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Assessment of Renal Function of *Plasmodium falciparum* Infected Children in Owerri, Eastern Nigeria

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Abstract: The levels of kidney function parameters were estimated in *Plasmodium falciparum* malaria infected children. About 45 children with *P. falciparum* infection were selected based on clinical symptoms. About 15 apparently healthy children with no malaria parasitaemia were included as the control subjects. *P. falciparum* malaria and kidney function parameters (serum urea, creatinine, sodium, potassium, bicarbonate, chloride and protein in urine) were determined using standard procedures. 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 respective control values. The relationship between malaria parasitaemia 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 the controls. Children within 0-5 years of age had higher malarial parasitaemia (8677.48±3241.82 μL^{-1}) than those between 6-12 years of age (4881.72±872.36 μL^{-1}) and these children had higher levels of serum urea (6.44±0.36 mmol L^{-1}), serum creatinine (126.88±12.24 μmol L^{-1}) and protein in urine (28.07±2.66 mg dL^{-1}) when compared with children between 6-12 years (serum urea = 5.27±0.91 mmol L^{-1}, serum creatinine = 123.76±4.32 μmol L^{-1} and protein in urine = 19.64±3.91 mg dL^{-1}). The result suggests that there is a form of renal impairment associated with malaria infection in children in Owerri, Eastern Nigeria.

Key words: Renal function, *Plasmodium falciparum*, children, Nigeria, kidney, malaria

INTRODUCTION

Malaria is essentially a tropical disease occurring in regions between latitude 62^0N and 40^0S with an altitude of 1,500 m. This region is formed mainly within the tropics and subtropics and this makes malaria endemic in this zone (Walter and Davis, 1976). There are two epidemiological extremes of malaria known as stable and unstable malaria (Butler *et al*., 1996). Epidemiological factors that make malaria endemic in the tropics include climatic factors (relative humidity, altitude, rainfall level, mean temperature between 18-19°C) and socioeconomic factors as all these have effects on the availability of vectors which maintain that transmission of malaria (Butler *et al*., 1996). Malaria can be transmitted by three known ways; vector transmission (Anderson *et al*., 1981), blood transfusion (Strickland, 1991) and congenital transmission (Ezechukwu *et al*., 2004). The vector for malaria parasite is the female anopheles mosquito (Cheesbrough, 1998). Malaria is a protozoan infection caused by the parasite Plasmodium. There are four species of the parasite that infect man, namely *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium vivax* being the most common (McGee *et al*., 1992). 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

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Boucher, 1991). It is characterised by severe proteinuria (Rees *et al*., 1972; Rui-Mei *et al*., 1998; Ogbadoyi and Tembeng, 1999; Sinniah *et al*., 1999) rise in blood urea, low urine specific gravity, low ratio of urinary to blood urea (Van Velthysen, 1996) and hyper-kalaemia and metabolic acidosis (Boonpucknaviq and Sitprija, 1979). Acute respiratory failure occurs in about 60% of all the cases of complicated malaria (Boonpucknaviq and Sitprija, 1979; Sitprija, 1988; Nanda *et al*., 2004). In *P. 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, 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 on the presence of acute renal failure, death increases three 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 we investigated the renal function parameters among Nigerian children diagnosed with *P. falciparum* malaria and studied the correlation between renal function and malaria parasitaemia.

MATERIALS AND METHODS

The study was conducted in the town of Owerri, Imo state, Nigeria, between June, 2009 and August, 2009. Owerri lies on latitude 5.485°N and longitude 7.035°E and is located in a rainforest belt of Imo state, endemicfor *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. Owerri has a population comprising workers in the private sector, civil servants, students, traders, self employment, etc. 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 children 45 with *P. falciparum* malaria parasite who reported ill with fever (axillary temperature >37.5°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. The children who did not meet these criteria were excluded from the study. Apparent healthy children, consisting of 15 subjects who were 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 1 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.

Plasmodium 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 (1969). The data obtained were subjected to statistical analysis.

RESULTS AND DISUSSION

The levels of serum urea, serum creatinine and protein in urine and the intensity of infection (Malarial parasitaemia) of the volunteers are shown in Table 1 the infected volunteers had higher mean concentration of serum urea (5.46±0.88 mmol L^{-1}) and these differences were statistically significant at $p<0.05$ when compared with the control counterparts. The mean concentration of serum creatinine (120.76±10.40 μmol L^{-1}) and protein in urine (25.46±3.01 mg dL^{-1}) in the infected counterparts were statistically significant at $p<0.05$ when compared with the control counterparts.

The relationship between malarial parasitaemia, 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 negatively correlated with the malarial parasitaemia (r = -0.44). The levels of serum electrolytes and intensity of infection (malarial parasitaemia) of the volunteers are shown in Table 2. There were no significant changes ($p>0.05$) in the levels of serum electrolytes in the infected counterparts

Table 1: Urea, creatinine and protein levels and intensity of infection (Malaria parasitaemia) of test and control subjects

Intensity of infection μL^{-1}	No. of infected	Urea Mmol L^{-1}	Creatinine µmol L^{-1}	Protein Mg dL^{-1}
Mild/moderate<7000 μL^{-1} (4634.0±1261.62)	33	5.01±0.86	115.44±7.66	19.48±2.13
Severe>7000 μL^{-1} (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^{-1})	45	5.46±0.88*	120.76±10.40*	25.46±3.01*
Mean control volunteers (0.00±0.00 μL^{-1})	15	4.98±0.32	110.66±4.77	14.66±1.42

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

Table 2: Serum electrolytes levels and intensity of infection (Malaria parasitaemia) of test and control subjects

Intensity of infection μL^{-1}	No. of infected	Sodium Mmol L^{-1}	Potassium Mmol L^{-1}	Bicarbonate Mmol L^{-1}	Chloride Mmol L^{-1}
Mild/moderate<7000 μL^{-1} (4634.0±1261.62)	33	130.66±1.04	4.00±0.06	28.84±0.66	102.15±0.93
Severe>7000 μL^{-1} (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^{-1})	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^{-1})	15	130.06±0.95	4.05±0.69	28.22±0.40	103.33±0.96

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

Table 3: Urea, creatinine and protein levels and intensity of infection (malaria parasitaemia) according to the age of the infected and control children

Groups	Age (years)	Urea Mmol L^{-1}	Creatinine µmol L^{-1}	Protein Mg dL^{-1}	No. of Children	Malaria parasitaemia μL^{-1}
Infected	0-5	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±872.360
Control	0-5	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	-

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

Table 4: Serum electrolytes levels and intensity of infection (malaria parasitaemia) according to the age of the infected and control children

Groups	Age (years)	Sodium mmol L^{-1}	Potassium mmol L^{-1}	Bicarbonate mmol L^{-1}	Chloride mmol L^{-1}	No. of children	Malaria parasitaemia μL^{-1}
Infected	0-5	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	0-5	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	-

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

compared with the control counterparts. The levels of serum urea, serum creatinine and protein in urine and malarial parasitaemia according to the age of the infected and control children are shown in Table 3. Children between 0-5years old had the highest *Plasmodium 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^{-1}) than those between 6-12 years of age (5.27±0.91 mmol L^{-1}). The serum creatinine concentration (126.88±12.24 mmol L^{-1}) and concentration of protein in urine (28.64±2.66 mg dL^{-1}) were higher in younger children within 0-5 years but were lower in those children between 6-12 years when compared. However, there was significant differences at $p<0.05$ in the serum urea, serum creatinine and protein in urine of malaria infected children, 0-5 years of age and 6-12 years of age compared with their control counterparts. The levels of serum electrolyte and malaria parasitaemia according to the age of the infected and control children are shown in Table 4. There was no significant change ($p>0.05$) in the serum electrolytes levels of infected children between the ages of 0-5 and 6-12 compared to their control counterparts. 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 than the levels for controls. 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 was significantly higher ($p<0.05$) than the control subjects (Table 1). This observation confirms earlier report (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 reabsorbed allowing no protein or only small 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 twice the amounts in non malarious subjects is

indicative of some level of renal dysfunction. That this is attributable to malaria is the 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). Apparently healthy individuals especially children excretes small amounts of protein demonstrable renal disease 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 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 between parasitaemia and creatinine levels. 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 (Narayabnan and Appelton, 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 as compared to 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 controls (Table 2). *Falciparum* malaria is not known to be associated with remarkable disturbance in electrolyte balance (Naqvi *et al*., 2003). This probably explains why we have been unable to show electrolyte levels in most of t he *P. falciparum* infected children that significantly differed from those of the controls.

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 0-5 years old are more prone to malaria associated kidney dysfunction 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. 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 observed in infected kidneys include features of mesangiocapillary glomerular and sub-endothelial immune complex deposits containing IgG, C3 and Malarial antigen (Das, 2008).

CONCLUSION

In this study the observed evidence of impairment of renal function in malaria is very important because Nigeria is an endemic country and more so when 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.

RECOMMENDATIONS

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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