Full Length Research Paper

The influence of malaria infection on kidney and liver function in children in Akoko area of Ondo state, Nigeria

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Renal and hepatic dysfunctions are part of the pathological effect of malaria infection common in children and pregnant women. Renal dysfunction is characterized by increase in creatinine, urea, and some of the electrolytes in the serum, while hepatic dysfunction is characterized by increase in liver enzyme activities. Two hundred and seventy children (age ranged 0 to 5 years) were recruited into this study. Malaria positive children were divided into two groups based on the number of parasite per µl. Those that had parasitaemia below 10,000 parasite per µl were considered mild infection, while those that had parasitaemia above 100,000 parasite per µl were considered severe infections. Malaria negative children were used as control. The result showed significant increase (P < 0.05) in serum creatinine and urea level in the malaria positive when compared with the control group. Among malaria positive children, the level of creatinine and urea were higher in the severe group than in the mild group. Sodium, potassium, bicarbonate, and chloride levels were significantly higher (P < 0.05) in the control group than in malaria infected children, with the exception of the potassium which was significantly higher in the severe group than in the control group. Among malaria positive, serum Na⁺, HCO₃⁻ and Cl⁻ levels were significantly higher in the mild infection than in the severe infection. Serum protein was also significantly higher (P < 0.05) in the control group than in the infected children. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were significantly higher in the severe group than in the mild and control groups. This study showed that malaria infection has effect on renal and hepatic functions, and the level of dysfunction is determined by the severity of the infection.

Key words: Malaria, liver function, kidney function, serum electrolyte, liver enzymes, children.

INTRODUCTION

The prevalence of malaria infection is more pronounced in the tropics, especially in the Sub-Saharan Africa than in other parts of the world (Taulil, 2006). One of the reasons for this, is climatic condition that favours the reproduction pattern of the vector and rapid development of the parasite within the vector and the host (Ross and
Smith, 2010). The attitude of the people in the community and lack of basic infrastructural facilities may also be responsible for the rampant prevalence of malaria infections (Modiano et al., 1996). Developed countries have been able to eradicate malaria infection because of the high level of technical knowhow and human resource. The control or eradication of the vectors would go a long way towards the eradication of the malaria infection in the tropics. Despite the concerted efforts of the World Health Organization (WHO), government, and private organizations, the elimination of malaria parasite remains elusive in the tropical region (Akanbi et al., 2014). Because of the development of drug resistant strains of the parasite, the attention on malaria parasite has now been shifted to the prevention of malaria rather than eradication.

Prevalence and severity of malaria infection have been reported to be higher among children and pregnant women than in any other groups (Zaki et al., 2013; WHO, 2010), and it is the main cause of morbidity and mortality in endemic areas (Gomes et al., 2011). Among the malaria parasites that infect man, Plasmodium falciparum is the major cause of severe malaria and deaths from malaria cases. Effect of P. falciparum varies from asymptomatic to multi-organ manifestation, which could lead to the death of the victim (Zaki et al., 2013). Malaria has been implicated as one of the factors responsible for renal and hepatic dysfunction in malaria endemic area countries (Mishra et al., 2003; Ogbadoyi et al., 2007; Sharma et al., 2004). The malaria parasites usually affect the kidney, liver and brain (Dzeing-Ella et al., 2005).

The level of severity of malaria infection can be determined by both renal and hepatic malfunction. The clinical manifestation of renal involvement is associated with infection by P. falciparum and Plasmodium malariae (Naqvi et al., 2003), and may be responsible for an immune complex mediated glomerular disease leading to nephrotic syndrome. Other implications range from urinary sediment abnormalities, mild proteinuria and electrolyte changes to acute renal failure with metabolic acidosis (Padhi and Mishra, 2012). In addition, renal tubular changes have been reported to be associated to P. falciparum infection more than glomerular changes, and complication may range from minor to acute tubular necrosis and acute renal failure (ARF) accompanied by frequent oliguria and hypercatabolism (Gomes et al., 2010).

ARF can be diagnosed by the presence of oliguria and increased serum creatinine and blood urea nitrogen (Gomes et al., 2010). Malaria has been reported to be one of the factors responsible for acute renal failure among children in malaria endemic areas (Mockenhaupt et al., 2004), and this adverse effect of malaria parasite on the kidney could lead to an increase in blood urea, hyper-nareemia, hyper-kalaemia, low urine specific gravity, metabolic acidosis and low ratio of urinary to blood urea (Padhi and Mishra, 2012). The sudden increase in the urea level and imbalance in the electrolytes level such as sodium, potassium, bicarbonate, and chloride in malaria infected people could serve as indicators for kidney dysfunction (Uzuegbu, 2011; Ebele et al., 2010; Jasani et al., 2012). Liver dysfunction is a common complication that usually occurs in malaria infection. Some studies have reported a sudden increase in liver enzymes in malaria infected individuals as an indication of liver dysfunction (Jarike et al., 2002; Onyesom and Onyemakonor, 2011). This could be as a result of the invasion of liver cells by the sporozoite during malaria parasite life cycle (Onyesom, 2012).

The changes caused in the hepatic cell by sporozoite can lead to the leakage of parenchymal and membranous enzymes of the liver into the circulatory system, which can be responsible for the increase in liver enzymes (Burtis and Ashwood, 2001). The severity of malaria infection has been linked with the increase in the level of liver enzymes in the body (Onyesom and Onyemakonor, 2011). As a result of high level of complication and death of children due to malaria infection, there is need to evaluate the extent of renal and hepatic dysfunctions in malaria cases so that there will be proper management of malaria infection and its associated complication (Ogbadoyi et al., 2009). The place where this study was conducted is a peri-urban area with high episode of malaria infection, especially among children. There is no information on the pathology of malaria infection in children in this area so far.

Therefore, this study assessed the pathological effect of malaria infection on liver and kidney functions in children in Akoko area of Ondo state, Nigeria.

MATERIALS AND METHODS

Study centre and subjects studied

The samples for this study were collected at Comprehensive health centre, Akungba-Akoko, Ondo state, Nigeria, and paediatric unit of the specialist hospital, Ikare, Ondo state, Nigeria from May to September 2011 and June to September, 2012, respectively. Two hundred and seventy children within the age range 0 to 5 years who were sick with temperature > 37°C, diarrhoea, headache, vomiting, and some other malaria symptom were recruited for this study. One hundred and ninety were malaria positive, while 80 were malaria negative (control). The children that were malaria positive were divided into two groups based on the number of parasite per µl.

Those that had below 10,000 parasites per µl were considered mild infection, while those that had parasitaemia levels above 100,000 parasites per µl were considered severe infection. The children that were malaria negative after screening for malaria parasite were used as control. The details of the study were explained to the mother or guardian of the children and the verbal consent was sought for and obtained from them. Questionnaires were distributed among the parents who gave their consent in order to get some information about their children. The study was
reviewed and approved by Local Institution Review Committee.

Collection of blood
About 4 ml of blood was collected by venepuncture from each child by a trained technologist under the supervision of the medical doctors using 5 ml needles and syringe. 2 ml of the whole blood was immediately transferred into ethylene diaminetetra acetic acid (EDTA) bottle that was used for the haematological study, while the remaining 2 ml was transferred into plain bottle and was allowed to clot and serum was later separated. The level of electrolytes, total protein, creatinine, urea and liver enzymes were determined from the serum. The parasitaemia was determined using the whole blood.

Determination of parasitaemia
Thick blood film was prepared on the slide from the whole blood collected from each child. The slide was stained with Giemsa’ stain and left for about 10 min, after which the slide was washed and allowed to dry. The slide was mounted on the light microscope and screened for the presence of malaria parasite. A slide was considered negative when no parasite was found after screening of 200 fields. For those slides that were positive the number of parasites counted per 200 white blood cells was used to calculate parasite density on the basis of 8000 leucocyte per µl of blood.

Kidney function test
Kidney function test was done by determining the level of creatinine, urea and electrolytes in the serum of all the groups studied.

Determination of serum urea
Serum urea was determined by using the method described by Di Giorgio (1974). Urea reacted with diacetylmonoxime to form yellow diazinederivative. The colour change was measured at 520 nm being directly proportional to the concentration of urea in the sample.

Determination of serum creatinine
Serum creatinine level was measured by the method described by Narayanan and Appleton, (1980). Protein present in 0.5 ml of serum was precipitated with 0.5 ml of sodium tungstate and centrifuged at 3000 rpm for 5 min. The supernatant was separated, and 0.5 ml of alkaline picrate was added to 0.8 ml of supernatant which formed a red complex. The absorbance was read in a spectrophotometer at 520 nm against a reagent blank, after incubation for 15 min at room temperature.

Electrolyte assays
The serum electrolytes (Na⁺, K⁺, HCO₃⁻ and Cl⁻) levels were determined by standard assay kit procedure from Teco Diagnostics, Anaheim, U.S.A. as described by Cheesbrough (1991).

Determination of serum protein ALT, AST and ALP
Serum ALT, AST and ALP activities were used to determine the liver function in the samples using the spectrophotometric method with standard assay kits obtained from Randox laboratories, UK. ALT, AST and ALP levels were measured by the pyruvate, oxaloacetate and thymolphthalein monophosphate methods, respectively (Christen and Metzier, 1985). Serum protein levels were determined by the Biuret method (Gornall et al., 1949).

Statistical analysis
The data were analyzed by the one-way analysis of variance and the means are separated by Duncan’s Multiple Range Test with 95% confidence intervals (SPSS 15.0, SPSS Inc., Chicago, IL, USA). The results were expressed as mean ± standard deviation (SD).

RESULTS
The urea level was significantly lower (P < 0.05) in the control group than in the malaria infected children. The level of creatinine was significantly increased (P < 0.05) in the severe group when compared with the level in the mild and control groups, while it was only marginally higher in the mild group than in the control group (Table 1). Total protein was found to be significantly reduced in the severe group when compared with both mild and control groups, but serum protein level was not significantly higher in the control group than in the mild group (Table 1). The levels of Na⁺, HCO₃⁻ and Cl⁻ were significantly higher (P < 0.05) in the control group than in the malaria positive children.

There was a significant increase (P < 0.05) in the Na⁺, HCO₃⁻, and Cl⁻ levels in the mild group when compared with the severe group. The potassium was significantly higher (P < 0.05) in the severe groups than in the control and mild group but was only marginally higher in the mild group when compared with the control group (Table 2). Table 3 shows the effect of malaria infection on liver enzymes. The AST and ALT levels were significantly higher (P < 0.05) in the severe group than in the control and mild groups, but they were not significantly higher in the mild group than in the control group. The ALP level was higher in the control group than in the severe and mild groups but it was not significantly higher.

DISCUSSION
Malaria is a major parasitic disease that is responsible for a high death rate in children in the world, especially in the tropical region where it is endemic (WHO, 2010). Almost all the complications and death that occur as a result of malaria infection in children are caused by P. falciparum. Among complications that are associated with falciparum malaria, renal and hepatic dysfunctions are common in both children and adults living in malaria endemic regions (Ogbadoyi et al., 2009; Uzugbue et al., 2011). These two organs are very important in the body and their impairment...
Table 1. Effect of malaria infection on urea, creatinine, and protein level in children.

<table>
<thead>
<tr>
<th>Severity of infection</th>
<th>No.</th>
<th>Urea (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>Protein (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>95</td>
<td>18.63±1.3 a</td>
<td>0.41±0.1 a</td>
<td>27.06±2.5 a</td>
</tr>
<tr>
<td>Severe</td>
<td>95</td>
<td>24.95±0.3 b</td>
<td>0.47±0.3 b</td>
<td>16.73±2.5 b</td>
</tr>
<tr>
<td>Control</td>
<td>80</td>
<td>18.21±2.3 a</td>
<td>0.40±0.1 a</td>
<td>28.90±1.2 a</td>
</tr>
<tr>
<td>Total</td>
<td>270</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are means ± SD. Means followed by similar letters within the same column are not statistically different (p < 0.05 was considered significant). No. stands for number of children enrolled.

Table 2. Effect of malaria infection on the electrolytes level in children.

<table>
<thead>
<tr>
<th>Severity of infection</th>
<th>Na⁺ (mmol/l)</th>
<th>K⁺ (mmol/l)</th>
<th>HCO₃⁻ (mmol/l)</th>
<th>Cl⁻ (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>129.0±1.6 b</td>
<td>4.3±0.1 a</td>
<td>27.2±0.2 c</td>
<td>100.1±3.0 b</td>
</tr>
<tr>
<td>Severe</td>
<td>123.2±3.4 c</td>
<td>4.9±0.2 b</td>
<td>26.1±0.3 b</td>
<td>91.6±4.3 c</td>
</tr>
<tr>
<td>Control</td>
<td>133.4±2.3 a</td>
<td>4.4±0.1 a</td>
<td>29.1±0.5 a</td>
<td>110.1±3.1 b</td>
</tr>
</tbody>
</table>

Values are means ± SD. Means followed by similar letters within the same column are not statistically different (p < 0.05 was considered significant).

Table 3. Effect of malaria infection on serum AST, ALP and ALT in children.

<table>
<thead>
<tr>
<th>Level of infection</th>
<th>No.</th>
<th>AST (U/L)</th>
<th>ALP (U/L)</th>
<th>ALT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>95</td>
<td>134.6±3.0 b</td>
<td>65.0±9.5 a</td>
<td>62.3±3.7 b</td>
</tr>
<tr>
<td>Severe</td>
<td>95</td>
<td>139.5±3.1 a</td>
<td>67.5±13.1 a</td>
<td>73.9±6.1 b</td>
</tr>
<tr>
<td>Control</td>
<td>80</td>
<td>130.5±2.1 b</td>
<td>69.4±12.5 a</td>
<td>60.1±3.5 b</td>
</tr>
<tr>
<td>Total</td>
<td>270</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are means ± SD. Means followed by similar letters within the same column are not statistically different (p < 0.05 was considered significant). No. stands for number of children enrolled.

Management needs to be detected early and managed appropriately. This study showed a significant increase in the creatinine and urea in children with severe malaria infection when compared with the group that had mild malaria infection and control group. Low levels of creatinine and urea in the group with mild malaria suggests that the severity of malaria infection has great influence on the level of creatinine and urea in the body of infected person. The observed increase in creatinine and urea in the severe group could be a result of sequestration of the parasite into the renal microvasculature bed which may lead to ischemia (Zaki et al., 2013). This indicates that the group with severe malaria may be more likely to have transient renal dysfunction which could be limited for the period of the infection. A study has reported a reduction in the clearance of endogenous creatinine during acute malaria infection returning to normal levels after recovery (Mishra et al., 2007). The serum protein levels were significantly reduced in the severe group when compared with the mild and control groups. A previous study reported a reduction in the serum protein in malaria patients (Akanbi et al., 2014), which was probably a result of intervention of malaria parasite in the synthesis of protein.

Electrolyte imbalances in the body may also serve as an indicator of renal failure and this has been indicated in malaria-infected individuals (Kirk and Horner, 1995). Some of the electrolytes were used as an indicator of renal dysfunction including Na⁺, Cl⁻, K⁺ and HCO₃⁻ (Uzuegbu, 2011). The levels of electrolyte in this study were reduced in malaria positive children when compared with the control group. This shows that malaria infection could influence the level of body electrolyte in infected individuals. The significant decrease in Na⁺, Cl⁻, and
HCO$_3^-$ levels in the group with severe malaria infection when compared with the mild group in this study shows that the level of kidney dysfunction may be determined by the severity of malaria infection in the infected individuals. The reduction in the level of Na$^+$ may be due to losses in sweat and urine in the body which may serve to compensate for increased lactase and urea levels commonly found in *P. falciparum* patients (Etim et al., 2011; Mayne, 1994). A significant increase in K$^+$ level recorded in the severe group in this study could lead to metabolic acidosis (Etim et al., 2011). This result concurs with some previous report of hyponatraemia and hyperkalemia in malaria infected individuals (Etim et al., 2011; Olaniyan, 2005). It has been reported that impaired glomerular filtration as a result of malaria infection could be responsible for the reduction in the Na$^+$ available in the renal tubule for K$^+$ exchange. This may lead to the increase in the serum K$^+$ level (Wolfswinkel et al., 2010; Etim et al., 2011) as a result of imbalance in hydrogen ions which will lead to the retention of K$^+$ in the serum.

The invasion and development of the malaria parasite into the liver during the life cycle may be responsible for liver dysfunction by causing organ congestion, cellular inflammation, and sinusoidal blockage (Anyasor and Olorunsogo, 2011). The increase in the serum ALT and AST in the severe and mild group when compared with the control group in this study shows that malaria parasite infection may be responsible for the increase in the liver enzymes, which may lead to liver dysfunction. This agrees with a previous study that showed that *P. falciparum* infection may be responsible for the increase in the liver enzymes (Onyesom et al., 2011). The increase in serum ALT and AST in malaria positive children could be as a result of leakage of these enzymes from the liver, as a result of damages to liver cell during the liver stage of the life cycle of malaria parasite. The ALT and AST level were higher in the group with severe group as compared with the mild group which is an indication that the level of liver dysfunction may be determined by the level of parasitaemia in the body. This study agrees with the previous study which showed a positive correlation between the level of liver dysfunction and parasitaemia (Onyesom and Onyemakonor, 2011). The ALP level was not significantly higher in the control than in the infected groups. The factors that may be responsible for this contrary result when compared with the previous studies are not known, therefore, there is a need for further study to confirm this.

**CONCLUSION**

This study concluded that malaria infection has an immense impact on the liver and kidney function in children, especially among those who were severely infected.

**RECOMMENDATION**

To avoid the damage done to the liver and kidney of malaria infected children by the malaria parasite, it is therefore recommended that malaria test should be conducted regularly for every child below the age of 5 years, so that appropriate treatment could be applied before the infection becomes severe. Children living in malaria endemic areas should be given intermittent preventive malaria treatment along with other vaccinations as recommended by the WHO. The use of treated mosquito net for the children should be overemphasized to the expectant mothers during antenatal clinic and when the children are brought for routine vaccination.

**ACKNOWLEDGEMENT**

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**Conflicts of interest**

The author has none to declare.

**REFERENCES**


