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ABSTRACT:

In the paediatric age group, particularly in infancy, hypoglycaemia is a common metabolic problem complicating a variety of clinical conditions, and its coexistence may influence the outcome of the primary disease. This study assesses the prevalence of hypoglycaemia among patients presenting at the University of Benin Teaching Hospital, Benin City, Nigeria with cholestasis of infancy. Forty patients aged between 15 days and 12 months who presented with cholestasis of infancy were admitted and screened for hypoglycaemia, using Acutrend glucometer. For patients with low blood glucose values, blood samples were further analyzed, using the standard glucose-oxidase method. Of 2,835 patients admitted over a five-year period, 40 (1.4%) had cholestasis of infancy, giving an incidence of 14 cases per 1000 admissions, with a sex ratio of 2.1: 1 in favour of males. Nine (22.5%) of the 40 infants with cholestasis had at least one blood glucose concentration less than 2.6 mmol/L (hypoglycaemia). Of the nine hypoglycaemic infants, three (33.3%) had one blood glucose concentration less than 1.6 mmol/L (severe hypoglycaemia). Seven (77.8%) of the nine hypoglycaemic infants were diagnosed in the first 36 hours of admission. Lethargy and poor feeding were observed in three infants with severe hypoglycaemia. Six (66.7%) of the hypoglycaemic infants were below 3 months of age. Hypoglycaemia was observed among patients with cholestasis of infancy; the prevalence was higher among infants below 3 months of age.

Key words: Hypoglycaemia, Cholestasis, Infancy, Neonatal Cholestasis Syndrome.
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INTRODUCTION:

In the paediatric age group, particularly in infancy, hypoglycaemia is a common metabolic problem encountered in association with a variety of disorders, such as malaria, kwashiorkor and hepatic diseases (e.g., hepatitis, cirrhosis, metabolic liver disorders)[1-4]. The coexistence of hypoglycaemia and other diseases may influence the outcome or clinical course of the primary disease, if not appropriately addressed.

The term cholestasis refers to a group of disorders associated with bilirubin excretion and accompanied by a rise in serum conjugated bilirubin levels and often, bile salts and phospholipids [3]. Some of the key clinical features of cholestasis of infancy are: jaundice persisting beyond the age of 14 days, jaundice with elevated serum conjugated bilirubin fraction (> 2.0 mg/dl or > 20% of total bilirubin), variably acholic stool, dark urine that stain the diaper yellow, bilirubinuria, and hepatomegaly [4,5]. Clinically, the hallmark of cholestasis is itching but this may not be recognized in early infancy. Itching becomes apparent after the age of six months [5]. Before the age of six months, irritability is a common feature of itching. The estimated incidence of cholestasis of infancy is 1 in 2,500 infants [1,6]. Among the components of liver function tests, elevated Alkaline Phosphatase is one of the sensitive tests of cholestasis [7]. The liver plays an important role in the maintenance of blood glucose levels, which is highly regulated by insulin and insulin counter-regulating hormones. Thus, a patient with liver dysfunction manifesting with cholestasis of infancy may be at increased risk of developing hypoglycaemia [8,9]. It has been recommended that the initial investigation of an infant with a liver disease should focus on identification of associated abnormalities, such as hypoglycaemia that require urgent specific treatment [4,10]. In infants, hypoglycaemia is defined as blood glucose concentration of 2.5mmol/L and below [11]. The association of cholestasis of infancy with hypoglycaemia has been documented [5,12]. Some studies have demonstrated links between hepatic dysfunction, hypoglycaemia and congenital hypopituitarism [13,14]. Although the mechanisms are not clearly understood, involvement of growth hormone and cortisol have been hypothesized [12,14,15]. Lablanc et al, [12] indicated that cortisol deficiency might be the main endocrine abnormality responsible for both hypoglycaemia and liver dysfunction. Reports of other studies support this view [16-18]. Thus, adrenal function tests should be requested for infants with hypoglycaemia and liver dysfunction [12,16,18]. On the other hand, link between mitochondrial respiratory chain enzyme deficiency, neonatal cholestasis and hypoglycaemia have been variously reported [13,19]. Although the biochemical mechanisms of occurrence of hypoglycaemia in association with cholestasis of infancy has

been studied, [12-19] the prevalence of hypoglycaemia among patients with cholestasis of infancy has not been well documented, especially in Nigeria. This study assesses the prevalence of hypoglycaemia among patients with cholestasis of infancy in the University of Benin Teaching Hospital (UBTH), Nigeria.

PATIENTS AND METHODS:

All infants (aged 15 days to 12 months) diagnosed with cholestasis of infancy and admitted between January, 2004 and December, 2008 into the under-five-paediatric ward of the Department of Child Health, University of Benin Teaching Hospital (UBTH) were recruited into the study after obtaining informed consent from the parents/caregivers. In this study, standard clinical features were used for the diagnosis of patients [4,5].

The glucometer (Acutrend meter product 128485) was used for measurement of blood glucose [18,19]. Laboratory confirmation of blood glucose level was requested for all infants with blood glucose level below 3.0mmol/L [20]. Appropriate monitoring of blood glucose level was observed for all the infants. For infants with at least one blood glucose level below 2.0 mmol/L, the glucose level was monitored for at least one day after the level had returned to normal or after the therapy had been discontinued. When the blood glucose level was below 1.6 mmol/L or the infant was symptomatic (irrespective of blood glucose value), intravenous administration of 10.0 % glucose was started immediately [8,11]. Haematocrit values of all the infants were determined and recorded. Blood films were prepared and examined for malaria parasite, and liver function tests (LFT) were performed using standard procedures. All the infants were examined clinically for features of kwashiorkor and congenital conditions. In the present study, infants with blood glucose level of 2.5mmol/L and below were characterized as hypoglycaemic [11]. Appropriate statistical methods were used for analysis of data; odd ratios were computed and Z-test was used in ascertaining the significance of differences in proportions with p-value set at < 0.05.

RESULTS:

During the 5-year period covered by this study, a total of 2,835 children were admitted into the under-five ward in UBTH; 40 (1.4%) of them had cholestasis of infancy, giving an incidence of 14 cases per 1000 admissions. Of the 40 infants with cholestasis of infancy, 27 (67.5%) were males and 13 (32.5%) were females, giving a male-to-female ratio of 2.1:1. Nine (22.5%) of the 40 infants with cholestasis had at least one blood glucose concentration below 2.6mmol/L (hypoglycaemia). Of the nine hypoglycaemic infants, three (33.3%) had one blood glucose concentration below 1.6mmol/L (severe hypoglycaemia). The remaining 6 (66.7%) had one or more blood glucose concentration between 1.6 and 2.5 mmol/L. Seven (77.8%) of the hypoglycaemic infants

were diagnosed within the first 36 hours of admission while two (22.2%) were diagnosed between 36 and 72 hours of admission. Lethargy and poor feeding were present in the three infants with severe hypoglycaemia. Hypoglycaemia was observed only among infants who were between 15 days and 6 months old (Table 1).

Table 1: Age at presentation and prevalence of hypoglycaemia among patients with cholestasis of infancy

	Blood glucose concentration (mmol/L)			
Age at presentation	<1.6mmol/L	1.6 – 2.5mmol/L	>2.5mmol/L	Z-stat
15 days to <3 months (n = 24)[a]	3 (12.5%)	3 (12.5%)	18 75.0%)	p= 0.072; a vs b
3 – 6 months (n = 10)[b]	0	3 (30.0%)	7 (70.0%)	p>0.05
≥7 months (n = 6)	0	0	6 (100.0%)	
Total (n = 40)	3 (7.5%)	6 (15.0%)	31 (77.5%)	

Table 2: Gender distribution among the 40 infants with cholestasis of infancy

	Blood glucose concentration (mmol/L)			
Gender	<1.6mmol/L No (%)	1.6 – 2.5mmol/L No (%)	>2.5mmol/L No (%)	Odd ratio (95% CI)*
Male (n = 27)	2(7.4)	4 (14.8)	21 (77.8)	0.95
Female (n = 13)	1 (7.7)	2 (15.4)	10 (76.9)	(1.31, 2.61)
Total (n = 40)	3 (7.5)	6 (15.0)	31 (77.5)	

*CI = Confidence interval

None of the infants older than 6 months at the time of presentation had hypoglycaemia (Table 1). The prevalence of hypoglycaemia was 22.2% in males and 23.1% in females (Table 2). There was no association between the Serum Alkaline Phosphatase level and the occurrence of hypoglycaemia (Table 3). Similarly, there was no association between the Serum Aminotransferase levels and occurrence of hypoglycaemia (Table 4). Clinical examination of the males revealed normal external male genitalia and bilateral scrotal testis. The female infants also had normal female external genitalia.

There was no pedal oedema. Total serum bilirubin concentrations ranged from 6. 5 – 17.6 mg/dl with the conjugated fraction ranging from 1.5- 5.4 mg/dl and generally was more than

20% of the total serum bilirubin concentrations. Serum albumin concentration ranged from 36 - 48 g/L. The blood glucose concentration obtained using the Acutrend glucometer correlated well with the values obtained from the hospital central laboratory.

Table 3: Distribution of serum Alkaline Phosphatase (ALP) levels among the 40 patients with cholestasis of infancy

	Blood glucose concentration in mmol/L				
Serum ALP levels (U/L)	<1.6mmol/L No (%)	1.6 – 2.5mmol/L No (%)	>2.5mmol/L No (%)	z- statistics (p-value)	Odd ratio (95% CI)*
160-250 (n = 28)*	1 (3.6)	4 (14.3)	23 (82.1)	a vs b = 1.001	0.43
>250 (n = 12)[b]	2 (16.7)	2 (16.7)	8 (66.6)	(> 0.05)	(1.34, 2.58)
Total (n = 40)	3 (7.5)	6 (15.0)	31 (77.5)		

*CI = Confidence Interval

Table 4: Distribution of serum Alanine Transaminase (ALT) and Aspartate Transaminase (AST) levels among the 40 patients with cholestasis of infancy

	Blood glucose concentration in mmol/L				
Serum ALP levels (U/L)	<1.6mmol/L No (%)	1.6 – 2.5mmol/L No (%)	>2.5mmol/L No (%)	z- statistics (p-value)	Odd ratio (95% CI)*
ALT					
30 - 99 (n = 31)[c]	2 (6.5)	3 (9.7)	26 (83.9)	c vs d = 0.698 (>0.05)	0.24 (1.27, 2.65)
>99 (n = 9)	1 (11.1)	3 (33.3)	5 (55.6)		
Total (n = 40)	3 (7.5)	6 (15.0)	31 (77.5)		
ASP					
65 – 100 (n = 28)	1 (3.6)	2 (7.1)	25 (89.3)	e vs f = 0.000 (>0.05)	0.12 (1.25, 2.67)
>100 (n = 12)[e]	2 (16.7)	4 (33.3)	6 (50.0)		
Total (n = 40)[f]	3 (7.5)	6 (15.0)	31 (77.5)		

*CI = Confidence Interval

DISCUSSION:

The overall prevalence (22.5%) of hypoglycaemia among patients with cholestasis of infancy was 3.7 times lower than that reported by Leblanc et al in France [12]. The lower prevalence observed in the present study may be accounted for by differences in study population. Their study population was patients with either primary or secondary cortisol deficiency [12]. Although infants with cholestasis whose age was between 15 days and 3 months had a higher frequency of occurrence of hypoglycaemia than the other age groups, the difference was not statistically significant. This in keeping with the report of Lablanc et al [12] in which they observed that of six patients with hypoglycaemia associated with cholestasis of infancy, four were below three months of age. In the present study, although there were more males than females with cholestasis of infancy, the prevalence of hypoglycaemia was similar, suggesting that there was no gender difference in the frequency of occurrence of hypoglycaemia. Lablanc et al [12] indicated that of the five infants with cholestasis, four (80.0%) were males. In contrast, the Gonc et al,[18] reported two cases, one male (3 months of age)and one female (6 months of age), with both infants manifesting episodes of hypoglycaemia. These authors stated that cholestasis among their patients was due to primary or secondary cortisol deficiency [12,18]. It has been suggested that the age of appearance of the cortisol deficiency is an important predictor of occurrence of cholestatic hepatitis, and consequently, occurrence of hypoglycaemia [17,18,21]. It is assumed that cortisol deficiency manifesting in the neonatal or early infancy period causes cholestatic hepatitis. Five of six patients with isolated cortisol deficiency who presented beyond early infancy did not have cholestatic hepatitis [21]. Such an assumption cannot be made from the present study because it was not designed to identify the specific aetiology of cholestasis of infancy.

In the present study, serum levels of ALP, ALT and AST did not appear to influence the prevalence of hypoglycaemia. No specific explanation can be given for these findings. Whether this is related to the fact that hepatocyte mass in some metabolic disorders is lost by apoptosis rather than cell necrosis, resulting in serum Aminotransferases being only moderately elevated [1] and consequently, unrelated to occurrence of hypoglycaemia is not clear.

Although the present study had some limitations, most authorities agree that the presence of conjugated hyperbilirubinaemia (after the age of 14 days) and bilirubinuria are indicative of cholestasis [4,5].

In conclusion, hypoglycaemia was observed among patients with cholestasis of infancy, especially in the first three months of life.

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