A retrospective analysis of dysglycaemia and its risk factors in a cohort of human immunodeficiency virus infected antiretroviral therapy naïve children in Makurdi, Nigeria

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Abstract

Background: Human immunodeficiency virus (HIV) endocrinopathy involving the pancreas manifests clinically as dysglycaemia, including hypoglycaemia and hyperglycaemia. Dysglycaemia increases mortality in sick children, underlying the need for its evaluation and management.

Objective: To assess the prevalence and risk factors of dysglycaemia in a cohort of antiretroviral therapy (ART)-naïve children at the point of enrolment into a paediatric ART clinic of the Federal Medical Centre, Makurdi, Nigeria.

Method: A retrospective cross-sectional study was carried out between June 2010 and June 2012. Hypoglycaemia was defined as random blood glucose level <2.2 mmol/l and hyperglycaemia as random blood glucose >6.6 mmol/l. Potential risk factors of dysglycaemia were tested for significance in bivariate and multivariate regression analyses. *P*-value less than 0.05 was considered to be significant.

Results: 429 children, aged 1-15 years, including 223 males and 206 females were studied. The median age was 5 years. Twelve (2.8%) children had hypoglycaemia and 35 (8.2%) had hyperglycaemia. In multivariate regression analysis, no factor significantly predicted the risk of hypoglycaemia, whereas children co-infected with hepatitis C were at a significant risk of hyperglycaemia (adjusted odds ratio; 2.06, 95% CI; 1.05-8.52, P=0.03).

Conclusions: In this study HIV-infected Nigerian children who were not on ART had a low prevalence of hypoglycaemia but a high prevalence of hyperglycaemia. Hepatitis C co-infection was a significant independent risk factor for hyperglycaemia.

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Introduction

About 400,000 Nigerian children were living with human immunodeficiency virus (HIV) in 2013[1]. Before the access to Highly Active Anti-Retroviral Therapy (HAART), 50% of perinatally HIV infected children died before their second birthday[2]. However, with the easy access to, and the success of HAART in reducing mortality from acquired immune deficiency syndrome (AIDS)[3,4], the attendant increased longevity is making co-morbidities like HIV-endocrinopathies more frequent[5].

HIV-endocrinopathies involve the pituitary, the thyroid, the adrenal, the gonads and the pancreas[6]. HIV pancreatic dysfunctions manifest clinically as hypoglycaemia and hyperglycemia[7-15] and are seen in both antiretroviral therapy (ART)-experienced and ART-naïve patients[11,12]. The mechanisms of HIV pancreatic dysfunctions include pancreatic infection by HIV and other opportunistic organisms including cytomegalovirus and toxoplasma[7], infiltration of the pancreatic gland by malignancies[7], and the effects of therapeutic interventions[8-10]. For example, pancreatic beta cell toxicity by pentamidine has been found to result in hypoglycaemia with hyperglycaemia and diabetes developing in the long term[8]. Also, reports of insulin resistance and the development of hyperglycaemia and overt diabetes increased with the routine clinical use of protease inhibitors (PI)[9] with a reversal of hyperglycaemia following the replacement of the PI with another class of medication[10]. Furthermore, evidence is also available suggesting the possibility of insulin resistance, as a HIV disease–associated component, among ART- naïve patients with AIDS[11]. On the other hand, Hommes *et al.*[12] reported that clinically stable HIV infected patients are protected against hyperglycaemia and diabetes as they were found to have increased sensitivity of peripheral tissues to insulin and increased non-oxidative glucose disposal[12].

There is a dearth of data on dysglycaemia among HIV-infected children, although a Thailand study revealed that about 4% had hyperglycaemia in a

cohort of ART experienced children (non-PI based)[13]. Several studies[14-17]among HIV-infected Nigerian children have reported a high prevalence of malnutrition, diarrhoeal disease, pneumonia, septicaemia and malaria, all of which are known confounders of hypoglycaemia[18-22] and hyperglycaemia[18,23,24] outside the context of HIV infection. Regardless of the aetiopathogenesis of hypoglycaemia and hyperglycaemia in HIV-infection, both have been associated with increased morbidity and mortality in severely ill and non-severely ill children, underlining the need for their evaluation, whenever they may be present[25,26].

Objectives

To retrospectively determine the prevalence and the associated risk factors of dysglycaemia (hypoglycaemia and hyperglycaemia) among ART naïve HIV infected children, at the point of recruitment into an ART programme, at the Federal Medical Centre (FMC), Makurdi, Nigeria, between June 2010 and June 2012.

Method

Ethics: Approval to use the data for this study was obtained from the Research and Ethics Committee of the FMC, Makurdi and the AIDS Prevention Initiative in Nigeria (APIN)/Harvard PEPFAR (The USA President's Emergency Plan for AIDS Relief) programme. The parents/legal care providers had earlier given written informed consent for the use of the childrens' data for research purposes at the recruitment of these children into the ART programme of the FMC, Makurdi. The process of obtaining the written informed consent was in accordance with the Helsinki Declaration of 1975, as revised in 2000.

*Selection and study population:*A minimum sample size of 384 was calculated using the Leslie Kish's method[27] at a standard normal deviate of 1.96, assuming 50% target population and tolerating 5% sampling error. A total of 429 children whose data were relevant to this study were all abstracted from a pool of 454 HIV-infected children that were enrolled into the ART programme of the FMC, Makurdi, between June 2010 and June 2012. The remaining twenty five children whose data were missing for one reason or the other, were excluded from the present study. This cohort of HIV-infected ART naïve children had been previously studied for dyslipidaemia[28].

Inclusion and exclusion criteria: Included in the study were HIV infected children (≤ 15 years of age) who were ART naïve (except for the purpose of prevention of mother-to-child transmission of HIV) and whose venous blood glucose level results were available. HIV-infected ART naïve children with no blood glucose result and/or incomplete records of clinical variables of interest (i.e. demographic, some specific symptoms and signs/physical examination findings, laboratory findings and some comorbidities including tuberculosis, oesophageal candidiasis, diarrhoeal disease, sepsis, malarial fever, pneumonia and undernutrition) and HIV-infected ART-experienced children were excluded.

Operational definitions

The definition of *hypoglycaemia* in infants and children continues to be controversial, but for this study, hypoglycaemia was defined as a blood glucose <2.2 mmol/l (40 mg/ dl)[29,30]. *Normoglycaemia* was blood glucose between 2.2–6.6 mmol/l (40–120 mg/ dl) and *hyperglycaemia* was blood glucose over 6.6 mmol/l (>120 mg/ dl)[31,32]. Abnormal blood glucose, or dysglycaemia, was defined as any of these 2 categories above. *Hypocholesterolaemia* (total cholesterol value below 160mg/dl) and *hypercholestrolaemia* (total cholesterol value above 200 mg/dl) were according to the Lipid Research Clinics (LRC) prevalence study[33]. To define under-nutrition in children less than 5 years, the weight for height Z-score less than -2 standard deviations (wasting) from World Health Organization (WHO) reference median was computed using the WHO Anthro software (version 2.0, 2008) which was based on WHO child growth standards of 2006[34]. For children ≥ 5 years, the body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in metres (kg/m^2). Values <18.5 kg/m^2 was defined as under-nutrition, >25kg/m^2 as overweight and >30 kg/m^2 as obesity[35]. Hepatotoxicity was defined as alanine aminotransferase (ALT) of 1.25-fold over the upper limit of normal of 37 IU/L[36]. The definitions of "fever", "malaria fever", "diarrhoea", "chronic diarrhoea", "pneumonia", "tuberculosis", "oropharyngeal candidiasis", "oesophageal candidiasis", and "sepsis" were as described in the WHO *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses*[37].

The blood glucose was analysed by the glucose oxidase method (GM6 Analox instruments, UK) and it did not require fasting. The total cholesterol was determined enzymatically by cholesterol esterase and cholesterol oxidase and with the Cobas Mira chemistry analyzer. In addition to determining the CD4 count and the viral load, venous blood samples were also collected for haemoglobin concentration, malaria parasites (Giemsa stain), a full blood count (Coulter Micro Diff II, UK), hepatitis B surface antigen and hepatitis C virus antibody (using the third generation ELISA technique, EIAgen HBsAg Kit, EIAgen HCV Ab Kit) and catalytic activity of ALT (determined in serum using a Cobas Mira chemistry analyzer). All tests were done at the APIN/PEPFAR laboratory of FMC, Makurdi.

Statistical analysis: Descriptive statistics were tabulated as numbers and percentages for categorical variables. The main outcome variable in the analysis was dysglycaemia (i.e. hypoglycaemia and hyperglycaemia considered separately) versus normoglycaemia. The prevalence proportions of hypoglycaemia and hyperglycaemia were calculated. Potential risk factors for dysglycaemia (hypoglycaemia and hyperglycaemia considered separately) were tested for significance in a bivariate logistic regression. These potential risk factors included age and gender, some presenting symptoms and signs on physical examinations and the WHO HIV/AIDS clinical stage, some laboratory findings [CD4 count, alanine aminotransferase (ALT), haemoglobin level, HBsAg, HCV antibodies and viral load], and some co-morbidities/opportunistic infections (tuberculosis, oesophageal candidiasis, diarrhoeal disease, sepsis, malarial fever, pneumonia and undernutrition). Risk factors that achieved a significance level of 0.1 at bivariate analyses were modelled into multivariate logistic regression analyses in one block. For all analyses, p-values less than 0.05 were considered statistically significant. Statistical analysis was done using SPSS version 16.

Results

There were 206 females and 223 males with a F:M ratio of 1: 1.1. The median age was 5 years with an interquartile range of 3 to 8 years. Twelve children (2.8%, 12/429) were found with hypoglycaemia and 35 (8.2%, 35/429) had hyperglycaemia.

Table1 depicts the risk factors of hypoglycaemia among the cohorts.

Table 1: ***Risk factors of hypoglycaemia among the cohorts***

Clinical variable	Hypoglycaemia (<2.2 mmol/l) Number (%)	Normoglycaemia (2.2-6.6mmol/l) Number (%)	Bivariate analysis			Multivariate analysis
			COR	*95% CI*	*P -value*	*P -value*
Demography						
Age (years)						
<5	04 (33.3)	197(47.2)	0.558	(0.166 – 1.88)	0.341	NA
≥5 (Ref)	08 (66.7)	220 (52.8)				
Gender						
Male	07 (58.3)	216 (51.8)	1.30	(0.407 – 4.17)	0.655	NA
Female (Ref)	05 (41.7)	201 (48.2)				
Symptoms						
Irritability						
Yes	10 (83.3)	04 (01.0)	516.25	(84.53– 3153.16)	<0.001	0.999
No (Ref)	02 (16.7)	413 (99.0)				
Convulsions						
Yes	08 (66.7)	04 (10)	185.22	(43.74– 975.34)	<0.001	0.987
No (Ref)	04 (33.3)	413 (99.0)				
*Food refusal						
Yes	12 (100.0)	57 (13.7)				
No (Ref)	0 (0.0)	360(86.3)				
*Vomiting						
Yes	12 (100.0)	70(16.8)				
No (Ref)	0 (0.0)	347(83.2)				
Physical Signs						
Fever						
Yes	03 (25.0)	67 (16.1)	1.74	(0.459 – 6.60)	0.668	NA
No (Ref)	09 (75.0)	350 (83.9)				
Oral thrush						
Yes	11 (91.7)	37 (08.9)	112.97	(14.19 – 899.56)	<0.001	0.786
No (Ref)	01 (08.3)	380 (91.1)				
Hepatosplenomegaly						
Yes	05 (41.7)	34 (8.2)	8.05	(2.42 – 26.75)	0.001	0.982
No (Ref)	07 (58.3)	383 (91.8)				
Hepatomegaly						
Yes	03 (25.0)	42 (10.1)	2.98	(0.775 – 11.42)	0.236	NA
No (Ref)	09 (75.0)	375 (89.9)				
*Splenomegaly						
Yes	0(0.0)	05 (01.2)				
No (Ref)	12 (100.0)	412 (98.8)				
WHO clinical staging			0.975	(0.209 – 4.54)	0.974	NA
1&2	10 (83.3)	346 (83.0)				
3&4 (Ref)	2 (16.7)	71 (17.0)				

**=Omitted because of collinearity , COR=Crude Odd Ratio, CI=Confidence Interval, NA=Not applicable, WHO=World Health Organization*

Table 1: ***Risk factors of hypoglycaemia among the cohorts (continued)***

Clinical variable	Hypoglycaemia (<2.2 mmol/l) Number (%)	Normoglycaemia (2.2-6.6mmol/l) Number (%)	Bivariate analysis			Multivariate analysis
			COR	*95% CI*	*P -value*	*P -value*
Laboratory findings						
CD4 count ≤200 >200 (Ref)	 02 (16.7) 10 (83.3)	 81 (19.4) 336(80.6)	0.830	(0.178 – 3.86)	0.812	NA
*Viral load (copies/ml) <1000 ≥1000 (Ref)	 0 (0.0) 12 (100.0)	 38 (9.1) 379 (90.9)				
Haemoglobin (g/dl) <10 ≥10 (Ref)	 11 (91.7) 01 (08.3)	 247 (59.2) 170 (40.8)	7.57	(0.986 – 59.19)	0.050	0.992
Hepatitis B surface antigen Yes No (Ref)	 03 (25.0) 09 (75.0)	 46 (11.0) 371 (89.0)	2.69	(0.702 – 10.29)	0.299	NA
*Hepatitis C antibodies Yes No (Ref)	 0 (0.0) 12 (100.0)	 11 (2.6) 406(97.4)				
Alanine aminotransferase Elevated (>46.3) Normal (≤46.3) (Ref)	 03 (25.0) 09 (75.0)	 71 (17.0) 346 (83.0)	1.62	(0.429 – 6.15)	0.739	NA
Hypocholesterolaemia Yes No (Ref)	 11 (91.7) 01 (8.3)	 368 (88.2) 49 (11.8)	1.47	(0.185 – 11.59)	0.716	NA
Diagnosed co-morbidities /opportunistic infections						
Tuberculosis Yes No (Ref)	 01 (08.3) 11 (91.7)	 51 (12.2) 366 (87.8)	0.652	(0.082 – 5.16)	0.683	NA
*Oesophageal candidiasis Yes No (Ref)	 0 (0.0) 12 (100.0)	 08 (01.9) 409 (98.1)				
Diarrhoeal disease Yes No (Ref)	 01 (08.3) 11 (01.7)	 11 (02.6) 406 (97.4)	3.36	(0.398 – 28.32)	0.238	NA
*Sepsis Yes No (Ref)	 0 (0.0) 12 (100.0)	 14 (3.4) 403 (96.6)				
Malaria fever Yes No (Ref)	 03 (25.0) 09 (75.0)	 54 (12.9) 363 (87.1)	2.24	(0.588 – 8.53)	0.435	NA
Pneumonia Yes No (Ref)	 04 (33.3) 08 (66.7)	 21 (5.0) 396 (95.0)	9.43	0.000	0.983	NA
Weight for height Z score <-2 SD ≥-2 SD (Ref) Not Counted =228	 02 (50.0) 02 (50.0)	 63 (31.9) 134 (68.1)	2.09	(0.288 – 15.22)	0.835	NA
Body mass index ≥18.5 <18.5 (Ref) Not Counted=201	 07 (87.5) 01 (12.5)	 186 (84.5) 34 (15.5)	1.32	(0.158 – 11.09)	0.796	NA

**=Omitted because of collinearity , COR=Crude Odd Ratio, CI=Confidence Interval, NA=Not applicable,*

In bivariate analyses, children with the symptom of convulsions, those with irritability, oral thrush and hepatosplenomegaly on physical examination, and those with co-morbidity of pneumonia were found to be significantly associated with hypoglycaemia. Children with convulsions were associated with a 185 folds risk of hypoglycaemia (OR; 185, 95%CI; 43.7-975.3, P<0.001). Also, irritability significantly increased the odds of hypoglycaemia by 516 times (OR; 516.3, 95%CI; 84.5-3153.2, P<0.001). Furthermore, children with oral thrush were 112 times more at risk of having hypoglycaemia (OR; 112.9, 95%CI; 14.2-899.6, P<0.001) and those with hepatosplenomegaly 8 times more (OR; 8.1, 95%CI; 2.4-26.8, P=0.001). Pneumonia was also associated with hypoglycaemia (OR; 9.4, 95%CI; 2.63-33.8, P<0.001). However at multivariate analyses, none of these risk factors was found to be associated with hypoglycaemia.

Table 2 shows the risk factors of hyperglycaemia among the cohorts.

Table 2. The risk factors of hyperglycaemia

Clinical variables	Hyperglycaemia (>6.6mmol/l) Number (%)	Normoglycaemia (2.2-6.6mmol/l) Number (%)	Bivariate analyses			Multivariate analyses
			COR	*95% CI*	*P -value*	*P-value*
Demography						
Age (years) <5 ≥5 (Ref)	 15 (42.9) 20 (57.1)	 186 (47.2) 208 (52.8)	 0.839	 (0.417 – 1.69)	 0.621	 NA
Gender Male Female (Ref)	 20 (57.1) 15 (42.9)	 203 (51.5) 191 (48.5)	 1.26	 (0.624 – 2.52)	 0.524	 NA
Symptoms						
*Irritable Yes No (Ref)	 0 (0.0) 35 (100.0)	 14 (03.6) 380 (96.4)				
*Convulsions Yes No (Ref)	 0 (0.0) 35 (100.0)	 12 (03.0) 382 (97.0)				
Food refusal Yes No (Ref)	 03 (08.6) 32 (91.4)	 66 (16.8) 328 (83.2)	 0.466	 (0.139 – 1.57)	 0.207	 NA
Vomiting Yes No (Ref)	 04 (11.4) 31 (88.6)	 78 (19.8) 316 (80.2)	 0.523	 (0.179 – 1.53)	 0.228	 NA
Physical Signs						
Fever Yes No (Ref)	 06 (17.1) 29 (82.9)	 64 (16.2) 330 (83.8)	 1.07	 (0.426 – 2.67)	 0.890	 NA
Oral thrush Yes No (Ref)	 02 (05.7) 33 (94.3)	 46 (11.7) 348 (88.3)	 0.458	 (0.106 – 1.97)	 0.428	 NA
Hepatosplenomegaly Yes No (Ref)	 02 (05.7) 33 (94.3)	 37 (09.4) 357 (90.6)	 0.585	 (0.135 – 2.54)	 0.676	 NA
*Hepatomegaly Yes No (Ref)	 0 (0.0) 35 (100.0)	 45 (11.4) 349 (88.6)				
*Splenomegaly Yes No (Ref)	 0 (0.0) 35 (100.0)	 05 (01.3) 389 (98.7)				
WHO Clinical staging 1&2 3&4 (Ref)	 31 (88.6) 4 (11.4)	 325 (82.5) 69 (17.5)	 0.608	 (0.208 – 1.78)	 0.359	 NA

**=Omitted because of colinearity, COR=Crude Odds Ratio, CI=Confidence Interval, NA=Not applicable, WHO=World Health Organization*

Table 2. The risk factors of hyperglycaemia (continued)

Clinical variables	Hyperglycaemia (>6.6mmol/l) Number (%)	Normoglycaemia (2.2-6.6mmol/l) Number (%)	Bivariate analyses			Multivariate analyses
			COR	*95% CI*	*P -value*	*P-value*
Laboratory findings						
CD4 count >200 (Ref) ≤200	 32 (91.4) 3 (8.6)	 314 (79.7) 80 (20.3)	0.368	(0.110 – 1.23)	0.092	0.079
*Viral load (copies/ml) <1000 ≥ 1000 (Ref)	 0 (0.0) 35 (100.0)	 31 (07.9) 363(92.1)				
Haemoglobin (g/dl) <10 ≥10 (Ref)	 16 (45.7) 19 (54.3)	 242 (61.4) 152 (38.6)	0.529	(0.264 – 1.06)	0.069	0.059
Hepatitis B surface antigen Yes No (Ref)	 04 (11.4) 31 (88.6)	 45 (11.4) 349 (88.6)	1.00	(0.338 – 2.97)	0.999	NA
Hepatitis C antibodies Yes No (Ref)	 03 (08.6) 32 (91.4)	 08 (02.0) 386 (98.0)	4.51	(1.14 – 17.85)	0.019	0.029†
Alanine aminotransferase Elevated (>46.3) Normal(≤46.3) (Ref)	 06 (17.1) 29 (82.9)	 68 (17.3) 326 (82.7)	0.992	(0.396 – 2.482)	0.986	NA
Hypocholestrolemia Yes No (Ref)	 31 (88.6) 04 (11.4)	 348 (88.3) 46 (11.7)	1.02	(0.346 – 3.03)	0.965	NA
Diagnosed co-morbidities / opportunistic infections						
Tuberculosis Yes No (Ref)	 02 (05.7) 33 (94.3)	 50 (12.7) 344 (87.3)	0.417	(0.097 – 1.79)	0.346	NA
Esophageal candidiasis Yes No (Ref)	 02 (05.7) 33 (94.3)	 06 (01.5) 388 (98.5)	3.92	(0.761 – 20.19)	0.269	NA
*Diarrhoeal disease Yes No (Ref)	 0 (0.0) 35 (100.0)	 12 (03.0) 382 (97.0)				
Sepsis Yes No (Ref)	 01 (02.9) 34 (97.1)	 13 (03.3) 381 (96.7)	0.862	(0.109 – 6.79)	0.888	NA
Malaria fever Yes No (Ref)	 08 (22.9) 27 (77.1)	 49 (12.4) 345 (87.6)	2.09	(0.897 – 4.85)	0.139	NA
Pneumonia Yes No (Ref)	 01 (02.9) 34 (97.1)	 24 (06.1) 370 (93.9)	0.453	(0.059 – 3.45)	0.685	NA
Weight for Height Z score <-2 SD ≥-2 SD (Ref) Not counted =228	 03 (20.0) 12 (80.0)	 62 (33.3) 124 (66.7)	0.492	(0.134 – 1.80)	0.423	NA
Body Mass Index ≥18.5 <18.5 (Ref) Not counted = 201	 14 (70.0) 06 (30.0)	 179 (86.1) 29 (13.9)	3.91	(0.139 – 1.10)	0.131	NA

**=Omitted because of colinearity, COR=Crude Odds Ratio, CI=Confidence Interval, NA=Not applicable, WHO=World Health Organization. Adjusted Odds Ratio 2.06, 95% CI; 1.05-8.52*

In both bivariate and multivariate analyses, only Hepatitis C co-infection was found to be significantly associated with the risk of hyperglycaemia. At the adjusted regression model, the trend was such that subjects who were co-infected with Hepatitis C were at significant risk of hyperglycaemia compared to those who had mono infection with HIV (Adjusted Odds Ratio 2.06, 95% CI; 1.05-8.52, P=0.03).

Discussion

This is the first study that described the burden and the risk factors of dysglycaemia among Nigerian HIV-infected ART-naïve children. The study reveals that whilst the prevalence of hypoglycaemia was low at 2.8%, that of hyperglycaemia was high at 8.2%. The prevalence of hypoglycaemia of 2.8% in this study was lower than the 5.6% and 6.4% in a cohort of Nigerian children admitted at the emergency paediatric units in Lagos[38] and Ile-Ife[39]

respectively. In other settings outside Nigeria, the prevalence of hypoglycaemia of 2.8% in this study was lower than the respective 7.1% and 8.2% among paediatric admissions in Mozambique[40] and in Kenya[30]. Apart from Lagos and Ile-Ife studies which used a higher cut-off value of less than 2.5 mmol/l to define hypoglycaemia, the Kenyan[30] and Mozambique[40] studies utilized the same value of less than 2.2 mmol/l with ours, thereby underscoring the fact that the prevalence of hypoglycaemia was in fact higher in their own cohorts[30,40]. In making comparisons however, caution must be exercised because of differences in the composition of the subjects that populated the different studies[30,38-40]. Ours was essentially among HIV-infected ART-naïve children.

It is also noteworthy that apart from pneumonia which was found to be significantly associated with hypoglycaemia in bivariate analyses, some other known confounders of hypoglycaemia including malarial infestations, sepsis, undernutrition and diarrhoeal disease[18-24] were not seen to be associated with hypoglycaemia in this study. This finding is in contrast to that of Ile-Ife[39] where severa malaria, sepsis, pneumonia and malnutrition were found to be associated with hypoglycaemia and to that of Lagos[38] where severe malaria, sepsis, marasmus and diarrhoeal disease were found to be associated with hypoglycaemia. In Mozambique[40] hypoglycaemia was found to be significantly associated with severe malaria, protein energy malnutrition, and pneumonia. In Kenya[30], malaria and malnutrition were also associated with hypoglycaemia.

The pathophysiology of hypoglycaemia in pneumonia may be due to a combination of mechanisms including increased glucose utilization by macrophage-rich tissues of the liver, lung, spleen, ileum, and skin and also from depressed hepatic gluconeogenesis that may result from the decreased sensitivity to stress hormones and/or adrenal failure, both of which can be triggered by pulmonary infections[29]. There was also a significant association at bivariate analyses between convulsions, irritability, oral thrush, hepatomegaly and hypoglycaemia.

Irritability and convulsions are known neurological symptoms of hypoglycaemia and as such, the significant association between these symptoms and hypoglycaemia may not be too difficult to explain. However, the absence of these clinical symptoms does not always indicate that the glucose concentration is normal or that it has not fallen below optimal level for brain metabolism[38]. Although subjects with oral thrush may be expected to eat poorly, this alone cannot explain the association with hypoglycaemia as "food refusal", surprisingly, was not found to be associated with hypoglycaemia in these subjects. The interaction with other confounders in the multivaraiate analysis may have reduced the importance of oral thrush as a risk factor of hypoglycaemia in this study. Hepatosplenomegaly depicts a progression in HIV disease and may also accompany many infectious diseases that may be seen in HIV/AIDS and as such, hepatosplenomegaly may be associated with hypoglycaemia of infectious diseases as earlier explained[12,29].

Among paediatric admissions into hospitals, the prevalence of hyperglycaemia of 8.2% in the present study was lower than 10.9% reported by Sambany et al in Magadascar[29], the 25% by Palacio et al in Atlanta, USA[31], but was higher than the 2.7% reported by Osier et al in Kenya[30]. The various definitions ascribed to hyperglycaemia could explain the different prevalence of hyperglycaemia in our study and those of others[29-31]. Whilst we used > 6.6 mmol/l as a cut-off value for hyperglycaemia in our own study, it was >8.3 mmol/l, >7.1 mmol/l and >10mmol/l in the studies in Madagascar, Atlanta and Kenya respectively. Also, the different spectrum of diseases among our HIV-infected ART-naive children and the children in other settings[29-31] could also explain the varying burden of hyperglycaemia.

Although there is a dearth of data on the prevalence of hyperglycaemia among HIV-infected ART naive children, the prevalence of 8.2% in our study and 21.5% in the study of Shen et al [41] among the adult population in China, have shown that the prevalence of hyperglycaemia in untreated HIV-infection persons could be high. Dube[11] had earlier suggested that there may be an insulin resistance occurring as an association of HIV-disease and thus may provide an explanation for the hyperglycaemia of HIV-infection. Also, the stress of HIV-infection can cause elevations in plasma concentrations of hyperglycaemic hormones such as glucocorticoids, catecholamines, glucagon and growth hormones with a resultant alterations in the metabolism of glucose and other energy substrates and may thus explain the hyperglycaemia seen[29].

In this study, only hepatitis C was independently associated with hyperglycaemia in multivariate analyses. Wohl et al[42] had also mentioned hepatitis C infection as a risk factor for hyperglycaemia among HIV-infected adults. The pathophysiology of hyperglycaemia in hepatitis C infection is not completely understood. However, studies have suggested that an expression of the hepatitis C virus core protein can induce hepatic insulin resistance through alterations in insulin receptor substrate-1 pathway. With a progressive increase in insulin resistance, the compensatory increase in insulin

secretion by the β-cell reaches fails and hyperglycaemia thus emerges[43].

There are some limitations to the study. It was not determined if the hyperglycaemia at the point of recruitment represents a diagnosis of diabetes mellitus or just a response to the stress of HIV infection in our cohort. Unfortunately, being a retrospective study, a longitudinal follow-up of serum glucose level was not done. Also, the range of the potential risk factors that were evaluated for dysglycaemia was limited by the retrospective design of the study. Furthermore, the prevalence of dysglycaemia may have been underestimated as many more critically ill HIV-infected ART naïve children presented at the Emergency Unit of the FMC, Makurdi, rather than at the ART clinic where the data was abstracted.

Conclusions

- In this study HIV-infected Nigerian children who were not on ART had a low prevalence of hypoglycaemia but a high prevalence of hyperglycaemia.
- Hepatitis C co-infection was a significant independent risk factor of hyperglycaemia.

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