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Should Stress Hyperglycemia be Considered as Severity Criteria for Malaria and Sepsis in Children?

Should stress hyperglycemia be considered as severity criteria for malaria and sepsis in children?

Suzanne Sap Ngo Um, Isabelle Mekone, Kenneth Nabengu Okenye, Helène Kamo, Jocelyn Tony Mbono Ritha, Claude Kalla, Paul Olivier Koki.

Suzanne Sap*, Faculty of medicine and biomedical sciences, Department of paediatrics, the University of Yaounde 1, Mother and child Center Yaounde suzysap@gmail.com
Isabelle Mekone, Yaounde General Hospital, Department of paediatrics, the University of Yaounde 1 isamekone@yahoo.fr
Kenneth Nabengu Okenye Faculty of medicine and biomedical sciences, Department of paediatrics, the University of Yaounde 1 nabengukenneth90@yahoo.com
Hélène Kamo, Faculty of medicine and biomedical sciences, The University of Garoua, Regional Hospital Ngaoundéré, nisselena@yahoo.ca
Jocelyn Tony Faculty of medicine and biomedical sciences, Department of paediatrics, the University of Yaounde 1, Mother and child Center Yaounde tnengom@gmail.com
Claude Kalla Faculty of medicine and biomedical sciences, Department of paediatrics, University Teaching Hospital Yaounde, claudekalla@yahoo.fr
Paul Olivier Koki Faculty of medicine and biomedical sciences, Department of paediatrics the University of Yaounde 1 koki_paul@hotmail.com

***Corresponding autho**r Pr Suzanne Sap Ngo Um Email: suzysap@gmail.com
Phone +237 677594797
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RÉSUMÉ

Introduction. Abnormal blood sugar level (dysglycemia) on admission in severely ill children is metabolic response to acute stress. This is not found in all patients and we hypothesized that in non-diabetic children, abnormal glycaemic profile on admission worsened patient's evolution in hospital. **Materials and methods.** We carried out a prospective cohort study in a paediatric emergency unit during 6 months. We included children with a severe acute medical condition, aged between 28 days and 16 years. Blood sugar level was tested in each patient on admission. The data on final diagnosis, evolution were collected. We compared data of children with or without dysglycemia on admission. Pearson's chi square test and Fisher's exact test were used to compare categorical variables while Kruskal-Wallis test and Mann Whitney U were used to compare numerical variables. **Results.** We included 203 children with median age 30 months (IQR: 14-68 months). The prevalence of hypoglycemia on admission was 3.45% and stress hyperglycemia on admission 31.53%. Unconsciousness and respiratory distress were the most frequent symptoms significantly associated with dysglycemia (P<0.05). Children with dysglycemia were 7.1 times more likely to be transferred to the intensive care unit and 7.4 times more likely to die compared to those with a normal glycemia (p<0.01). **Conclusion.** Dysglycemia occurs in 34.9% of patients admitted in our paediatric emergency unit and was associated with higher risk of mortality.

ABSTRACT

Introduction. Un taux anormal de glucose ou dysglycémie peut être une réponse au stress chez le patient grave en pédiatrie. Cette réaction métabolique n'est pas retrouvée chez tous les patients. Nous avons émis l'hypothèse que chez les patients non diabétiques, un profil glycémique est un facteur de gravité et d'évolution défavorable. **Patients et méthodes**: Nous avons réalisé une étude de cohorte prospective en unité d'urgences pédiatriques du Centre Mère Enfant de la Fondation Chantal Biya durant 06 mois. Nous avons inclus les patients âgés de 28 jours à 16 ans, présentant une pathologie aigue sévère. La glycémie était prélevée chez tous les patients à l'admission. Les données sur le diagnostic final, l'évolution étaient notées. Nous avons comparés les données des patients avec ou sans dysglycémie à l'admission. Le test de Chi carré et de Fisher ont été utilisés pour comparer les variables catégorielles. Le test de Kruskall-Wallis et de Mann Whitney ont servis à la comparaison des variables quantitatives. **Résultats**: Nous avons inclus 203 patients dont l'âge médian était 30 mois (EIQ: 14-68 mois). La prévalence de l'hypoglycémie à l'entrée était de 3,45% et l'hyperglycémie de stress 31.53%. le coma et la détresse respiratoire étaient les signes les plus fréquemment associé à l'hyperglycémie (p<0,05). Les patients avec glycémie anormale avaient un risqué 7,4 fois plus élevé d'être transférés en unité de soins intensifs que ceux avec glycémie anormale. (p<0.01). **Conclusion**: La dysglycémie était retrouvée chez 34,9% des patients reçus aux urgences pédiatriques et est associé à un risque élevé de mortalité.

INTRODUCTION

The response to the stress produced by an acute illness in children can present itself in the form of an abnormal blood sugar level (dysglycemia) (1, 2). Expected reaction to stress is hyperglycemia but in some critical situation this response may be inadequate (exaggerated or altered). (3-5). Admission dysglycemia has been shown to be associated with many situations amongst which are pneumonia, severe malaria and shock (2, 3, 6).

Dysglycemia is described in 3.8 to 31.7% of children presenting in emergency room (1, 7). The degree of dysglycemia on admission is an important prognostic marker of morbidity / mortality in variety of settings. (1, 7, 8-15) but hyperglycemia is not considered as a severity criteria of malaria (16, 17). Little data are available in our country concerning dysglycemia on admission of children in emergency unit therefore and the outcome of. There is presently no data on abnormal blood sugar concentrations as well as on their potential relationship with in-hospital clinical outcomes in children with acute illnesses in our setting. We therefore hypothesized that admission dysglycemia is associated with adverse in hospital clinical outcomes in children at the mother and child center, and stress hyperglycemia may be considered as severity criteria for malaria in our context. Our aim was to explore the relationship between admission dysglycemia and adverse in hospital clinical outcomes in patients admitted to the hospital through the Paediatric Emergency Unit (PEU).

PATIENTS AND METHODS

This study was a prospective cohort study where each patient was seen from admission till discharge or death, from September 2015 to March 2016. Patients were recruited at the Paediatric Emergency Unit (PEU) of the Mother and Child Centre (MCC) of Yaounde. The MCC is a tertiary care center. We consecutively included patients aged 28 days to 1 years, admitted in PEU with a severe acute condition. We excluded known diabetic patients, patients who received glucose intravenously prior arrival, patient referred from another health structure with an undocumented treatment and those whose parents refused to participate in the study.

The sample size was calculated using the following formula,

$$\mathbf{n}=\frac{\mathbf{1}}{\mathbf{1}-\boldsymbol{f}} * \left[\frac{\mathbf{2}*(\boldsymbol{Z\alpha}+\boldsymbol{Z\beta})^{2}*\boldsymbol{P}*(\mathbf{1}-\boldsymbol{P})}{(\boldsymbol{P0}-\boldsymbol{P1})^{2}}\right]$$

considering a prevalence of dysglycemia of 31.7% found in Ghana [1] giving a minimal sample of 125 patients for a power of 80%, level of confidence et 95% and α <5% .

During the study period, all severely ill patients who came to the emergency unit had their blood sugar level tested systematically using a One Touch^{R} glucometer (LifeScan Europe, Switzerland) and urine glucosuria was checked with a dipstick (Cybow^{TM}, DFI Co., Ltd, Gyung-Nam, Korea).

They were classified as hyperglycaemic (blood sugar >150 mg/dl as measured by a single chemstrip glucose result), hypoglycaemic (blood sugar <45 mg/dl) (1, 12, 14) and euglycaemic. A urine dipstick was then done on all hyperglycaemic children to exclude diabetes mellitus.

We collected the following information from patient file: presenting complaints, past medical history, anthropometric parameters (weight to the nearest 0,1 gr), length or height (average of 2 measurements to the nearest 0,1cm), body temperature to the nearest 0.1°C**.** Upon discharge, we collected information on patient's diagnosis, affected systems, intensive care unit transfer or not, patient survival, length of hospitalisation.

All children meeting inclusion criteria were recruited in the study after parent's consent.

Aute illness and severe illness were defined according to world health organization (WHO) (18). Acute illness is a disease with a rapid onset and or a short course. Most of the times it concerns a vital system: cardiovascular system, nervous system, hematopoietic system, respiratory system, gastrointestinal system and the urinary system. Severe illness is considered in any patient presenting with the following : inability to drink or breastfeed, repeated vomiting, repeated convulsions, lethargy or unconsciousness, difficulties in breathing, diarrhoea with moderate or severe dehydration, very febrile patient (≥ 38.5 ° c), severe acute malnutrition , severe acute pains.

Ethics

An ethical clearance was obtained from the "Institutional Ethics Committee for Research" of the FMBS, university of Yaoundé I on the 16/12/2015. The present study met all Helsinki principles for research. Data remained confidential. All parents gave their written consent out of stress, when the patient was stabilized.

Statistics

All data was collected and recorded using a questionnaire and transferred to the Statistical Package for Social Sciences software, SPSS (Version 20.0). Pearson's Chi square or Fisher's exact tests was used to compare categorical variables as appropriate while Kruskal-Waliis test was used for numerical data and non-normally distributed variables. Relative risks (RR) was calculated with Taylor series 95% confidence intervals. We considered p values <0.05 as statistically significant. All dysglycaemic groups were compared to normoglycaemic children.

Associations between admission blood glucose and case fatality (died in hospital or taken home critically ill, not expected to survive) was investigated using univariate analysis. Mortality (died in hospital or taken home critically ill, not expected to survive) was evaluated in univariate analysis according to glycaemic status and duration of hospitalization.

RESULTS

Prevalence of dysglycemia

Two hundred and three (203) patients in total presenting with a severe acute medical condition at the PEU were recruited to participate in this study from which 108 males (53.2%) males and 95 (46.8%) females. The median age of our study population was 30 months (IQR: 14-68). Children less than 5 years (143) represented 70.4% of all the patients. The most frequent presenting symptoms on admission were fatigue (99.5%) and poor feeding (87.5%). Severe malaria was the most frequent diagnosis (n=202, 64%) followed by severe sepsis (n=31, 15%). The prevalence of admission dysglycemia in the total population was 34.9%. Seven (3.4%) patients had hypoglycemia and 64 (31.5%) patients had hyperglycemia.

In the 64 hyperglycaemic children, all (100%) had fatigue, 56 (87.5%) had fever and poor feeding. Amongst the 7

hypoglycaemic children, poor feeding and fatigue were present in all (100%) of them. Six (85.7%) had fever on admission. (Table I)

Table I: Clinical features of children presenting with a severe acute medical condition at the PEU by blood sugar status (n= 203)

Symptoms	**Normal blood sugar** n (%)	**Abnormal blood sugar**		Total n (%)	P** value
		Low n(%)	High n(%)		
Fever	**115 (57)**	**6 (3)**	**56 (28)**	**177 (87)**	**0.96**
Vomiting	65 (32)	3 (2)	25 (12)	93 (46)	0.18
Cough	24 (12)	0 (0)	19 (9)	43 (21)	0.15
Convulsions	39 (19)	3 (2)	27 (13)	69 (34)	0.07
Abdominal pains	30 (15)	2 (1)	10 (5)	42 (21)	0.33
Diarrhoea	25 (12)	5 (3)	14 (7)	44 (22)	0.19
Poor feeding	111 (55)	7 (3)	56 (28)	174 (86)	0.37
Fatigue	131 (65)	7 (3)	64 (31)	202 (99)	1.00
Respiratory distress	25 (12)	5 (2)	24 (12)	54 (26)	**0.01**
Unconsciousness	11 (5)	5 (2)	19 (9)	35 (17)	**<0.001**
Other*	50 (24)	0 (0)	27 (14)	77 (38)	

* Headache, rhinorrhoea, polyarthralgia, persistent crying. ** Chi square test

Severe malaria was the main severe condition found in emergency followed by sepsis (Table II). Of the 130 children with severe malaria, 38 (30%) were hyperglycaemic and 5 (4%) were hypoglycaemic. Prostration and severe anaemia were the most frequent severity criteria of malaria occurring in 119/130 (91.5%) and 103/130 (79.2%) respectively, of children who had severe malaria. (Tablle III).

Table II: Diagnosis on admission in children presenting with a severe acute medical condition at the PEU (n = 203)

Diagnosis	**Normal blood sugar** n (%)	**Abnormal blood sugar** (%)		Chi square	P value
		Hypoglycaemia	**Hyperglycaemia**		
Severe malaria	85 (42)	5 (2.5)	38 (18.7)	0.23	0.65
Severe sepsis	19 (9.4)	0 (0)	14 (7)	0.77	0.37
Severe acute gastroenteritis	5 (2.5)	0 (0)	2 (1)	0.13	0.72
Sickle cell disease emergency	15 (7.4)	0 (0)	4 (2)	1.78	0.18
Severe acute malnutrition	3 (1.5)	2 (1)	3 (1.5)	2.77	0.09
Other*	5 (2.5)	0 (0)	3 (1.5)		
Total n (%)	132 (65.3)	7 (3.5)	64 (31.5)		

* Severe acute otitis media, severe acute laryngitis, acute pulmonary edema, pediatric HIV infection.

Table III: Distribution of severity criteria of malaria among children with severe malaria n= 130

Severity criteria	**Admission blood sugar status**			**Total n(%)**
	Low n (%)	Normal n (%)	High n (%)	
Coma or somnolence	5 (3.8)	21 (16.2)	19 (14.6)	45 (34.6)
Severe anaemia	5 (3.8)	67 (51.5)	**31 (23.8)**	**103 (79.2)**
Temperature > 39.5 °C	2 (1.5)	51 (39.2)	26 (20)	79 (60.8)
Convulsion	3 (2.3)	30 (23.1)	20 (15.4)	53 (40.8)
Prostration	5 (3.8)	81 (62.3)	**33 (25.4)**	**119 (91.5)**
Persistent vomiting	1 (0.8)	21 (16.2)	11 (8.5)	33 (25.4)
Dehydration	1 (0.8)	9 (6.9)	7 (5.4)	17 (13.1)
Abnormal bleeding	0 (0)	1 (0.8)	0 (0)	1 (0.8)
Deep breathing	2 (1.5)	4 (3.1)	5 (3.8)	11 (8.5)
Jaundice	1 (0.8)	5 (3.8)	5 (3.8)	11 (8.5)
Agitation/confusion	1 (0.8)	8 (6.2)	7 (5.4)	16 (12.3)
Hemoglobinuria	0 (0)	3 (2.3)	4 (3.1)	7 (5.4)
Respiratory distress	3 (2.3)	15 (11.5)	10 (7.7)	28 (21.5)
Total	**5 (3.8)**	**86 (66,2)**	**39 (30,0)**	130 (100.0)

Among the 31 children with severe sepsis, 13 (42%) were hyperglycaemic, no hypoglycemia was found in this group. . Of all with severe sepsis, 13 (41.9%) had as point of focus the lower respiratory tract (pneumonia). Five (16.1%) of those with pneumonia were hyperglycaemic. Thirteen (41.9%) children had meningitis. (Table IV). Two children with hypoglycemia were admitted for acute severe malnutrition.

Table IV: Distribution of the different points of focus of sepsis among the children with severe sepsis (n=31)

Point of focus of sepsis	**Admission blood sugar status**		**Total**	**P* value**
	Low n (%)	High n (%)	**n (%)**	
Lower respiratory tract	**8 (25.8)**	5 (16.1)	**13 (41.9)**	0.54
Cutaneous origin	1 (3.2)	0 (0)	1 (3.2)	1.00
Meningial	6 (19.4)	**7 (22.6)**	**13 (41.9)**	**0.18**
Bones/articulation	1 (3.2)	1 (3.2)	2 (6.5)	1.00
Digestive	2 (6.5)	0 (0)	2 (6.5)	0.50
Total	18 (58.1)	13 (41.9)	31 (100)	-

*chi square test

In hospital outcomes

The in-hospital outcomes studied in this work were length of hospital stay, transfer to ICU and in-hospital mortality rate (case fatality rate). The median length of hospital stay in our study population was 4 days (IQR: 3-6 days, range: 30 days). The median length of hospital stay among children who were hypoglycaemic was < 24 hours (IQR: 0-1, range: 8 days). That for hyperglycaemic and euglycemic children were each 4 days (IQR: 1.25-7 and 3-6; ranges: 29 days and 30 days respectively). Children with high or normal blood sugar stayed longer in hospital compare to those with hypoglycemia using the independent-samples Kruskal-Wallis test (P=0.005).but not the independent sample median test (p=0.2)

Table V : In hospital outcomes

	Blood sugar level				
	Low	Normal	High	Total	p
Transfer to ICU n (%)	5 (71.4)	6 (4.5)	18 (28.1)	29 (14)	<0.0001
In Hospital mortality n (%)	6 (85.7)	6 (4.5)	18 (28.1)	30 (14.8)	<0.0001
Median length of hospital stay in days (IQR)	< 24 hours (0-1)	4 (1.25 – 7)	4 (3-6)	-	0.005

Twenty nine patients were transferred to the ICU of which 23 had abnormal blood sugar: five with low blood sugar (71.4% of hypoglycaemic children) and 18 with high blood sugar (28.1% of hyperglycaemic children) (chi square=29.24, df=1, p<0.001). The risk to be transferred to the ICU for children with abnormal blood sugar was 7.1 times (95% CI: 3- 16.7) higher than for children with normal blood sugar

Of the 203 children in our study, 30 died giving an in-hospital mortality of 14.8%. Of the 30 patients who died, 24 presented abnormal blood sugar level. Among the 24 patients with dysglycemia who died, 6 had hypoglycemia (85.7% of subjects with hypoglycemia) and 18 had hyperglycemia (28.1% of children with hyperglycemia) (chi square= 28.96, df= 1, P<0.001). Among the 132 children who had a normal blood sugar level, 6 died giving a case fatality rate of 4.5%. Overall, the risk of dying in children with dysglycemia was 7.4 times (95% CI: 3.2-17.3) higher than for euglycemic children (p < 0.001). Up to 90% (27/30) of the total deaths and 22/24 (91.7%) of dysglycaemic deaths occurred within the first 24 hours of hospitalisation.

DISCUSSION

Limits of the study

This study was designed to evaluate the relationship that exists between admission blood sugar levels and adverse in-hospital clinical outcomes in children at the Mother and Child Centre of the Chantal Biya Foundation. These results should be thus interpreted with care due to the small sample size that was used in this study. Another limit was that no case matching was done between the euglycemic and dysglycemic group. This made the two groups to be different.

Prevalence of dysglycemia

In our study, we registered 71 patients with dysglycemia out of 203 patients giving a prevalence of 34.98% (31.54% for hyperglycemia and 3.44% for hypoglycemia). Our prevalence was comparable to the results of Ameyaw et al in Ghana (1) who found a prevalence of 31.75% (27.5% hyperglycemia and 4.25% hypoglycemia). The later also included patients who were not critically ill, explaining the slight differences in results. Our prevalence of hypoglycemia was similar to the 3.2% found by Madrid et al in Mozambique in 2016(11) but lower than that of Elusiyan et al in Nigeria in 2006 (8), 6.4 %, Osier et al in Kenya in 2003 (12), 7.3% . This difference may be due to sampling, some studies including not only critically ill children and exclusion of those who received glucose infusion before admission. Despite these differences, these findings show that hypoglycemia is a common feature in ill children.

Concerning hyperglycemia, Ameyaw et al in Ghana had comparable results to ours (1) but Bhisitkul et al (7) in the United States found a lower prevalence of 3.8%. This high prevalence in Africa could be explained by late arrival in hospital in compared to developed countries. This lateness may expose children to stress due to disease for longer time before admission, hence a higher biological response of the body with corresponding higher glycaemic levels.

The most frequent symptoms in children with a severe acute medical condition in our study were fatigue (99.5%), fever (87.2%), and poor feeding (85.7%). They were also the most frequent symptoms in both the hypoglycaemic and the hyperglycaemic patients. Unsurprisingly, these findings are similar to those obtained by Ameyaw et al(1) who had fever (88%), poor feeding (53%) and vomiting as most frequent presenting symptoms. These are common features of malaria and sepsis in children, most frequent diseases in Sub Saharan countries.

Numerous diseases have been shown to be associated with admission dysglycemia (1, 3, 8, 14, 19-21). Elusiyan et al in Nigeria (8) observed that hypoglycemia was associated with septicaemia, malnutrition, pneumonia and severe malaria among children who were admitted in an emergency ward. Ameyaw et al in Ghana(1) found that dysglycemia was associated with gastroenteritis, septicaemia, severe malaria and acute respiratory diseases. Respiratory, Infectious and cardiovascular disease were the most found by Toro-Polo et al in 2018 (21).

All children who were hypoglycaemic presented with fatigue and poor feeding. Diarrhoea was also more frequent (71.4%) among the hypoglycaemic children compared to the hyperglycaemic children. Respiratory distress and unconsciousness were the presenting complaints that were significantly associated with dysglycemia (P values of 0.01 and< 0.001 respectively). These findings are similar to those obtained by Ameyaw et al (1) who had fever (88%), poor feeding (53%) and vomiting as most frequent presenting symptoms. This means that dysglycemia should be suspected in every child presenting to the emergency with the above mentioned symptoms especially unconsciousness and respiratory distress.

In our study, hypoglycemia was found only in malaria and severe acute malnutrition. This may be explained by disturbance of neoglucogenesis present in these 2 conditions. In malaria, abnormal glucose level was mostly associated with other signs like coma, anemia and high grade temperature but not abnormal bleeding. Other authors had approximately same results (11, 15-16) The most common points of focus of severe sepsis were the lower respiratory tract and meninges. Elusiyan et al(8) also found meningitis and pneumonia to be common points of focus of infections.

In-hospital outcomes

The median length of hospital stay among children who had hypoglycemia was < 24 hours. This could be explained by the reason that many of such children died early, mostly on the first day of admission. There was no difference in the median length of hospital stay between children who had hyperglycemia and those who had a normal blood sugar level on admission. Our findings were similar to Elusiyan et al (8) who had a significant difference in the length of hospital stay between children with hypoglycemia and those without.

Dysglycemia on admission significantly increased the risk to be transferred to the ICU by 7.1 times (95% CI: 3- 16.7) compared to euglycaemic patients. This implies that both hyperglycemia and hypoglycemia are associated with a higher disease severity. Bhisitkul et al in the USA (7) also found that ICU transfer was highly associated with hyperglycemia in children who were admitted in a paediatric emergency department. The question of adding hyperglycemia in acutely ill children should then be raised.

Mortality of children with hyperglycemia is 6.2 times more than that for normoglycemic children. The overall in-hospital mortality in our study was similar to Osier et al in Kenya, but higher than that obtained by Ameyaw et al in Ghana in 2014 (1,12). Toro-Polo et al in Brazil had a mortality rate of 16.7% with a relative risk of death of 2.91 for those with hyperglycemia and 2.01 for those with hypoglycemia (21). In the group with hyperglycemia on admission, the mortality risk increases with glycemia (19, 20).

The case fatality rate among children with hypoglycemia was the highest found in African litterature (1, 3, 8-9, 11-12, 15). Unsurprisingly, the presence of hypoglycemia on admission was associated with death within the first 24 hours of admission (4, 5, 11, 14, 21).

WHO's severity criteria of malaria includes hypoglycemia but not hyperglycemia (3,17). Our results such as other authors reveals that hyperglycemia is also associated to high risk of mortality (19-21), of transfer in ICU and longer stay in hospital. Thus, we suggest that hyperglycemia should be also include in severity criteria of malaria.

CONCLUSION

Prevalence of dysglycemia, on admission, is 34.9% in children with severe medical condition in our center. Severe malaria, severe sepsis, severe acute malnutrition, were the most frequent diseases associated with dysglycemia. Dysglycemia be it hypoglycemia or hyperglycemia significantly increases the likelihood of dying and more so within the first 24 hours of hospitalisation.

DECLARATIONS

Conflicts of interests and fundi

No competing of interest
No funding

Ethics

Ethical approval obtained from IECR of the faculty of medicine and biomedical sciences of the Yaounde I University. Informed written consent was obtained from parents.

Author's contributions

Drafting: SSNU, KNO, IM, FM
Data collection: KNO, SSNU, IM

Stat Analysis: KNO, SSNU, IM
Bibliographic research: SSNU, KNO, HK, JT, CK, IM
Reviewing: SSNU, KNO, CK, HK, FM

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