Glycemic Abnormality in Children during Severe Malaria in Togo

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Abstract

Introduction: Hypoglycemia is a defining feature of severe malaria and many other infectious diseases in children, but the prevalence and prognosis of abnormal glucose levels, including hyperglycemia, have rarely been addressed in critically ill children. The objective of this study was to determine the glycemic profile of children with severe malaria admitted to the pediatric intensive care units (PICU) of Sylvanus Olympio University Hospital.

Methods: This is a descriptive cross-sectional study. It was conducted from December 14, 2016 to February 15, 2017. The study included children (1 month - 15 years) admitted to the PICU in whom a capillary blood glucose and rapid diagnostic test of malaria (RDT) were performed.

Results: A total of 231 children were included in the study with a mean age of 59 months and a sex ratio of 1.23 (male: female). The prevalence of malaria was 62.3% (144/231). There were fewer glycemic problems in children with positive malaria RDTs, and 89.6% of children diagnosed with malaria had normal blood glucose levels (P = 0.02). Hypoglycemia was predominant in the anemic forms (11.1%) and hyperglycemia in the neurological forms (12.3%) (p = 0.14). All cases of severe hemoglobinuric malaria had a normal blood glucose (100.0%).

Conclusion: Malaria was the most common pediatric intensive care condition and was the least commonly associated with hypoglycaemia. Cerebral malaria was the most common form of severe malaria during the study.

Keywords: Child; Glucose; Severe Malaria; Togo

Introduction

Malaria is a parasitic infection found mainly in the tropical and subtropical regions of South America, sub-Saharan Africa and South-East Asia. In 2017, it was estimated that there were a total of 219 million cases of malaria globally. Children under 5 are the most vulnerable to malaria. In 2017, they accounted for 61% (266,000) of all malaria deaths worldwide [1]. The developing brain of a child is more sensitive to hypoglycemia than that of an adult. Hypoglycemia is particularly severe in newborns and infants, and during any period of prolonged fasting [2]. It is associated with a poor prognosis and brain damage that can lead to death [3]. At the same time, hyperglycemia commonly seen in pediatric emergency units, particularly in patients with serious illness [4]. Hyperglycemia in critically ill patients is a well-known factor in increased morbidity and mortality in intensive care units [5]. Overall, hypoglycemia and hyperglycemia are associated with increased morbidity and mortality rates in critically ill children in a variety of settings [6,7,8]. The determination of blood glucose is necessary for the diagnosis of blood glucose abnormalities especially when receiving emergency care. Hypoglycemia is a defining feature of severe malaria and many other infectious diseases in children, but the prevalence and prognosis of abnormal glucose levels, includ-

ing hyperglycemia, have rarely been addressed in critically ill children. The objective of this study was to determine the glycemic profile of children with severe malaria upon admission to intensive care units in the pediatric ward of the Sylvanus Olympio University Hospital.

Methodology

Our study was conducted in the pediatric intensive care units situated in Lomé University Hospital.

Type and period of study

This is a descriptive cross-sectional study. It was conducted from December 14, 2016 to February 15, 2017, for a total duration of two months.

Study population

The study included all children, aged 1 month to 15 years, admitted to one of the pediatric intensive care units during the study period, who had a blood glucose test and a rapid diagnostic test for malaria (RDT) and verbal consent from the parents. Patients with a known diagnosis of diabetes Mellitus were excluded.

Parameters studied

The main parameters studied were sociodemographic data, clinical characteristics, and laboratory results, specifically blood glucose and malaria RDT.

Operational definitions

- Hypoglycemia was defined as a blood glucose less than 2.5 mmol/l (0.45 g/dl).
- Hyperglycemia was defined according to ISPAD 2014 [9] as a blood glucose greater than 1.40 g/dl (7.8 mmol/l).
- Severe malaria was defined in 2000 by the World Health Organization (WHO), as *Plasmodium falciparum* parasitemia associated with at least one of the following clinical manifestations: convulsions, coma, anemia with a hemoglobin of < 6 g/dl, hypoglycemia < 0.40 g/dl, respiratory distress, hemoglobinuria, oliguria or renal failure, abnormal spontaneous bleeding, circulatory collapse, jaundice, or acidosis [10].

Methods and data collection tools

Research assistants were recruited and trained on how to complete the research questionnaire, how to use the glucometer, and how to perform the malaria RDTs. The research questionnaire was pre-tested by trained assistants on subjects who did not participate in the study. Sick children aged 1 month to 15 years admitted to the pediatric ICU and who were eligible were recruited by the research assistants as soon as consent was obtained. The completion of the research questionnaire was based on the patient's clinical booklet. The name and date of birth were collected from the child's health card. At the time of admission to the emergency room, prior to intravenous catheter placement, a random capillary blood glucose was performed using an Accu-Chek Active blood glucose meter meeting the ISO 15197:2013 requirements of the International Organization for Standardization. The blood glucose was tested by the glucose oxidase method and expressed in mg/l. The glucometers were calibrated at the CHU-SO biochemistry laboratory for every twentieth patient. A difference of less than 10% between the glucometer measurement and that of the biochemistry laboratory was considered acceptable [11]. The TDR used was the SD Bioline Malaria Ag Pf HRP2, 05FK50 (SDFK 50). This is a rapid, two-band qualitative test. The test lot used was the lot N°: 82206, date: 15/06/12. We used capillary blood glucose because venous plasma glucose was no longer available during night guard in our laboratory, in our context of limited African resources.

Patient/parents were interviewed as needed after initial patient stabilization to complete the questionnaire.

The children were classified into three groups according to their blood glucose. Normal blood glucose was defined as a blood glucose level of between 2.5 and 7.8 mmol/l (0.45 - 1.40 g/dl), hypoglycemia was defined as a blood glucose level below 2.5 mmol/l (0.45 g/dl),

and hyperglycemia was defined as a blood glucose greater than 7.8 mmol/l (1.40 g/dl). Patients with severe hypoglycemia immediately received an intravenous bolus of 5 ml/kg 10% dextrose over 5 minutes followed by a maintenance infusion of 5% dextrose. The blood glucose was reverified after fifteen minutes. Children with elevated blood glucose levels had urine samples taken to ascertain for glucosuria and ketonuria using keto-diastix urine strips. The urine strips were immediately dipped in the fresh urine samples. Reading was done after thirty seconds for ketonuria and after forty-five seconds for glycosuria. The results of glucosuria and ketonuria were expressed in crosses (1 - 4 crosses). Children with hyperglycemia had their blood glucose monitored every 6 hours until the blood glucose level fell within the normal range.

Statistical analysis

A database was designed with the Epidata Software version 3.1. Statistical analysis was done using statistical software R Studio version 3.3.2. The prevalence of hypoglycemia and hyperglycemia were calculated with a 95% level of confidence interval. Subsequently a descriptive analysis of the qualitative variables, presented as numbers and proportions, was performed. A comparative analysis was made between the blood glucose level and each variable collected. For this comparative analysis, the Fisher and chi-square tests was used.

Ethical consideration

This study was approved by the National Ethics Committee of the Ministry of Health in Togo and all respondents study (Opinion N ° 09/2017/CBRS). The parents or guardians of the included gave their informed consent for their participation in the study. The data collection cards were anonymous. A unique identifier was assigned to each patient and each sample during the study.

Results

Sociodemographic characteristics

A total of 231 patients were included in the study, of whom 122 were male, and 109 were female, for a sex-ratio of 1.23. The most represented age group of children (31.2%) was 25 to 59 months of age. The average age was 59.0 ± 47.6 months (range: 1 to 191 months).

Glycemic profiles and malaria RDT positivity

Of the 231 children who underwent malaria testing via RDT, 144 children were positive (62.3%), with a prevalence of 62.3% of malaria.

There were less abnormal blood glucose values in children with a positive malaria RDT than in children with a negative malaria RDT, 89.6% of children diagnosed with malaria had a normal blood glucose (Table 1).

		Hypoglycemia		Normoglycemia		Hyperglycemia		P
	N	n	%	n	%	n	%	
RDT								0,0246[++]
Negative	87	16	18,4	54	62,1	17	19,5	
Positive	144	8	5,5	129	89,6	7	4,9	

Table 1: Prevalence of children's glycemic status according to the result of malaria RDT.

[++]= Fisher test.

Diagnoses

Malaria was the leading cause of admission to the pediatric intensive care unit. Severe and simple forms of malaria accounted for 62.4% of all admissions, followed by respiratory infections (16.4%), and gastroenteritis (8.6%). Simple malaria was associated with other conditions.

For severe malaria, the most prevalent forms were cerebral malaria in 24.7% (57) of cases and severe malarial anemia in 11.7% (27) of cases (Table 2).

	Total (N = 231)	
Diagnostic	**N**	**%**
Respiratory infection	38	16,4
Gastroenteritis	20	8,6
Sickle cell crisis	12	5,2
Septicémia	9	3,9
Meningitis	8	3,5
Nephropathy	8	3,5
Asthma	5	2,2
poisoning	5	2,2
Urinary infection	3	1,3
Associated simple malaria (to other diagnoses)	33	14,3
Severe malaria (SM)	111	48,1
Form of severe malaria		
N	57	24,7
A	27	11,7
H	12	5,2
NA	7	3,0
NHA	5	2,2
NH	3	1,3

Table 2: Distribution of children by selected diagnosis.

N: Neurological; A: Anemic; H: hemoglobinuric; NA: Neurological and Anemic; NHA: Neurological Anemic and Hemoglobinuric; NH: Neurological and Hemoglobinuric.

The glycemic profiles of children with severe malaria

Hypoglycemia was more common in severe malarial anemia (11.1%). In contrast, hyperglycemia was predominant in cerebral malaria (12.3%). All cases of severe hemoglobinuric malaria had normal blood glucose (100.0%) (Table 3).

		Hypoglycemia		Normoglycemia		Hyperglycemia		P
	N	**n**	**%**	**n**	**%**	**n**	**%**	
Severe malaria	111	9	8,2	91	82	11	9,9	0,1428[++]
N	57	2	3,5	48	84,2	7	12,3	
A	27	3	11,1	21	77,8	3	11,1	
H	12	0	0,0	12	100,0	0	0,0	
NA	7	2	28,6	4	57,1	1	14,3	
NHA	5	1	20,0	4	80,0	0	0,0	
NH	3	1	33,3	2	66,7	0	0,0	

Table 3: Distribution of the glycemic status of children according to the form of severe malaria.

[++]= Fisher test.

Discussion

This study enabled us to explore blood glucose levels in children with severe malaria. In this study, trends seemed to emerge leading us to wonder about the association between the glycemic status of children and the form of severe malaria diagnosed.

The main limitation of the study was its duration which was short. However, during the two months of the study we were able to include enough patients allowing us to describe the different forms of severe malaria that the patients have and to characterize them with one of the three glycemic profiles.

The most common forms of severe malaria were cerebral malaria (24.7%) followed by anemic form (11.7%). In the same department, from the year 2000 to 2002, the anemic form was the most prevalent [12]. This could be explained by the improved living conditions of the Togolese population leading to a reduced prevalence of anemia among Togolese children. According to the Demographic and Health Survey published in 2015 in Togo, anemia was most prevalent in children aged 6 - 8 months (90%). The proportion of anemic children declined steadily with age, reaching its lowest level at 48 - 59 months. In our study the average age was 59 months. Additionally, the Demographic and Health Survey showed that children in rural areas were more affected by anemia (73%) than those in urban areas [13].

In our study, severe malaria was not strongly associated with hypoglycemia, contrary to the findings of Elusyian., *et al.* [14], Solomon., *et al.* in Mozanbique [15], Tanzania [16], Togo (11.6%) [17], Uganda (11.4%) [18], the Gambia (31%) [19] and Malawi (20%) [20]. Most of these are older studies. This finding could be due to two factors. First, there has been an improvement in the living conditions of the Togolese population. Secondly, since 1994 - 1995 the WHO has raised community awareness of the lethality of cerebral malaria and hypoglycemia [21].

Severe malaria was the most common pathology in our intensive care (48%) which is not surprising since we are in a malaria endemic zone. Malaria was also the most common pathology of all children with abnormal blood glucose (57.1%). Hypoglycemia could be due to digestive disorders or due to disruption of the mechanism of glycemic regulation by the malaria parasite. Differences in frequencies of hypoglycemia in severe malaria in Africa compared to other continents suggest a possible genetic predisposition [22].

Among the cases of severe malaria, we noted a predominance of hyperglycemia in cerebral malaria. Eltahir., *et al.* [23] have linked this presence of hyperglycemia to the capacity of cerebral malaria to increase insulin resistance on the one hand and probably reduce insulin production on the other hand. Additionally, during convulsions and hyperthermia (> 39^{0}C), increased levels of cytokines such as interleukin-1 and TNF-α inhibit insulin secretion and stimulate cortisol which leads to hyperglycemia. When both of these clinical states are present (fever and convulsion) the impact on blood glucose levels is magnified. This combination of clinical states, which is observed in both cerebral malaria and meningitis, cans explain an association between cerebral malaria and hyperglycemia. Contrary to our results, Elusiyan., *et al.* [14] found that cerebral malaria was more likely to cause hypoglycemia. They did not find a cause-and-effect link but explain that the sequestration of red blood cells in the capillaries and venules is a pathogenetic process common to both cerebral malaria and hypoglycemia.

Conclusion

During the study period, malaria was the most common diagnosis in the pediatric intensive care and was the least commonly associated with hypoglycemia. Cerebral malaria was the most common form of severe malaria. In order to improve patient survival, blood glucose abnormalities, which serve as severity indicator and very deleterious aggravating factor of diseases, should be detected and corrected in time. Further studies are needed to define a severity threshold of glycemic troubles correlated with mortality or morbidity.

Conflict of Interest

None.

Source of Funding

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