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Full Length Research paper

Assessment of renal function of Nigerian children infected with *Plasmodium falciparum*

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The levels of kidney function parameters were estimated in children infected with *Plasmodium falciparum* malaria to determine its association with renal impairment. Apparently healthy children with no malaria infection were included as the control subjects. It was observed that the levels of serum urea, serum creatinine, and protein in urine were significantly higher in infected children when compared with the control values. The relationship between parasitaemia density and serum urea were negatively correlated (r = -0.44), but serum creatinine (r = 0.61) and protein in urine (r = 0.47) were positively correlated. There was no significant change in serum electrolytes levels in the infected subjects compared to the control. Children within 1 - 5 years of age had higher parasitaemia density (8677.48 ± 3241.82 /µL) than those between 6 - 12 years of age (4881.72 ± 872.36 /µL). These children (1 - 5 years) had higher levels of serum urea (6.44 ± 0.36 mmol/L), serum creatinine (126.88 ± 12.24 µmol/L) and protein in urine (28.07 ± 2.66 mg/dl) when compared with children between 6 - 12 years (serum urea = 5.27 ± 0.91 mmol/L, serum creatinine = 123.76 ± 4.32 µmol/L and protein in urine = 19.64 ± 3.91 mg/dl). The result suggested that renal impairment was associated with malaria infection.

Key words: Children, *Plasmodium falciparum*, renal function.

INTRODUCTION

Malaria is endemic in the tropics and subtropics. Malaria accounts for an estimated 2 - 3 million deaths annually and is also responsible for untold morbidity and in approximately 300 - 500 million people annually and infant death and abortion. Susceptible groups are children and adults who have host or never acquired immunity (Mishra et al., 2002). It precipitates such terribly mutilating afflictions (in children) as Cancrum oris and has numerous complications such as anaemia, pulmonary oedema, renal failure and coma, which may be fatal (Eze and Mazeli, 2001). Malaria parasite interferes with three organs in the body namely the brain, kidney and liver (Edington, 1967). Serious cases of renal problems associated with malaria take the form of nephritic syndrome, which gradually progress to renal failure (Rees et al., 1972; Edwards and Boucher, 1991). It is characterised by severe proteinuria (Rees et al., 1972; Rui-Mei et al., 1998; Ogbadoyi and Tembeng, 1999) gravity, low ratio of urinary to blood urea (Van-Velthysen, 1979), and hyper-kalaemia and metabolic acidosis (Boon Sinniah et al., 1999) rise in blood urea, low urine specific (Sitprija, 1979) . Acute respiratory failure occurs in about 60% of all the cases of complicated malaria (Boon and Sitprija, 1996; Sitprija, 1988; Nanda et al., 2004). In *Plasmodium falciparum* malaria, acute respiratory failure occurs in 1 - 5% of cases (Sheehy and Reba, 1967; Prakash et al., 1996) with mortality of 15 - 45% (Barsoum, (2000).

Considering the endemicity of malaria in Nigeria, the mortality rate across families, particularly in children and pregnant women, accurate prognosis and proper management are very necessary. The incidence of kidney problems is on the increase in Nigeria (Ogbadoyi and Gabi, 2000), malaria and other infectious diseases may be contributing factors. It is therefore important to know the prevalence level of renal involvement in malaria cases to ensure effective management of patients as they report to medical centres. This is important because in the presence of acute renal failure, death increases three

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Table 1. Urea, creatinine and protein levels and parasitaemia density according to the age of the infected and control children.

	Age (years)	Urea (mmol/L)	Creatinine (µmol/L)	Protein (mg/dl)	No. of Children	Malaria Parasitaemia /µL
Infected	1 - 5	6.44 ± 0.36*	126.88 ± 12.24*	28.07 ± 2.66*	14	8677.48 ± 3241.82
Subjects	6 -12	5.27 ± 0.91*	123.76 ± 4.32*	19.64 ± 3.91*	31	4881.72 ± 872.36
Control	1 - 5	4.96 ± 0.31	110.67 ± 2.81	13.04 ± 1.13	4	-
Subjects	6 -12	5.01± 0.44	111.45 ± 3.71	15.84 ± 0.59	11	-
P Values	1 - 5	0.022	0.042	0.016		
	6 -12	0.036	0.040	0.024		

Values are reported as mean ± standard deviation for 'n' number of children, *, means values are significantly different ($p < 0.05$) compared with the control, n = number of subjects.

fold, but with early detection and institution of frequent dialysis, mortality rate is reduced by 90% (Mishra et al., 2002). The severity of malaria associated renal impairment in a particular area is largely a function of the disease prevalence and other aetiological factors prevailing in the area (Naqvi et al., 2003). Not much has been done to establish the degree of renal involvement in malaria cases in Nigeria and in Owerri, in particular. To gain insight into this, they investigated the renal function parameters among Nigerian children diagnosed with *P. falciparum* malaria and studied the correlation between renal function and parasitaemia density.

STUDY AREA

A cross-sectional study of 60 children between the ages of 1 - 12 years was conducted in the town of Owerri, Imo state, Nigeria, between June, 2009 and August, 2009. Owerri lies on latitude 5.485^{O}N and longitude 7.035^{O}E and is located in a rainforest belt of Imo state (Ekeanyanwu et al., 2009), endemic for *P. falciparum* malaria parasite which is transmitted by the female anopheles mosquito. It has a rainy period from April - November which is when the bite of mosquito is more rampant. The rainforest belt where the state is located is also a very good site for mosquito habitat.

SUBJECTS

The study subject consists of 60 children between the ages of 1 - 12 years who attended the paediatric clinic of federal medical centre (FMC) Owerri, Nigeria. The study subjects were 45 children with *P. falciparum* malaria parasite, who reported ill with fever (axillary temperature > 37˚C) headache, vomiting, diarrhoea, respiratory distress, and other clinical signs and symptoms of malaria, as previously documented and also have not been placed on any anti- malarial drug. These children were also confirmed through appropriate laboratory tests to be suffering from only malaria parasite infection. The children who did not meet these criteria were excluded from the study. Apparent healthy children, consisting of 15 subjects who report for routine medical examination and found to be negative for *P. falciparum* in their peripheral blood were used as controls. Both groups of subjects must have resided in the city of Owerri for at least one year before the study. The scope, nature, and objective of the investigation were thoroughly explained to the parents/guardians of the children for their consent, which was sought and obtained. Approval was also obtained from the ethical committee of the Federal Medical Centre (FMC) and the Ministry of Health, Owerri, Imo State.

STUDY DESIGN

About 5 mls of blood were collected from each subject using a 5 ml syringe after formal consent. *P. falciparum* parasitaemia was determined in peripheral blood smears stained by Giemsa stain. The thick and thin films were analysed for the number of parasites per 200 white blood cells. Slides were considered negative if no parasites were seen in 100 fields in the film. Protein concentrations in urine of malarious and non-malarious subjects were estimated by the Biuret method (Ditterbrandt, 1948), creatinine was estimated using the alkaline Picrate slot method (Cheesbrough, 1991a), serum urea levels were estimated according to the method of Cheesbrough (1991b), sodium and potassium levels were estimated using flame photometry as described by Davidson and Henry (1979).

STATISTICAL ANALYSIS

The data obtained were presented as mean ± standard deviation. The degree of freedom between the test subjects and control group was analysed using simple student's test at 95% significance level, and compared using spearman's correlation.

RESULTS

The levels of serum urea, serum creatinine and protein in urine and parasitaemia density according to the age of the infected subjects and control subjects are presented in Table 1. Children between 1-5 years old had the highest

Table 2. Serum electrolytes levels and parasitaemia density according to the age of the infected and control children.

	Age (years)	Sodium (mmol/L)	Potassium (mmol/L)	Bicarbonate (mmol/L)	Chloride (mmol/L)	No. of children	Malaria parasitaemia/µL
Infected	1 - 5	124.81 ± 1.06	4.12 ± 1.06	26.86 ± 2.41	99.09 ± 3.47	14	8677.48 ± 3241.82
Subjects	6-12	126.76 ± 3.94	4.11 ± 0.06	27.41 ± 2.62	99.41 ± 3.86	31	4881.72 ± 872.36
Control	1 - 5	125.40 ± 1.01	3.69 ± 0.07	25.46 ± 2.04	99.66 ± 2.40	4	-
Subjects	6-12	129.64 ± 0.71	4.16 ± 0.81	28.71 ± 3.21	105.86 ± 0.12	11	-
P Values	1 - 5	0.089	0.067	0.109	0.140		
	6-12	0.086	0.098	0.066	0.122		

Values are reported as mean ± standard deviation for 'n' number of children, *means values are significantly different ($p < 0.05$) compared with the control, n = number of subject.

Table 3. Urea, creatinine, and protein levels and parasitaemia density of test and control subjects.

Parasitaemia density/µL	No. of subjects	Urea (mmol/L)	Creatinine (µmol/L)	Protein (mg/dl)
Mild/moderate infected <7000/µL(4634.0 ± 1261.62)	33	5.01 ± 0.86	115.44 ± 7.66	19.48 ± 2.13
Severe infected >7000/µL (11,261 ± 526.82)	12	5.56 ± 0.44	125.62 ± 12.86	27.94 ± 3.07
Mean infected volunteers (5827.12 ± 1,070.44/µL)	45	5.46 ± 0.88*	120.76 ± 10.40*	25.46 ± 3.01*
Mean control volunteers (0.00 ± 0.00/µL)	15	4.98 ± 0.32	110.66 ± 4.77	14.66 ± 1.42
P Values		0.008	0.007	0.047

Values are reported as mean ± standard deviation for 'n' number of children, *, means values are significantly different ($p < 0.05$) compared with the control, n = number of subjects.

P. falciparum load of 8677.48 ± 3241.82 in their peripheral blood. Also, these children had a higher serum urea concentration (6.44 ± 0.36 mmol/L) than those between 6 - 12 years of age (5.27 ± 0.91mmol/L). The serum creatinine concentration (126.88 ± 12.24 mmol/L), and concentration of protein in urine (28.64 ± 2.66 mg/dl) were higher in younger children within 1 - 5 years but were lower in those children between 6-12 years when compared. However, there were significant differences at $p < 0.05$ in the serum urea, serum creatinine and protein in urine of malaria infected children, 1 - 5 years of age and 6-12years of age compared with the control subjects.

The levels of serum electrolyte and malaria parasitaemia according to the age of the infected and control children are presented in Table 2. There was no significant change ($p > 0.05$) in the serum electrolytes levels of infected children between the ages of 1 - 5 and 6 - 12 compared to their control non infected subjects. The levels of serum urea, serum creatinine, and protein in subjects are presented in Table 3. The infected subjects had higher mean concentration of serum urea (5.46 ± 0.88 mmol/L), and these differences were statistically significant at $p < 0.05$ when compared with the control group. The mean concentration of serum creatinine (120.76 ± 10.40 µmol/L), and protein in urine (25.46 ± 3.01mg/dl) in the infected subjects were statistically significant at $p < 0.05$ when compared with the control subjects. The relationship between parasitaemia density, serum creatinine and protein in urine were strongly and positively correlated with r = 0.61 and r = 0.47 respectively. The serum level of urea was negatively correlated with the malarial parasitaemia (r = - 0.44). The levels of serum electrolytes and parasitaemia density of the volunteers are presented in Table 4. There were no significant changes ($p > 0.05$) in the levels of serum electrolytes in the infected subjects compared with the control groups.

DISCUSSION

Urine and the parasitaemia density of the test and control Malaria has protean clinical manifestation and the kidney is one of the affected organs. Analysis of data obtained showed that the levels of serum urea, serum creatinine, and protein in urine were higher among the test subjects than the control. The higher values observed in these parameters may be attributed to impairment in renal function associated with *P. falciparum* infection (Ogbadoyi and Gabi, 2000). It was observed that the levels of protein in urine in *P. falciparum* infected subjects were significantly higher ($p < 0.05$) than the control subjects (Table 1). This observation confirms earlier reports (Mishra et al., 2002; Ogbadoyi and Tembeng, 1999; Ogbadoyi and Gabi, 2000). High level of proteinuria is characteristics feature of renal dysfunction (Rui-Mei et al., 1998). In healthy kidneys, proteins are normally completely filtered from the blood stream and then

Table 4. Serum electrolytes levels and parasitaemia density of test and control subjects.

Parasitaemia density/µL	No. of subjects	Sodium (mmol/L)	Potassium (mmol/L)	Bicarbonate (mmol/L)	Chloride (mmol/L)
Mild/moderate infected <7000/µL (4634.0 ± 1261.62)	33	130.66 ± 1.04	4.00 ± 0.06	28.84±0.66	102.15 ± 0.93
Severe infected >7000/µL (11,261 ± 526.82)	12	130.54 ± 0.24	4.01 ± 0.12	27.62 ± 0.48	98.44 ± 4.62
Mean infected volunteers (5827.12 ± 1,070.44/µL)	45	129.86 ± 2.08	4.01 ± 0.80	27.88 ± 1.46	101.66 ± 1.92
Mean control volunteers (0.00 ± 0.00/µL)	15	130.06 ± 0.95	4.05 ± 0.69	28.22 ± 0.40	103.33 ± 0.96
P Values		0.077	0.096	0.110	0.160

Values are reported as mean ± standard deviation for 'n' number of children, *, means values are significantly different ($p < 0.05$) compared with the control, n = number of subjects.

reabsorbed, allowing no protein or only untraceable amounts of protein into the urine. Persistent presence of considerable amounts of protein in the urine is a useful indicator of a Form of kidney disease. Therefore, that the amounts of protein in the urine of malarious subjects were more than two times the amounts in non malarious subjects, this is an indicative of some level of renal dysfunction. This is attributable to malaria as there was positive correlation between proteinuria and level of parasitaemia. Asymptomatic bacteria may also have contributed to be high level of proteinuria recorded (Ogbadoyi and Tembeng, 1999). It is well known that apparently healthy individuals especially children also excretes small amounts of protein a condition known as orthostatic proteinuria (Edwards and Boucher, 1991).

Proteinuria as an indication of renal dysfunction should be taken with great caution. It will be very useful to measure the amounts of protein in urine after treatment to ascertain if the elevated levels are due to malaria alone. The elevated serum urea levels in malarious subjects which differed significantly from the non-malarious subjects may be primarily due to factors such as other than malaria as there was no positive correlation between parasitaemia and urea levels. Serum creatinine was also significantly elevated in malarious subjects with a positive correlation to parasitaemia density. Serum urea and creatinine concentrations are used for the assessment of renal sufficiency (Smith et al., 2006). Higher than normal values of serum urea and creatinine are indicators of deficiency in renal function (Narayanan and Appleton 1980; Whelton et al., 1994). In acute renal failure, serum urea increases more rapidly than serum creatinine concentration (Emian-Ong, 2002) . Despite all these consideration, serum urea levels do not reflect the performance of the kidneys like creatinine. This is because urea production is also affected by dehydration, food intake and tissue catabolism. Thus an increase in serum urea concentration with concomitant increase in serum creatinine concentration in the infected subjects suggests that the normal functioning of the kidneys have been compromised.

There was no significant difference ($p > 0.05$) in the levels of serum electrolytes of the malarious subjects compared with the control subjects (Table 2). *Falciparum* malaria is not known to be associated with remarkable disturbance in electrolyte balance (Naqvi et al., 2003). This probably explains why the study was unable to show a significant increase in electrolyte levels between the two groups. It was observed that children within the first 5 years of age had higher levels of serum urea, serum creatinine, and protein in urine than those between 6 - 12 years who had lower parasitaemia (Table 2), suggesting that children within 1 - 5 years old were more prone to kidney dysfunction associated malaria than those within 6 - 12 years of age. The results of the present study are in agreement with those of (Weber et al., 1999) who made similar observation in a study of renal involvement in Gambian children with malaria.

Conclusion

The Precise mechanism of impairment of renal function in *falciparum* malaria is not clearly known. Several hypotheses including mechanical obstruction by infected erythrocytes, immune mediated glomerular and tubular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation have been proposed. The pathogenesis of renal involvement is possibly mediated through immune complex deposition. Histopathological changes that have been observed in infected kidneys include features of mesangiocapillary glomerular and sub-endothelial immune complex deposits containing IgG, C3 and Malarial antigen (Das, 2008).

The observed evidence of impairment of renal function in malaria is very important because Nigeria is an endemic country and more so where quite a large number of populations still do not have access to proper hospital treatment. Even in urban areas where there are hospitals, most patients report at hospitals only when self medications have failed. There is therefore the potential danger of widespread acute renal failure, which may in some cases progress to chronic kidney disease, and the attendant mortality. It is therefore recommended that constant re-evaluation of the incidence and prevalence is done, preferably a country wide study, in order to

establish the true picture of the incidence and prevalence in Nigeria. This is especially important in children as malaria is recognised as one of the causes of acute renal failure in children in developing countries (Radhakrishan and Kiryluk, 2006). Children who report at hospitals for malaria treatment should also be subjected to routine kidney function tests to rule out renal impairment, especially in all cases of severe malaria, as early diagnosis will significantly reduce mortality rate.

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