Niger J Paed 2013; 40 (3): 238 –242

ORIGINAL

Onyiriuka AN
Peters OO
Awaebe PO

Hypoglycaemia at point of hospital admission of children below five years of age with falciparum malaria: prevalence and risk factors.

DOI:http://dx.doi.org/10.4314/njp.v40i3,7

Accepted: 26th December 2012

Onyiriuka AN (✉)
Department of Child Health,
University of Benin Teaching Hospital,
PMB 1111,
Benin City, Nigeria.
E-mail: alpndiony@yahoo.com,
didiruka@gmail.com

Olasimbo OP
Paediatrics Unit,
Awaebe PO
Medical Laboratory Unit,
St Philomena Catholic Hospital,
Benin City, Nigeria.

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 other features of severe malaria.
Objective: 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 -healthcare institution.
Methods: At the point of admission, venous blood sample was collected into an appropriate sample bottle (fluoride-oxalate bottle) from 502 children who were below 5 years of age for malaria parasite examination (Giemsa stain). The blood sample was analysed using the glucose-oxidase method.
Results: Ninety two (18.3%) of 502 children below five years of age with falciparum malaria had hypoglycaemia (blood glucose below 2.6 mmol/L) at the point of hospital admission. Twenty three percent, 78 of 339 children below 36 months of age were hypoglycaemic compared to 8.6%, 14 of 163 children aged 36 months and above; $p<0.01$. Forty (13.1%) of 305 children in whom the time of last meal was 12 hours and below had hypoglycaemia compared to 52 (26.4%) of 197 in whom the time of last meal was greater than 12 hours; $p<0.05$. The duration of illness and the parasite density did not have significant bearing with the prevalence of hypoglycaemia.
Conclusion: Age below 36 months and a time of last meal greater than 12 hours have significant bearing with occurrence of hypoglycaemia in children with falciparum malaria. Routine monitoring of blood glucose at point of hospital admission is suggested.

Key words: Hypoglycaemia, falciparum malaria, prevalence, risk factors, under-fives.

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.[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 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.[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 markers of disease severity 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. Given that hypoglycemia 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, regular monitoring has been ignored by clinicians[10] despite the fact that hypoglycaemia is associated with serious neurological sequelae when detection is delayed or treatment inadequate.[11]

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,[12,13] with the host's requirement being considerably greater.[12] 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.[12] 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, 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.[8,12-14]

Although various approaches have been applied to define the cut-off value for hypoglycaemia, an acceptable cut-off remains debatable. However, a review of the literature revealed that the most accepted concept is that of defining hypoglycaemia based on a practical operational thresholds for glucose values at which intervention should be considered.[11,15,16] In this regard, many experts now define hypoglycaemia in infants and children as blood glucose level below 2.6 mmol/L.[11,15,16] The relative appropriateness of this cut-off value is supported by the study of Koh et al[17] which showed evidence of acute neuro-physiological changes in young infants when blood glucose concentration dropped below 2.6 mmol/L, indicating the need for intervention.

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 hospital 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 non-immune infants, if appropriate therapy is not instituted promptly.[9]

The purpose of the present study was to determine the prevalence 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-healthcare 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 and consent was obtained from the parents. Following recruitment, pretreatment venous blood sample was obtained from each of the patients and a thick and a thin blood film for malaria parasites were performed. Giemsa stain was used in staining. The full blood count was obtained. Blood sample for 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 a dry fluoride-oxalate bottles and analysed using the glucose-oxidase reaction method.[18] Two medical laboratory scientists (with over 20 years experience) processed the samples urgently at the request of the admitting physician and average of the two plasma glucose values obtained was accepted. Inclusion criteria included: age below 60 months, Nigerian, positive falciparum malaria parasitaemia, absence of overt protein-energy malnutrition (kwashiorkor/marasmus), negative history of treatment with quinine and/or herbal concoctions. Patients with a coexisting morbidity were excluded. 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. The presence of a reddish chromatin dot with a purple or blue cytoplasm of the malaria parasites seen together was accepted as a definitive diagnosis of malaria. In the present study, hypoglycaemia was defined as blood glucose value below2.6 mmol/L and this was based on the current, most acceptable, concept of a practical operational thresholds for glucose values at which intervention should be considered. [11,15,16] The number of parasites were counted against 200 white blood cells (WBC) on a thick film and this was converted to parasite per microlitre using the formula:[19]

Parasite per µL of blood = Number of parasites counted X total WBC / Number of WBC counted.
An average WBC count of 8,000/µL was used as the total WBC. In this way, the parasite density was categorized as follows: < 100,000/µL, 100,000 to < 250,000/µL and ≥250,000/µL.

The data was analyzed using the Computer Package for Epidemiologist (PEPI). Descriptive statistics such as frequencies, means, ratios, standard deviations, confidence intervals, percentages were used to describe all the variables. 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 below five years of age were admitted for *Plasmodium falciparum* malaria (irrespective of severity). 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. Ninety two (18.3%) of the 502 children had hypoglycemia 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. Although the prevalence of hypoglycemia was slightly higher in girls than boys, it was not statistically significant [20.7% versus 16.3%, Odd ratio, OR =0.75 (95% Confidence Interval, CI = 0.48-1.18)]; Table 1. Of the 502 children with falciparum malaria seen during the study period, the duration of illness before presentation was four days and below in 375 (74.7%) cases and above four days in the remaining 127 (25.3%) cases.

Table 1: Distribution of hypoglycaemia according to age and gender

Age (months)	Hypoglycaemia Number	Percent
< 12 (n=82)	13	15.9
12-35 (n=257)	65	25.3
36-59 (n=163)	14	8.6
Total (n=502)	92	18.3
Gender		
Male (n=270)	44	16.3
Female (n=232)	48	20.7
Total (n=502)	92	18.3

Table 2, shows the duration of illness before presentation did not significantly influence the prevalence of hypoglycemia. The prevalence of hypoglycemia 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).

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

Duration of illness	Prevalence of hypoglycaemia Number	Percent	X^2 (p-value)
0-4 days (n=375)	70	18.7	0.11
>4 days (n=127)	22	17.3	(>0.05)
Total (n=502)	92	18.3	

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

Time of last meal	Prevalence of hypoglycaemia Number	Percent	X^2 (p-value)
≤12 hours (n=305)	40	13.1	14.10
>12 hours (n=197)	52	26.4	(<0.05)
Total (n=502)	92	18.3	

Table 4, shows the higher the parasite density the greater the prevalence of hypoglycaemia. Two of the eight (25.0%) cases with hypoglycaemia associated with parasite density ≥250,000/µL died (Table 4).

Table 4: Prevalence of hypoglycaemia according to parasite density

Parasite density (per µL)	Prevalence of hypoglycaemia Number	Percent	X^2 (p-value)
< 100,000 (n=270)[a]	43	15.9	a vs b =0.84 (>0.05)
100,000 to < 250,000 (n=198)[b]	38	19.2	a vs c =1.25 (>0.05)
≥ 250,000 (n=34)[c]	8	23.5	b vs c =0.15 (>0.05)
Total (n= 502)	92	18.3	

The mean blood glucose values for hypoglycaemic and non-hypoglycaemic children were 1.9±0.2 mmol/L (CI= 1.86-1.94) and 3.4±0.7 mmol/L (CI= 3.1-3.7) respectively; t-statistic=37.16, p-value 0.001. Of the 502 children admitted for falciparum malaria, 352(70.1%) had anaemia (haematocrit below 30%), comprising 236 (67.0%) as mild-to-moderate (haematocrit 20-29%) and 116(33.0%)as severe (haematocit below 20%). Of the 116 with severe anaemia, 84(72.4%) had very severe anaemia (haematorit below 15%).The presenting clinical features are shown in Table 5.

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

Presenting clinical features	Number *	Percent
Body temperature: 37.5 – 38.4^{0}C	397	79.1
Body temperature: 38.5^{0}C and above	105	20.9
Anaemia (haematocit below 30%)	352	70.1
Convulsion	206	41.0
Vomiting	201	40.1
Hepatosplenomegaly	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 features

Discussion

In the present study, the prevalence of hypoglycaemia at the point of hospital admission of children less than five years old with falciparum malaria was 18.3%. This was lower than the 25.5% and 46.9% reported from two Nigerian studies.[20,21] 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.[12] 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.[22] 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 age range of study populations. In the present study, a higher cut-off (<2.6 mmol/L, based on the concept of operational threshold blood glucose values) 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.[23] 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.[1,24] 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,[11,25] data from the present study revealed that children with falciparum malaria who were less than three years old 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,[24] 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 or less. This finding is in keeping with the report of other studies.[2,10,25] The increased 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 eight hours after the last meal being indicative of fasting.

Although the frequency of hypoglycaemia increased with increasing parasite density, it was not statistically significant. However, two out of the eight (25.0%) cases with hypoglycaemia co-existing with hyperparasitaemia ≥250,000/µL died, suggesting that there might be a link between hyperparasitaemia and hypoglycaemia in relation to mortality. This discrepant finding between parasite density and occurrence of hypoglycaemia may be explained by the report of Silamut and White in which they stated that some patients may have most of their parasite biomass sequestered, and others may have most of their parasites circulating.[26] In addition, the density of parasitaemia as measured in the peripheral circulation may wax and wane, emphasizing the importance of examining serial blood films at intervals of 6 to 12 hours.[27] However, the present study was not designed to address that issue as it focused on hypoglycaemia at point of hospital admission.

Numerically, more males than females were admitted, the prevalence of hypoglycemia was slightly higher in girls than boys but it was not statistically significant. A similar finding was reported from Ghana but with different percentages. [28] 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. [28] 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 hypoglycemia in the present study. This is in consonance to the finding by Osier et al,[10] in Kenyan.

Conclusion

Age below three years and a time of last meal greater than 12 hours were the significant risk factors for the occurrence of hypoglycaemia in children with falciparum malaria.

Conflict of interest: None
Funding: None

References

1. Solomon T, Felix JM, Samuel M, Dengo GA, Saddanba RA, Schapira A, Phillips RE. Hypoglycaemia in paediatric admissions in Mozambique. *Lancet 1994; 343: 149-150.*
2. Elusiyan JB, Adejuyigbe EA, Adeodu OO. Hypoglycaemia in a Nigerian paediatric emergency ward. *J Trop Paediatr 2006; 52 (2): 96-102*
3. Zijlmans WC, Van Kempen AA, Serlie MJ, Sauerwein HP. Glucose metabolism in children: influence of age, fasting, and infectious diseases. *Metabolism 2009; 58 (9):1356-1365.*

4. Wharton B. Protein-energy malnutrition: problems and priorities. *Acta Paediatr Scand Suppl 1, 1991; 374: 5-14.*
5. Bondi FS. Childhood coma in Ibadan: Relationship to socio-economic factors. *Trop Geogr Med 1991; 43: 288-292.*
6. Hendrickse RG. Child health in developing countries: an overview. In: Hendrickse RG, Barr DGD, Matthews TS eds. Paediatrics in the Tropics. *London, Blackwell Scientific Publishers, 1991: 1-14.*
7. Kapse AS. Malaria in children. In: Parthasarathy A. IAP Textbook of Pediatrics. 4th edition. New Delhi, Japee Brothers Medical Publishers Ltd, 2009: 423-440.
8. Planche T, Dzeing A, Ngou-Milama E, Kombila M, Stacpoole PW. Metabolic complications of severe malaria. *Curr Top Microbiol Immunol 2005; 295: 105-136.*
9. Krause PJ. Malaria (Plasmodium). In: Kliegman RM, Behrman RE, Jenson HB, Stanton RF. Nelson Textbook of Pediatrics. 18th edition. *Philadelphia, Saunders Elsevier, 2007: 1477-1485.*
10. Osier FHA, Berkley JA, Ross A, Sanderson F, Mohammed S, Newton CRJC. Abnormal blood glucose concentration on admission to a rural Kenyan district hospital: prevalence and outcome. *Arch Dis Child 2003; 88: 621-625.*
11. Ferry RJ, Allen DB. Hypoglycemia. In: Kappy MS, Allen DB, Geffner ME eds. Pediatric Practice: Endocrinology. *New York, McGraw Hill Companies, Inc 2010:393-408.*
12. World Health Organisation. Severe falciparum malaria. Trans Roy Soc *Trop Med Hyg 2000; 94 Suppl 1; 1-90.*
13. Davies TME, Looareesuwan S, Pukrittayakamee S, Levy JC, Nagachinta B, White NJ. Glucose turnover in severe falciparum malaria. *Metabolism 1993b; 42: 334-340.*
14. Cornblath M, Hawdon JM, William AF, Aynsley-Green A, Ward-Pratt MP, Schwartz R, Kalhan C. Controversies regarding definition of neonatal hypoglycaemia: suggested operational thresholds. *Pediatrics 2000;105(5):1141-1145.*
15. Hay WW Jr, Raju TN, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. J Pediatr 2009;155(5):612-617
16. Koh TH, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycaemia. Arch Dis Child 1988;63:1353-1358.
17. Roe JK, Pasvol G. New developments in the management of malaria in adults. Q J Med 2009; 102 (10):685-693.
18. Chesbrough M. District Laboratory Practice in Tropical Countries (Part 1). Cambridge, Cambridge University Press, 1998:340-348.
19. Ogun SA. Management of malaria. Nig Med Pract 2006;49(5):94-101.
20. Usman AD, Aishatu YM, Abdullahi B. Laboratory assessment of hypoglycaemia due to malaria in children attending General Hospital, Katsina. Bayero J Pure Applied Sci 2008;1(1):6-9.
21. Osonuga OA, Osonuga AA, Osonuga IO, Osonuga A, Derky K L. Prevalence of hypoglycaemia among severe malaria children in rural African population. *Asian Pacific J Trop Dis 2011;1:192-194.*
22. Gupta D, Chugh K, Sachdev A, Soni A. ICU management of severe malaria. *Indian J Pediatr 2001; 68(11): 1057-1061.*
23. Williams AF. Hypoglycaemia in the newborn: a review. *Bull World Health Organ 1997; 75(3): 261-290.*
24. Zijlmans WC, van Kempens AA, Ackermans MT, de Metz J, Kager PA, Sauerwein HP. Very young children with uncomplicated falciparum malaria have higher risk of hypoglycaemia: a study from Suriname. *Trop Med Int Health 2008; 13(5): 626-634.*
25. Thien HV, Kager PA, Sauerwein HP. Hypoglycaemia in falciparum malaria: Is fasting an unrecognized and insufficiently emphasized risk factor? *Trends Parasitol 2006; 22 (9): 410-415.*
26. Silamut K, White NJ. Relation of the stage of parasite development in the peripheral blood to prognosis in severe falciparum malaria. *Trans Roy Soc Trop Med Hyg 1993;87:436-443.*
27. White NJ, Chapman D, Watt G. The effects of multiplication and synchronicity on the vascular distribution of parasites in falciparum malaria. *Trans Roy Soc Trop Med Hyg 1992;86:590-597.*
28. Mockenhaupt FP, Ehrhardt S, Burkhardt J, Bosomtwe SY, Laryen S, Anemana SD, Otchwemah RN, Cramer JP, Dietz E, Gellert S, Bienzle U. Manifestations and outcome of severe malaria in children in Northern Ghana. *Am J Trop Med Hyg 2004; 7(2): 167-172.*