe Pallor	15	4.2
Altered sensorium	7	1.9
Rapid breathing*	5	1.4
Jaundice	3	0.8

#Most children had more than one clinical sign at presentation.

*Respiratory rate ≥ 50 cycles/minute in infants 2 to less than 12 months and ≥ 40, cycles/minute in children 1 to 5 years [1,2,3].

Table 3. Relative frequency of characteristics of the 55 patients with severe malaria

Variable*	Yes (%)	No (%)
Hyperpyrexia	54 (98.2)	1 (1.8)
Prostration	31 (53.4)	24 (46.6)
Severe anaemia	15 (27.3)	40 (72.7)
Multiple convulsions	10 (18.2)	45 (81.8)
Altered sensorium	7 (12.7)	48 (87.3)
Hyperparasitaemia	7 (12.7)	48 (87.3)
Respiratory distress**	5 (9.1)	50 (90.9)
Cerebral malaria	3 (5.5)	52 (94.5)
Jaundice	3 (5.5)	52 (94.5)

*Most patients presented with more than one manifestation of severe malaria. **Respiratory rate ≥ 50 cycles/minute in infants 2 to less than 12 months and ≥ 40, cycles/minute in children 1 to 5 years [1,2,3]

The mean malaria parasite count in patients was 15,602.22±61, 641.86 with a range of 500 to 695,500 parasites/μl. *Plasmodium falciparum* was the only specie found in all patients. The mean malaria parasite count was significantly higher in children with severe malaria than in those with the uncomplicated type (t = -7.24; p<0.001). The mean serum level of C-reactive protein was also significantly higher in children with severe than uncomplicated malaria (t = -15.57; p<0.001) as shown in Table 4.

The overall mean value of serum CRP for the patients was 11.97±13.97 (range 0.2 – 70.0mg/l), significantly greater than the 2.21±2.30 (range 0.2-10.0mg/l) in the control group. The mean differences in the mean serum CRP levels between the patients and controls was also statistically significant (t = 13.09; p< 0.001).

Table 4. Malaria parasite count and mean serum C-reactive protein levels in patients

Clinical malaria	Malaria parasite count (parasites/μl) Mean ± S.D	C-reactive protein level (mg/l) Mean ± S.D
Uncomplicated malaria	5234.43±50404.98	8.12±9.09
Severe malaria	73096.36±145336.6	33.30±16.88
T test (p-value)	-7.24 (0.001)*	-15.57 (0.001)*

*Statistically significant

The distribution of the malaria parasite count and serum C-reactive protein levels in the patients is shown in Table 5. The patients with hyperparasitaemia (>250,000 parasites/μl) [5,6] had the highest mean serum C-reactive protein level. Using the one way analysis of variance (ANOVA), the differences in the mean serum C-reactive protein levels among the various parasitaemia groups was statistically significant, (F = 87.13; p = 0.001). Also, the mean parasite count (parasites/μl) of patients with hyperpyrexia was 67841±141572.28 significantly greater than the 8774.69±24789.74 in febrile patients, and the 3409.09± 5068.07 in the afebrile patients (F = 26.76; p = 0.001).

Table 5. Distribution of the malaria parasite count and serum crp levels in the patients

Malaria parasite count/μl (range)	N	C-reactive protein (mg/l) Mean ± S.D	F (p value)
500 – 5000	195	5.96±7.01	87.13 (0.001)
>5000 – 100,000	86	11.43±10.97	
>100,000 – 250,000	72	25.20±16.73	
> 250,000	7	49.71±10.79	
Total	360	11.97±13.96	

ANOVA F = 87.13; p = 0.00

There was a 55% relationship between the natural log of malaria parasite count and natural log of C-reactive protein and this was statistically significant. This was a positive correlation (r = 0.55; p<0.001). Thus, as the malaria parasite count increased, there was a concomitant increase in serum C-reactive protein. This is shown in Fig. 1.

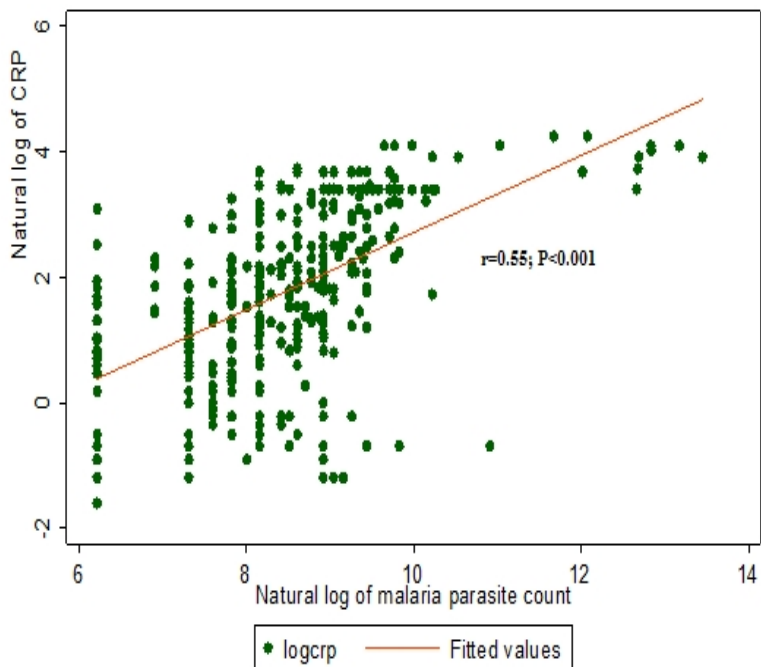


Fig. 1. Relationship between the malaria parasite count and serum C-reactive protein levels in patients

4. DISCUSSION

The findings from this study show greater mean serum CRP concentrations in patients with manifestations of severe malaria, than in the uncomplicated type. There has been similar reports from other authors in African children [19-21]. The various authors documented an association of severe malaria with high circulating levels of inflammatory cytokines such as tumour necrosis factor-alpha, interleukin-1 and interleukin-6. These cytokines responsible for acute malarial illness, is also responsible for the stimulation, production and sustained release of C-reactive protein.

The significantly higher serum CRP level in the febrile patients than the afebrile ones in the present study, was also documented in other African children by Hurt et al. [21] and Imrie et al. [22]. In Tanzania, Hurt et al. [21] found this trend of significantly increasing serum CRP levels in children with temperatures greater than 37.4°C. The children who presented with hyperpyrexia in present study had relatively higher parasite densities. This higher density of parasitaemia, schizont rupture and merozoite release into the bloodstream, may have resulted in febrile symptoms at presentation. It is known that fever accompanies cytokine release, which results from macrophage response to invading parasitaemia. Fever is triggered by endogenous pyrogens like interleukins 1 and 6, and tumour necrosis factor which are also responsible for the stimulation of CRP in malaria [23,24].

The higher levels of mean serum CRP concentration between the patients and controls in the various age groups in present study reinforces the effect of malaria antigen in the induction of CRP production [20,25,26]. Mononuclear cells which are activated by the *plasmodium* during malaria, produce inflammatory cytokines and stimulate the hepatic synthesis of acute

inflammatory proteins including CRP. This cytokine response is likely responsible for this observation.

The positive correlation of serum C-reactive protein levels in patients with higher levels of parasitaemia in study is similar to trends in children of Gambia [19,20], Tanzania [21] and Zambia [25] which are also endemic for malaria. This finding may be related to the higher parasite burden in these children which triggers the inflammatory response. However, contrasting reports, from Papua New Guinea [22] did not document a consistent increase in the serum CRP level with increasing parasitaemia. This may be explained by the wider age group of the Papuan study population, which included adolescent children up to seventeen years of age permanently resident in the malaria hyperendemic region. Most of these adolescent children, had already acquired malarial immunity. They therefore elicited lowered immune responsiveness to malarial antigens, and a corresponding reduction in pro-inflammatory mechanisms.

Children in this study were less than five years of age, and have been recognized to elicit more marked immune responses to invading malaria parasites. This increased inflammatory response, increases their CRP levels. This documented trend continues till malarial immunity has been acquired, and then it later plays an important protective role in the modulation of the immune responses to invading parasites, including severity of malarial episodes.

Limitations to this study include confounding factors for increased C-reactive protein which are viral fevers that can co-exist in children with malaria. Additional investigations such as viral screen studies were not available in our facility. This would have been employed to confirm any co-existing viral infection in the children with malaria.

5. CONCLUSION

C-reactive protein levels are increased in children with *P. falciparum* malaria infection, greater in those with the severe manifestations. This study can be used to gain insight as to the changes of C-reactive protein with regards to the severity and complications of malaria. It holds potential benefits for future use in children with *falciparum* malaria as it will help in the identification and prompt treatment of such children.

COMPETING INTEREST

The authors declare that they have no competing interests.

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