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Point-of-admission hypoglycaemia among under-five Nigerian children with plasmodium falciparum malaria: prevalence and risk factors

Alphonsus N. Onyiriuka[1], Olasimbo O. Peter[2], Louis C. Onyiriuka[3], Patience O. Awaebe[4], Fidelis U. Onyiriuka[5]

Department of Child Health, University of Benin Teaching Hospital, Pmb 1111, Benin City, Nigeria.

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Abstract

Background: Hypoglycaemia is a well recognized complication of falciparum malaria in children but its diagnosis may be overlooked because all the clinical features may be mimicked by severe malaria. To determine the prevalence of hypoglycaemia at the point of hospital admission of under-fives with falciparum malaria and identify its risk factors in patients seen in a Nigerian secondary-health-care institution.

Methods: During a 12-month period and at the point of hospital admission, venous blood sample was collected into an appropriate sample bottle (fluoride-oxalate bottle) from 502 children who were below 5 years of age with positive falciparum malaria parasitaemia. The blood sample was analysed using the glucose-oxidase method. The duration of illness, degree of parasitaemia and time of last meal were noted for each child.

Results: Ninety two (18.3%) out of 502 children below five years old with falciparum malaria had hypoglycaemia (blood glucose below 2.6 mmol/L or 50 mg/dl) at the point of hospital admission. Twenty three percent (78 out of 339) of children below 36 months old were hypoglycaemic compared to 8.6% (14 out of 163) children aged 36 months and above; (p=0.01). Prevalence of hypoglycaemia was higher in girls (20.7%) than boys (16.3%) [Odd ratio, OR = 0.75 (95% Confidence Interval, CI = 0.48-1.18)]. Forty (13.1%) out of 305 children whose time of last meal was 12 hours and below had hypoglycaemia compared to 52(26.4%) out of 197 whose time of last meal was greater than 12 hours; (p=0.02). Hypoglycaemia at admission point was associated with a significant increase in mortality rate; (p=0.00). The duration of illness and the degree of parasitaemia did not have significant difference with the prevalence of hypoglycaemia.

Conclusion: In falciparum malaria, a greater interval (between 2 meals) than 12 hours in children below 36 months old predisposed them to hypoglycaemia. Routine monitoring of blood glucose at the admission point is suggested in malaria endemic region.

Keywords: Hypoglycaemia, prevalence, under-fives, risk factors.

Introduction

In children, particularly among under-fives, hypoglycaemia is a common metabolic problem encountered in association with a variety of diseases (1-3). In countries with limited resources, undernutrition (4), infectious diseases (5), delayed presentation in hospital (6), administration of potentially toxic herbal concoctions (1,5,6) and lack of facilities for diagnosis, the frequency of hypoglycaemia may be increased. Hypogly-

1. **(Correspondence author)**, MD. Department of Child Health, University of Benin Teaching Hospital, Pmb 1111, Benin City, Nigeria. alpndiony@yahoo.com; didiruka@gmail.com
2. MD. Paediatric Unit, St Philomena Catholic Hospital, Benin City, Nigeria. olasimbosojinu1@yahoo.com
3. MD. School Of Medicine, College Of Medical Sciences, University Of Benin, Benin City, Nigeria. chinedu.louis@gmail.com
4. Medical Laboratory Unit, St Philomena Catholic Hospital, Benin City, Nigeria. patcoded@yahoo.com
5. School Of Medicine, College Of Medical Sciences, University Of Benin, Benin City, Nigeria. ivorytowersy2k@yahoo.com

caemia 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 (7-9). 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 malaria (7,10,11). In addition, hypoglycaemia is one of the disease severity markers in children with falciparum malaria (6,8,10). In the light of the above, hypoglycaemia should always be considered, assessed and, if present, treated in severe malaria.

Various pathogenic 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 due to fever and infection. In acute falciparum malaria, there is an increased glucose turnover due to increased glucose consumption both by the host and the parasite (11,12) with the host's requirement being considerably greater (11). Secondly, glycogen depletion and/or impaired gluconeogenesis may lead to hypoglycaemia. Fasting, even in well nourished children reduces glycogen storage rapidly. However, 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 (11). Planche et al (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. However, 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 (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 (7). The presence of hypoglycaemia at the point-of-admission has been shown to be significantly associated with death (2,8,10) and dying within the first 24 hours of admission (2) *Plasmodium falciparum* (the predominant species in Africa) accounts for majority of these deaths (9). It is estimated that the fatality rate might be up to 30% in nonimmune infants, if appropriate therapy is not instituted promptly (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 (8,10). However, monitoring at admission point has been ignored by some clinicians in developing countries, partly because of lack of diagnostic facilities (10). In a General Hospital in Katsina, Nigeria, Usman et al, (14) reported a prevalence of 25.5% of hypoglycaemia among children admitted for malaria.

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, thereby promoting awareness of this metabolic problem.

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 admission point, all children between the age of 1 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.

Table 1. Distribution of hypoglycaemia according to age and gender

	Hypoglycaemia		X^2
Age (months)	Number	Percent	(p-value)
< 12 (n=82)[a]	13	15.9	a+b versus c=15.29
12-35 (n=257)[b]	65	25.3	(p=0.01)
36-59 (n=163)[c]	14	8.6	
Total (n=502)	92	18.3	
Gender			
Male (n=270)	44	16.3	Odd ratio, OR=0.75
Female (n=232)	48	20.7	(95% CI = 0.48, 1.18)
Total (n=502)	92	18.	p=0.5

Table 2. Prevalence of hypoglycaemia according to duration of illness before presentation.

	Prevalence of hypoglycaemia		X^2
Duration of illness	Number	Percent	(p-value)
0-4 days (n=375)	70	18.7	0.11
>4 days (n=127)	22	17.3	(p=0.5)
Total (n=502)	92	18.3	

The study design was approved by the hospital authority. All patients suspected to have malaria had pretreatment venous blood samples for thick and thin blood films for malaria parasites collected and processed and those found to be positive for plasmodium falciparum were ultimately recruited into the study. Blood sample for 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 colorimetric (enzymatic) principle method as suggested by Cheesebrough (15). A medical laboratory scientist (with over 20 years experience) processed the samples urgently at the request of the admitting physician. Exclusion criteria included: presence of overt protein-energy malnutrition (kwashiorkor/marasmus), positive history of treatment with quinine and/or herbal concoctions and presence of a coexisting morbidity capable of causing fever. 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. Given that data was obtained from the entire population of children who met the inclusion criteria (age between one and 59 months and admitted for confirmed falciparum malaria, using thick and thin blood films), a sampling method was not required. Sample size calculation was performed using the formula suggested by Fink et al (16). The formula is given by:

$$N = (Z/e)2(P)(1-P) = (1.96/0.05)2\ (0.255)(1-0.255)=295.6$$

Where N= Sample size; Z= Standard score corresponding to a given confidence level (1.96 for 95th CI); e= the proportion of sampling error (i.e., 0.05 for 95th CI); P= Estimated proportion or incidence of cases. Using the mentioned formula, a sample size of 296 children was required. However, the study was conducted over period of one year because of seasonal differences in incidence of malaria. In the present study, hypoglycaemia was defined as blood glucose value below 2.6 mmol/L (50 mg/dl). Based on World Health Organization (WHO) Plus System, the degrees of parasitaemia are: += 1-10 parasites per 100 high power field (HPF); 2+ =11- 100 parasites per 100 HPF; 3+= 1-10 parasites per HPF; and 4+= greater than 10 parasites per HPF (17). In general, looking at 100 fields at a magnification of 600-700 is equivalent to 0.25 micro litre of blood (17).

Statistical Analysis: Statistical analysis involved calculation of Odd ratio and 95% Confidence Interval. The chi square test was

Table 3. Prevalence of hypoglycaemia according to time of last meal.

Time of last meal	Prevalence of hypoglycaemia		Odd Ratio	X^2
	Number	Percent	1.72	(p-value)
≤12 hours (n=305)	40	13.1	95% CI	14.10
>12 hours (n=197)	52	26.4	1.66-1.79	p=0.02
Total (n=502)	92	18.3		

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

Degree of parasitaemia	Prevalence of hypoglycaemia		X^2
	Number	Percent	(p-value)
1+ or 2+ (n=458)	86	18.8	0.71
3+ or 4+(n=44)	6	13.6	(p=0.5)
Total (n= 502)	92	18.3	

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 below five years of age were admitted for *Plasmodium falciparum* malaria. Of this number, 270 (53.8%) were males and the remaining 232 (46.2%) were females, giving a male-to-female ratio of 1.2:1. All socioeconomic groups were represented. Ninety two (18.3%) out of the 502 children had hypoglycaemia at admission point. Table 1 shows that 23.0% (78 out of 339) children aged below 36 months were hypoglycaemic compared to 8.6% (14 out 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= 0.75 (95% Confidence Interval, CI = 0.48-1.18; P=0.5]. The duration of illness before presentation was 4 days and below in 74.7% (375 out of 502) and above 4 days in 25.3% (127 out of 502). 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 whose last meal was greater than 12 hours compared to less than 12 hours; (p=0.02) (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). Among 502 children admitted for falciparum malaria, 352 (70.1%) had anaemia (haematocrit below 30%) comprising, 236 (67.0%) and 116 (33.0%), mild-to-moderate (haematocrit 20-29%) and severe (haematocit below 20%) anaemia respectively. Among the 116 cases, 84(72.4%) had very severe anaemia (haematocrit below 15%). The presenting clinical features are shown in Table 5. Among the 92 children with hypoglycaemia at admission point, 23(25.0%) died compared to 22(5.4%) out of 410 without hypoglycaemia at admis-

Table 5. Presenting clinical features in 502 children below 5 years of age admitted for falciparum malaria.

Clinical features	Number*	Percentage
Body temperature: 37.5 to 38.4^{0}C	397	70.1
Body temperature: 38.5^{0}C and above	105	20.9
Anaemia (haematocrit below 30%)	352	70.1
Convulsion	206	41.0
Vomiting	201	40.1
Hepatoslpenomegaly	175	34.9
Splenomegaly	159	31.7
Altered consciousness	70	13.9
Acidotic respiration	29	5.8

*Some patients had more than one presenting clinical feature.

sion point; (X^2= 35.50 p=0.00). Twenty three (79.3%) children (out of the 29) with acidotic respiration had concomitant hypoglycaemia. Fourteen (60.9%) children (out of the 23) with hypoglycaemia and acidotic respiration died. All died children with hypoglycaemia happened in the first 36 hours of admission. Sixteen (69.6%) children (out of the 23) with hypoglycaemia who died were below 36 months old.

Discussion

In the present study at St Philomena Catholic Hospital, Benin City, the prevalence of hypoglycaemia at the admission point 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 (14). 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 blood sample collection from the patients. The blood sampling was performed at the admission point 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 attendance 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 an even higher prevalence (30.0%) reported among patients on therapy for severe malaria admitted into an Intensive Care Unit (ICU) in India (18). The higher prevalence observed in the present study compared to the Kenyan study may be due to differences in 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 (19). In the present study, children less than five years old were studied whereas some of the subjects in the Kenyan study were older than five years. Some other studies have shown that the risk of hypoglycaemia is higher in younger children, particularly among those below three years of age (1,20). This view is further supported by 2.7 times higher prevalence of hypoglycaemia observed among children below three years compared to their counterparts who were three years and above. In consonance with other studies (11,20), data from the present study revealed that children less than three years old with falciparum malaria had a significantly higher risk of developing hypoglycaemia than their counterparts who were 3 years and above. A partial explanation might be found in the report of Zijlmans et al (20) 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 old have a comparatively lower glycogen reserve than children above three years old, resulting in a higher risk of hypoglycaemia in the former.

Data from the present study showed that among children with falciparum malaria, those whose last meal was greater than 12 hours were at a significantly higher risk of developing hypoglycaemia compared with their counterparts whose last meal was 12 hours and below. This finding is in keeping with the report of other studies (2,10,20,21). The increased risk of hypoglycaemia in patients whose 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.

Although the prevalence of hypoglycaemia was slightly higher in girls than boys, the difference was not statistically significant. This finding is in general agreement with report from Ghana (22). There is no readily available explanation for this female preponderance. However, the authors in the Ghanaian study attributed it to gender-related health-seeking behavior and/or genetic factor (22). A previous study in the same centre as 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 (23). However, the present study was not designed to address this issue, making it impossible to draw such a conclusion from it.

In the present study, both the duration of illness before presentation and the degree of parasitaemia did significantly influence the prevalence of hypoglycaemia. Similar findings were reported by Osier et al (10) in Kenyan. This is not surprising as the relationship between parasitaemia observed in the blood film to severity of illness is different in different populations (17). For example, partially immune children with higher level of parasitaemia may have milder symptoms than non-immune children with lighter degree of parasitaemia, or even scanty parasitaemia. In some populations, asymptomatic peripheral malaria parasitaemia is known to occur (17). In addition, Zijlmans et al (24) reported that plasma glucose concentration decreased less rapidly in the more severely infected children. Indeed, some studies have shown that glucose production was higher in children with severe malaria than in children with non-severe malaria (25,26).

As in previous studies (2,8,10) the presence of hypoglycaemia at the admission point was associated with a significant increase in case fatality rate. In agreement with previous reports, most of the deaths occurred in the first 36 hours of admission (27). Other presenting features associated with death include age below 36 months and acidotic respiration. Similar finding has been previously reported (11,22,27). The increased death rate in children with falciparum malaria complicated by hypoglycaemia and acidotic respiration may be explained by the decreased peripheral vascular resistance, decreased cardiac contractility resulting in peripheral circulatory failure, pulmonary oedema, and a lowered threshold for ventricular fibrillation associated with severe acidosis (28,29). Lack of glucose, in itself, leads to ketoacid production, potentiating the acidosis (28). Prolonged severe hypoglycaemia results in neuronal death, further providing a lethal pathway in such patients (19).

One limitation of the present study was lack of data on blood glucose values during admission. However, as implied in the title of this article, the focus of the present study was the prevalence of hypoglycaemia at the admission point. The prevalence of hypoglycaemia during the course of hospital admission will be the subject of another study. The use of WHO Plus System in designating degree of parasitaemia is not appropriate for monitoring severe disease as it does not objectively reflect changes in the parasite load. In the present study, it was not used for monitoring but to show degree of parasitaemia.

In conclusion, in plasmodium falciparum malaria, time of last meal greater than 12 hours in children below 36 months old predispose them to hypoglycaemia.

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