INTRODUCTION
In the paediatric age group, and particularly among under-fives, hypoglycaemia is a common metabolic problem encountered in association with a variety of diseases. In countries with limited resources, undernutrition, infectious diseases, delayed presentation in hospital, administration of potentially toxic herbal concoctions, and lack of facilities for diagnosis may increase the frequency of occurrence of hypoglycaemia. Hypoglycaemia is a well recognized complication of Plasmodium falciparum malaria with or without treatment with quinine and it is associated with increased mortality and neurologic sequelae, particularly among under-fives. In these patients, it is difficult to identify hypoglycaemia from clinical examination alone, because all the signs of hypoglycaemia may be mimicked by those of severe malaria.
ease severity in children with falciparum malaria.\textsuperscript{6,8,10} In the light of the above, hypoglycaemia should always be considered, assessed and, if present, treated in severe malaria.

Various pathogenetic mechanisms have been postulated to explain the occurrence of hypoglycaemia in children with falciparum malaria who have not been treated with quinine. Firstly, increased glucose consumption. Glucose consumption increases in fever and infection. In acute falciparum malaria, there is increased glucose turnover due to increased glucose consumption both by the host and the parasite\textsuperscript{11,12}, with the host’s requirement being considerably greater\textsuperscript{11}. Secondly, glycogen depletion and/or impaired gluconeogenesis. Although fasting reduces glycogen stores rapidly even in well nourished children, the presence of high substrate levels (lactate and alanine) and absence of ketosis in many children with hypoglycaemia suggest that other factors than starvation might be involved.\textsuperscript{11} Planche et al\textsuperscript{8} has postulated that hypoglycaemia in children with severe falciparum malaria is due to a combination of impaired hepatic gluconeogenesis and/or increased peripheral utilization of glucose as a result of increased anaerobic glycolysis. Obviously, the pathogenesis of hypoglycaemia in children with falciparum malaria is multifactorial and debatable, but it is generally agreed that it is due to a variable depletion of hepatic glycogen due to starvation, cytokine-induced impairment of hepatic glyconeogenesis and a 2 to 3-fold increase in glucose turnover.\textsuperscript{8,11-13}

Between the age of six months and five years, there is waning of all the malaria-protecting factors resulting not only in increased frequency of falciparum malaria, but also, increased occurrence of complications of which hypoglycaemia is one of the most important.\textsuperscript{7} The presence of hypoglycaemia at the point-of-admission has been shown to be significantly associated with death\textsuperscript{5,8,10}, particularly within the first 24 hours of admission.\textsuperscript{2} Plasmodium falciparum (the predominant species in Africa) accounts for the majority of these deaths.\textsuperscript{8} It is estimated that the fatality rate might be up to 30\% in nonimmune infants, if appropriate therapy is not instituted promptly.\textsuperscript{9} Given that hypoglycaemia is amenable to inexpensive and readily available treatment, various clinicians have recommended that children with falciparum malaria should be monitored frequently for hypoglycaemia,\textsuperscript{8,10} and where diagnostic facilities are lacking, presumptive treatment should be instituted.\textsuperscript{10}

The purpose of the present study was to determine the prevalence of hypoglycaemia at the point of hospital admission among under-fives with falciparum malaria and identify some of its risk factors.

**PATIENTS AND METHODS**

This cross-sectional study was conducted between January and December, 2010 at St Philomena Catholic Hospital (SPCH), Benin City, Nigeria. SPCH is a large secondary-health-care institution that cares for all categories of patients. It has a fairly well equipped laboratory manned by qualified laboratory scientists and offers a 24-hour laboratory service.

At the point of admission, all children between the age of one and 59 months who were suspected to have malaria were recruited into the study after explaining the relevant details of the study to their parents/caregivers and obtaining their consent subsequently. The study design was approved by the hospital authority. Following recruitment, pretreatment venous blood samples for blood film for malaria parasites (Giemsa stain), full blood count (automated) and plasma blood glucose estimation were collected into the appropriate sample containers and forwarded immediately to the hospital laboratory for processing. The venous blood glucose samples were collected into fluoride-oxalate bottles and analysed by the glucose-oxidase method.\textsuperscript{14} A medical laboratory scientist (with over 20 years experience) processed the samples urgently at the request of the admitting physician, guided by the following criteria: absence of overt protein-energy malnutrition (kwashiorkor/marasmus), negative history of treatment with quinine and/or herbal concoctions. Only patients who had positive plasmodium falciparum parasitaemia and no other identifiable cause for their fever after clinical and laboratory evaluation had their data analysed in this study. Data was obtained on the duration of illness and the time of last meal. To allow for comparison with previous studies, the prevalence of hypoglycaemia was compared between children aged below 3 years and those 3 years and above as well as duration of illness less than 4 days and 4 days and above. In the present study, hypoglycaemia was defined as blood glucose level less than 2.6 mmol/L.

Statistical analysis involved calculation of Odd ratio and 95\% Confidence Interval. The chi square
test was used in ascertaining the significance of differences between two proportions with the p-value set at < 0.05.

**RESULTS**

During the twelve-month study period, a total of 502 children, 270 males (53.8%) and 232 females (46.2%) below five years of age, were admitted for Plasmodium falciparum malaria. The male- to- female ratio was 1.2: 1. Ninety two (18.3%) of the 502 children had hypoglycaemia at the point of admission. Table 1 shows that 23.0%, 78 of 339 children aged below 36 months were hypoglycaemic compared to 8.6%, 14 of 163 children aged 36 months and above; $X^2 = 15.29$ $p < 0.01$. As shown in Table 1, prevalence of hypoglycaemia was slightly higher in girls than boys; 20.7% versus 16.3%. Odd ratio, OR = 1.3 (95% Confidence Interval, CI = 0.692-1.815). Of the 502 children with falciparum malaria seen during the study period, the duration of illness before presentation was 4 days and below in 375 (74.7%) cases and above 4 days in the remaining 127 (25.3%) cases. As shown in Table 2, the duration of illness before presentation did not significantly influence the prevalence of hypoglycaemia. The prevalence of hypoglycaemia was significantly higher in patients in whom the time of last meal was greater than 12 hours compared to those in whom the time of last meal was less than 12 hours; $X^2 =14.10$ $p < 0.05$ (Table 3). Majority (91.2%) of the patients
with falciparum malaria had one or two pluses of malaria parasitaemia but the degree of parasitaemia did not significantly influence the prevalence of hypoglycaemia (Table 4).

**DISCUSSION**

In the present study, the prevalence of hypoglycaemia at the point of admission among children below five years of age with falciparum malaria was 18.3%. This was lower than the 25.5% observed among under-fives with positive malaria parasitaemia seen at the General Hospital in Katsina, Nigeria\(^1\). On the other hand, the prevalence observed in the present study was 2.5 times higher than that reported from a district hospital in Kenyan\(^10\). The lower prevalence observed in the present study compared to the study in Katsina may be due to differences in timing of collection of blood sample from the patients. The blood sampling was performed at the point admission in the present study whereas it was collected any time in the first 24 hours of admission in the Katsina study. Besides, the investigators included patients on quinine before presentation in the hospital. Quinine is known to induce hypoglycaemia in children\(^11\). The implication is that inclusion of some patients on quinine might have resulted in the comparatively higher prevalence reported by the authors. This view is supported by the even higher prevalence (30.0%) reported among patients on therapy for severe malaria admitted into an Intensive Care Unit (ICU) in India\(^16\). The higher prevalence observed in the present study compared to the Kenyan study may be due to differences definition of hypoglycaemia used and the in age range of study populations. In the present study, a higher cut-off (< 2.6 mmol/L) was used in defining hypoglycaemia whereas 2.2 mmol/L was used as cut-off in the Kenyan study, partly accounting for the higher prevalence observed in the present study. Definition of hypoglycaemia used in a study is known to influence its prevalence\(^17\). The study population in the present study were children less than five years of age whereas some of the subjects in Kenyan study were older than five years. Studies have shown that the risk of hypoglycaemia is higher in younger children, particularly among those below three years of age.\(^1,\(^18\)\)

This view is further supported by the observation in the present study that the prevalence of hypoglycaemia was 2.7 times higher among children whose ages were below three years compared to their counterparts who were three years and above.

In consonance with other studies\(^11,\(^18\), data from the present study revealed that children with falciparum malaria whose ages were below three years had a significantly higher risk of developing hypoglycaemia than their counterparts whose ages were 3 years and above. A partial explanation might be found in the report of Zijlmans et al\(^18\), which stated that older children are better able to reduce peripheral glucose utilization during fasting, resulting in lower prevalence of hypoglycaemia among them. In that study, they reached this conclusion after showing that endogenous glucose production was not influenced by age in children with falciparum malaria. Planche et al\(^8\), proposed that the increased peripheral uptake of glucose was due to increased anaerobic glycolysis. It is also possible that children below three years of age have a comparatively lower glycogen reserve than children above three years of age, resulting in higher risk of hypoglycaemia in the former.

Data from the present study showed that among children with falciparum malaria, those in whom the time of last meal was greater than 12 hours were at higher risk of developing hypoglycaemia compared with their counterparts in whom the time of last meal was 12 hours and below. This finding is in keeping with the report of other studies\(^2,\(^10,\(^18,\(^19\). The increased

### Table 4. Prevalence of hypoglycaemia according to degree of parasitaemia.

<table>
<thead>
<tr>
<th>Degree of parasitaemia</th>
<th>Prevalence of hypoglycaemia</th>
<th>X² (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+ or 2+ (n = 458)</td>
<td>86 18.8</td>
<td>(&lt; 0.05)</td>
</tr>
<tr>
<td>3+ or 4+ (n = 44)</td>
<td>6 13.6</td>
<td>(&gt; 0.05)</td>
</tr>
<tr>
<td>Total (n = 502)</td>
<td>92 18.3</td>
<td></td>
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</tbody>
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risk of development of hypoglycaemia in patients in whom the time of last meal was greater than 12 hours might be explained by depletion of glycogen store during fasting; more than 8 hours after the last meal being indicative of fasting.

In the present study, the prevalence of hypoglycaemia was 1.3 times higher in girls than boys. This finding is in general agreement with 1.8 times reported from Ghana\textsuperscript{20}. There is no readily available explanation for this female preponderance. However, the authors in the Ghanaian study attributed it to gender-related health-seeking behaviour and/or genetic factor\textsuperscript{20}.

A previous study in the same centre with the present one, reported a gender-bias against the female child as reflected in the longer duration of illness before parents sought for medical help and comparatively more severe illness in girls than boys\textsuperscript{21}. However, the present study was not designed to address this issue, making it impossible to draw such a conclusion from it.

The duration of illness before presentation did not significantly influence the prevalence of hypoglycaemia in the present study. In Kenyan, Osier et al\textsuperscript{10}, reported a similar finding. There is no readily available explanation for this finding. If a longer duration of illness represents a more severe malarial disease, then the finding in two separate studies might be a handy explanation. The studies reported that during an extended fasting in children with falciparum malaria, glucose level decreased faster in non-severe group compared to severe group\textsuperscript{22,23}. In the context that longer duration of illness correlate with severe disease, these reports indirectly support our finding.

In another study among children with falciparum malaria, Dekker et al\textsuperscript{24} concluded that it is the precursor supply that limits gluconeogenesis and hence, glucose production. In this context, therefore, occurrence of hypoglycaemia may depend more on availability of precursor rather than mere duration of illness.

In conclusion, at the point of admission in children below 5 years of age with falciparum malaria, hypoglycaemia occurs more frequently in those below 3 years of age as well as those in whom the time of last meal was greater than 12 hours.

REFERENCES

12. Davies TME, Looareesuwan S, Pukrittayakamee S,


