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# Hypoglycaemia at point of hospital admission of under-five children with acute diarrhoea: prevalence and risk factors

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**Abstract** *Background:* Hypoglycaemia is one of life-threatening immediate complications of acute diarrhoea among under-five children but its diagnosis may be overlooked because all the symptoms may be mimicked by severe dehydration.
*Objective:* To determine the prevalence of hypoglycaemia at the point of hospital admission of under-five children with acute diarrhoea and identify some of the risk factors.
*Methods:* At the point of hospital admission, venous blood sample was collected into an appropriate sample bottle (fluoride-oxalate bottle) from 201 under-five children with acute diarrhoea for blood glucose determination. The blood samples were analysed using the glucose-oxidase method. One of the authors administered a questionnaire to each of the caregiver to obtain information on the socio-demographic characteristics and the clinical profile (e.g., presence or absence of vomiting, duration of acute diarrhoea, time of last meal of the patients, and administration of ORS at home. Hypoglycaemia was defined as blood glucose value below 2.6 mmol/L.
*Results:* At the point of hospital admission, 7.7% (14 of 183; CI = 3.7-11.7) under-five children with acute diarrhoea had hypoglycaemia (blood glucose < 2.6 mmol/L) but dropped to 4.9% (CI=2.9-6.9) when a cutoff point of < 2.2 mmol/L was applied. The risk factors for hypoglycaemia were the presence of severe dehydration ($p<0.001$), hypernatraemia and acidosis ($p<0.001$). The prevalence of hypoglycaemia was 7 times higher in children whose time of last meal was ≥ 8 hours compared with their counterparts whose time of last meal was < 8 hours. Mortality rate was significantly higher in children with acute diarrhoea and hypoglycaemia compared with their counterparts with normoglycaemia ($p<0.01$).
*Conclusion:* In acute diarrhea, hypoglycaemia is an important comorbidity among children aged below 36 months and the significant associated risk factors for hypoglycaemia are severe dehydration, hypernatraemia and acidosis. Under-five children presenting with acute diarrhoea and hypoglycaemia at point of hospitalization are at a significantly greater risk of death.

**Key words:** Acute diarrhoea, hypoglycaemia, hypernatraemia,

## Introduction

Acute diarrhoea refers to diarrhoea of sudden onset (generally, over hours rather than days), lasting for less than 14 days.[1] In developing countries, diarrhoeal diseases is a leading cause of morbidity and mortality among under-five children with an average of 3.3 episodes of diarrhoea being experienced per child per year.[2] Acute diarrhoea is associated with a high mortality rate among under-five children.[3]
Although dehydration and electrolyte derangement have been clearly established as the immediate life-threatening complications of acute diarrhoea, a non-dehydrating complication like hypoglycaemia is equally important.[4-7] Even in areas where oral rehydration therapy is being practised, mortality from acute diarrhoea still remains high,[8] suggesting that other factors may be playing a role in the observed mortality rates. In Africa, there is limited data on hypoglycaemia as one of the clinical problems encountered in the management of children with acute diarrhea.[9] This scenario might be related to the fact that the symptoms of severe

dehydration and hypoglycaemia resemble each other, resulting in difficulty in differentiating between these two clinical conditions .[4-6] The co-existence of severe dehydration and hypoglycaemia in patients with acute diarrhorea has been shown to worsen prognosis ,[4,5,7] implying that early detection and adequate treatment of the hypoglycaemia in such patients might improve outcome. Hypoglycaemia is a common clinical problem and it is associated with serious neurological sequelae when detection is delayed or treatment inadequate. Even though low blood glucose may often be transient, hypoglycaemia itself is never physiological and should not be disregarded when detected.[10] Some risk factors that have been identified include female gender, seizure, altered level of consciousness, vomiting, acidosis, duration of diarrhoea less than 72 hours, and bacteraemia.[4,7,11]

A review of the literature revealed that the prevalence of hypoglycaemia in children with acute diarrhoea varied from 4.5-11.0%.[4-6] This variability in prevalence rates have been observed at different times, even within the same country .[4,6] In a study in Calabar, Nigeria, 4.0% of under-five children presenting with acute diarrhoea were found to have hypoglycaemia.[7] A study in a rural district hospital in Kenya, reported a prevalence of hypoglycaemia as high as 23.3% among children with acute diarrhoea at the point of hospital admission.[12] All previous Nigerian studies on this subject were conducted in tertiary-healthcare hospitals and none in secondary-healthcare hospital, yet a significant number of children are cared for in secondary-healthcare facilities.[7] Considering that in developing countries, childhood diarrhoea itself is grossly under-reported and its incidence underestimated,[13] the magnitude of the paucity of information on hypoglycaemia coexisting with diarrhoea becomes more obvious. At present, in Nigeria, the extent to which hypoglycaemia occur in children with diarrhoea is uncertain. We are not aware of any study in Benin City that has determined the prevalence of hypoglycaemia or examined its risk factors among under-five children with acute diarrhoea. The factors highlighted above prompted us to conduct the present study.

The purpose of the present study was to determine the prevalence of hypoglycaemia at the point of hospital admission of under-five children with acute diarrhoea in Benin City and identify some of the risk factors. Hopefully, such information would be useful to clinicians in developing appropriate protocol for management of children hospitalized for acute diarrhoea, thereby improving outcome.

## Patients and methods

This descriptive cross-sectional study was conducted between January and December, 2010 at St Philomena Catholic Hospital (SPCH), Benin City, Nigeria. SPCH is a centrally located, easily accessible large secondary-healthcare institution that cares for all categories of patients. It has a fairly well equipped laboratory manned by qualified medical 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 presented with acute diarrhoea 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 sample was obtained from each of the patients for blood glucose estimation. The blood sample was collected into the appropriate sample containers (dry fluoride-oxalate bottles) and forwarded immediately to the hospital laboratory for processing. The blood glucose concentration was determined using glucose-oxidase reaction method.[14] The urea and electrolyte profile of the patients was also determined. Based on the serum sodium level, the type of dehydration was categorized as hyponatraemic (serum sodium < 130 mmol/L); normonatraemia (serum sodium 130-150 mmol/L); and hypernatraemia (serum sodium > 150 mmol). Two medical laboratory scientists (with over 20 years experience) processed the samples urgently at the request of the admitting physician and the average of the two plasma glucose values obtained was accepted. A blood film for malaria parasitaemia was performed. Inclusion criteria were age below 60 months, Nigerian, negative malaria parasitaemia, absence of overt protein-energy malnutrition (kwashiorkor/marasmus), negative history of treatment with quinine and/or herbal concoctions. Subjects with a coexisting morbidity (e.g., malaria, pneumonia) that are known to cause hypoglycaemia were excluded. A structured questionnaire was administered to the caregiver of each of the patients by one of the authors (ANO). Information obtained included socio-demographic characteristics such as age, gender, parents' educational attainment and occupation. Data were also obtained on history of duration of diarrhoea, presence of vomiting or fever, time of last meal.

The severity of dehydration was determined for each patient by physical examination. In the present study, hypoglycaemia was defined as blood glucose value below 2.6 mmol/L while hyperglycaemia was defined as blood glucose value greater than 8.3 mmol/L.[10] All the children found to have hypoglycaemia were treated with 10% dextrose in water at 4ml/kg/hour. No treatment was given to the two children with hyperglycaemia. Attention was equally paid to their fluid and electrolyte status with treatment as determined by the child's clinical condition. 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 Z-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 230 under-five children were admitted for acute diarrhoea. Of this number, 37 (16.1%) had a positive malaria parasitaemia and were excluded because malaria, itself, is an established cause of hypoglycaemia. Ten (4.3%) mothers declined to participate in the study, leaving 183 patients whose data analysis is presented. The 183 patients consisted of 99(54.1%) males and 84(45.9%) females, giving a male-to-female ratio of 1.2:1. At the point of hospital admission, 7.7% (14 of 183; 95%CI 3.7-11.7) had hypogycaemia (blood glucose < 2.6 mmol/L), When a cutoff point of < 2.2 mmol/L was applied, the prevalence dropped to 4.9% (9 of 183); 95% CI = 2.9-6.9). Two (1.1%) of 183 under-fives with acute diarrhoea had hyperglycaemia. Comparing the age prevalence of hypoglycaemia among children aged below 36 months and their counterparts aged between 36-59 months, it was 8.3% versus 5.1% respectively; Z-statistic = 0.761 p>0.05. The mean age of the subjects was 14.6±10.5 months (95% CI= 13.1-16.1). Vomiting accompanied diarrhoea in over half of the cases (Table 1). The mean electrolyte values are shown in Table 1. The distribution of type of dehydration (based on serum sodium concentration) among the study population was as follows: hyponatraemic dehydration 58.5% (107 of 183), isonatraemic dehydration 36.6% (67 of 183) and hypernatraemic dehydration 4.9% (9 of 183). Seven (77.8%) of 9 cases of hypernatraemia had acidosis and hypoglycaemia.

**Table 1:** Characteristics of the 183 children with acute diarrhoea.

| Parameter | Number | % |
|---|---|---|
| Duration of diarrhoea < 3 days* | 101 | 55.2 |
| Duration of diarrhoea ≥3 days | 82 | 44.8 |
| Vomiting present | 96 | 52.5 |
| Vomiting absence | 87 | 47.5 |
| Fever present | 85 | 46.4 |
| Fever absent | 98 | 53.6 |
| Used ORS at home | 100 | 54.6 |
| Did not use ORS at home | 83 | 45.4 |
| | Mean±SD (95% CI) | |
| Mean serum sodium (mmol/L) | 130.2±7.4 (129.1-131.3) | |
| Mean serum potassium (mmol/L) | 3.1±0.8 (3.0-3.2) | |
| Mean serum chloride (mmol/L) | 98.4±8.5 (97.2-99.6) | |
| Mean serum bicarbonate (mmol/L) | 13.5±4.4 (12.9 -14.1) | |
| Mean serum urea (mg/dl) | 27.1±16.8 (24.7-29.5) | |

*Before presentation

**Table 2:** Prevalence of hypoglycaemia stratified by age and gender

| Age (months) | Subjects No (%) | Hypoglycaemia No (%) | Normoglycaemia* No (%) | Z-statistic (p-value) |
|---|---|---|---|---|
| < 12[a] | 81(44.3) | 7(8.6) | 74(91.4) | a vs b= 3.212 (p<0.01) |
| 12-35[b] | 63(34.4) | 5(7.9) | 57(91.9) | b vs c=0.847 (p>0.05) |
| 36-59[c] | 39(21.3) | 2(5.1) | 36(92.3) | a vs c=0.614 (p>0.05) |
| Total | 183(100.0) | 14(7.7) | 165(90.2) | |
| *Gender* | | | | |
| Male | 99(54.1) | 8(8.1) | 90(90.9) | Odd Ratio 1.1 |
| Female | 84(45.9) | 6(7.1) | 77(91.7) | |
| Total | 183(100.0) | 14(7.7) | 167(91.3) | |

*Two subjects had hyperglycaemia

As depicted in Table2, 12(85.7%) of 14 children with hypoglycaemia were below 36 months of age. Only two (14.3%) were aged 36 to 59 months. Nine (64.3%) of 14 children with hypoglycaemia had acidosis. The duration of diarrhoeal illness before presentation did not significantly influence the prevalence of hypoglycemia. Table 3 shows that the risk of hypoglycaemia was seven times higher when the time of last meal was ≥ 8 hours compared to when it is < 8 hours. Children with severe dehydration were at a significantly greater risk of hypoglycaemia than their counterparts with a lower degree of dehydration (Table 4).

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

| Time of last meal | Subjects No (%) | Hypoglycaemia No(%) | Normoglycaemia* No(%) | Odd Ratio |
|---|---|---|---|---|
| <8 hours | 118(64.5) | 8(6.8) | 109(92.4) | 7.2 |
| ≥8 hours | 65(35.5) | 6(9.2) | 58(89.2) | |
| Total | 183(100.0) | 14(7.7) | 167(91.3) | |

*Two subjects had hyperglycaemia

**Table 4:** Prevalence of hypoglycaemia according to hydration status

| Hydration status | Total No (%) | Hypoglycaemia No (%) | Normoglycaemia * No (%) | Z-statistic (p-value) |
|---|---|---|---|---|
| Mild dehydration | 46(25.1) | 0(0.0) | 45 (97.8) | |
| Moderate dehydration | 118(64.5)[a] | 5(4.2) | 112(94.9) | a vs b =3.723 |
| Severe dehydration | 19(10.4)[b] | 9(47.4) | 10(52.6) | (0.001) |
| Total | 183(100.0) | 14(7.7) | 169(92.3) | |

*Two subjects had hyperglycaemia

As shown in Table 5, the commonest type of dehydration was hyponatraemic dehydration while hypernatraemic dehydration was the form of dehydration most commonly associated with hypoglycaemia. A total of eight of 183 children died, representing a case fatality rate 4.4%. Five (62.5%) of the eight had hypoglyaemia. None of the two subjects with hyperglycaemia died. When mortality rate between the hypoglycaemic group was compared with the normoglycaemic group, it was 35.7% (5/14) versus 1.8% (3/169); Z-statistic = 2.627 p<0.01. Three of the five children with hypoglycaemia who died, also had hypernatraemia and acidosis. The remaining two hypoglycaemic children who died had a combination of hyponatraemia and acidosis. Of the

normoglycaemic children who died, two had severe hyponatraemia with acidosis and one had hypernatraemia with acidosis. In this series, it is of note that acidosis was a common factor among all the deaths.

**Table 5:** Prevalence of hypoglycaemia according to type of dehydration

| Type of dehydration | Subjects No (%) | Hypoglycaemia No (%) | Normoglycaemia * No (%) | Z-statistic (p-value) |
|---|---|---|---|---|
| Hyponatraemic | 107(58.5)[a] | 5(4.7) | 101(94.4) | a vs b=0.582(p>0.05) |
| Isonatraemic | 67(36.6)[b] | 2 (3.0) | 64(95.5) | b vs c = 1.996 (p<0.05) |
| Hypernatraemic | 9(4.9)[c] | 7 (77.8) | 2(22.2) | a vs c = 5.220 (p<0.001) |
| Total | 183(100.0) | 14(7.7) | 169(92.3) | |

*Two subjects had hyperglycaemia

## Discussion

In the present study, the prevalence of hypoglycaemia at the point of hospital admission of under-five children presenting with acute diarrhoea was 7.7%. This was higher than the 4.0% and 4.5% reported from Calabar, Nigeria[7] and Dhakar, Bangladesh[15] respectively. On the other hand, the prevalence being reported here is lower than 11.0% reported from another study in Bangladesh among under-five diarrhoeal children.[4] The higher prevalence rate observed in the present study compared to the previous study in Calabar may be explained by the differences in definition of hypoglycaemia used in the two studies. In the present study, a higher cut-off (<2.6 mmol/L, based on the concept of operational threshold blood glucose values[16]) was used in defining hypoglycaemia whereas < 2.2 mmol/L was used as cut-off in the Calabar study, partly accounting for the higher prevalence observed in the present study. The definition of hypoglycaemia used in a study is known to influence its prevalence.[17] This was amply demonstrated in the present study because when a cut-off of less than 2.2 mmol/L was applied it resulted in a lower prevalence rate (4.9%). The explanation for the higher prevalence rate in the present study compared to the prevalence rate (4.5%) observed in the study in Bangladesh may be due to differences in the age group of the study population. The present study involved only under-five children whereas the Bangladesh study [15] included children up to the age of 15 years. Studies have shown that the risk of hypoglycaemia is higher in under-five children compared to older children.[18]

On the other hand, the lower prevalence rate (7.7%) observed in the present study compared with 11.0% found in the study by Huq et al[4] may be explained by selection bias. In that study, they investigated only those children suspected to have hypoglycaemia. The mechanism by which diarrhoea predisposes to hypoglycaemia is poorly understood. However, Bennish et al,[15] linked it to defective gluconeogenesis. In that study, they observed that the glucose counterregulatory hormones were appropriately elevated in the children with hypoglycaemia whereas the substrates for gluconeogenesis were inappropriately low in them, leading to the conclusion that hypoglycaemia in such children was most likely due to impaired hepatic gluconeogenesis. The report of another study also linked hypoglycaemia associated diarrhoeal illnesses in children to glycogen depletion and impaired hepatic gluconeogenesis.[19] The higher risk of hypoglycaemia observed in the present study among under-five children with diarrhoea in whom the time of last meal was 8 hours and above is in tandem with glycogen depletion as one of the pathogenetic mechanisms of hypoglycaemia in diarrhoeal illnesses.

Hyperglycaemia was present in one out of every hundred patient in the present study. There was no mention of the occurrence of hyperglycaemia in the study in Calabar,[7] making it impossible to judge whether or not any of their subjects had hyperglycaemia. A study in Kenya has reported a similar observation.[12] In that study, 12.9% of 96 children with hyperglycaemia had gastroenteritis as their diagnosis, representing a prevalence of 3.7%. The prevalence of hyperglycaemia was higher in the Kenyan study than in the present one despite the fact that they used a higher cut-off value of > 10 mmol/L. The reason for this difference is not clear. In contrast to the Kenyan study, none of the two patients with hyperglycaemia died.

Data from the present study revealed that among under-five children with acute diarrhoea, severe dehydration, hypernatraemia and acidosis were significant risk factors for hypoglycaemia. This is not surprising as similar observation has been reported previously.[7,15] The severe dehydration and acidosis may impair the function of various enzymes involved in gluconeogenesis as well as interfere with the transport of substrates.[15] However, in contrast, Ntia et al[7] did not find any relationship between the frequency of hypoglycaemia and serum electrolyte profile. Given the fact that they did not document in their results, the serum electrolyte profile of their patients, it is possible they did not focus on electrolytes in relation to hypoglycaemia. However, in that report, they did state that five of the six children with hypoglycaemia in their series had metabolic acidosis, supporting, albeit indirectly, the significant association between acidosis and frequency of hypoglycaemia observed in the present study.

What is the clinical implication of these findings? Case management efforts in childhood diarrhoeal illnesses usually focus on correction of fluid and electrolyte derangement. Clinicians need, in addition, to consider the role of non-dehydrating complication like hypoglycaemia in causing death in children presenting with diarrhoea. Thus, it might be beneficial for clinicians to consider the possibility of hypoglycaemia when developing appropriate protocol for management of children hospitalized for acute diarrhoea, thereby reducing the already high mortality associated with childhood diarrhoeal illnesses in developing countries. After treatment of shock, the use of dextrose-containing intravenous

solution in hospitalized children requiring parenteral fluid therapy is advocated, particularly where facilities for determination of blood glucose level is not available. All children presenting with diarrhoea and acidotic breathing should, in addition to correcting the acidosis, treated empirically for hypoglycaemia.

and the significant associated risk factors are severe dehydration, hypernatraemia and acidosis. Routine assessment of blood glucose at the point of hospital admission is advocated and where facility for determination of blood glucose level is not available, treat empirically for hypoglycaemia to improve outcome.

## Conclusion

Hypoglycaemia is an important co-morbidity of acute diarrhoea among children below the age of 36 months

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