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Glucose-6-phosphate dehydrogenase deficiency; the single most important cause of neonatal hyperbilirubinaemia in Kano, Nigeria

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Abstract*: Introduction:* Glucose-6-phosphate dehydrogenase deficiency is the most common enzymatic disorder of the red cell and an important risk factor for neonatal jaundice.
Methodology: The aim of the study was to determine the incidence of G-6-PD deficiency among jaundiced neonates, and describe the associated morbidity and mortality pattern in them.
A prospective cross sectional study was conducted and we studied one hundred consecutive jaundiced neonates (55 males, 45 females) presenting at Aminu Kano Teaching Hospital from between 2004 and August 2005. G-6-PD activity was assayed by Quantitative spectrophotometric method of Kornberg; serum bilirubin and haemoglobin levels were estimated by standard techniques. Exposure to possible Icterogenic agents, clinical features of kernicterus and the outcome were noted.
Results: The incidence of G-6-PD deficiency was found to be 46% with male to female ratio of 3:1 (X^2 = 15, p = 0.001). A higher proportion (60.6%) of the inborn neonates had G-6-PD deficiency (x^2 = 5.5, p = 0.06). Jaundice was noticed significantly earlier in the G-6-PD deficient neonates (mean = 2.0, SD = 1 days) compared to (mean = 2.7, SD = 1.6 days) in the sufficient neonates (t = 2.3, p = 0.02). Sixteen (16%) neonates developed kernicterus, of these 10 (63%) were G-6-PD deficient. The mortality rate among G-6-PD deficient neonates was 15% (7 of 46) twice as much as in the sufficient neonates 7% (4 of 54). Only six neonates 0.6% ware exposed to naphthalene of whom three were G -6PD deficient. Five babies were given traditional medicine two of which were G6-PD deficient.
Conclusion: G-6-PD deficiency is an important risk factor for neonatal jaundice. Jaundice appeared early in the deficient neonates. There is high incidence of kernicterus and mortality among them. Low admission weight significantly contributed to the mortality.

Key Words: G-6-PD deficiency; Neonatal Jaundice; Kernicterus

Introduction

The enzyme Glucose-6-Phosphate Dehydrogenase is present in all cells of the body.[1] G-6-PD deficiency is a genetic disorder in which the enzyme is inadequate in quantities or lacking in the red blood cells. It is inherited as an X-linked recessive disorder It plays a key role in the protection of cells against oxidative damage through its role in glutathione metabolism.
It has been well-documented [2-5] that G-6-PD deficient neonates are more prone to neonatal jaundice than neonates with sufficient enzyme activity. An incidence of G-6PD deficiency among jaundice neonates was found to be 12.8% among African Americans neonates,[3] and as high as 35% among Sephardic Jews, [5] 61% in Ghana.[6] In Southern Nigeria reported incidence was 25 to 34.4% among neonates with jaundice.[7,8] About 60% of all full term babies and 80% of preterm babies will develop jaundice.[9] Significant hyperbilirubinaemia is seen in 10.5% of full term neonates and 25.3% near term infants[10] G-6-PD deficiency predisposes to development of significant hyperbilirubinaemia in the neonates, with a reported relative risk of 3.27.[3,11] In 1994 neonatal jaundice was identified as one of the serious diseases affecting child health not covered by WHO programs in developing countries.[12]

The aim of the study was to determine the prevalence of G-6-PD deficiency, morbidity and mortality associated with G-6-PD deficiency among jaundiced neonates in

our area. There is paucity of data concerning the incidence of G-6-PD deficiency and its relationship with hyperbilirubinaemia from Kano. This temporal gap along as well as the fact neonatal mortality and morbidity has continued to be unacceptably high in Nigeria, the findings of this study will help in planning preventive measures, and consequently decreasing the burden of hyperbilirubinaemia. Neonates aged 0 to 28 days with clinical jaundice

Materials and methods

The study was prospective descriptive in nature, it was carried at Aminu Kano Teaching Hospital, Kano Nigeria from between November 2004 to and August 2005. Clearance was obtained from the ethical committee of the hospital. Consent was obtained from the mothers of the neonates. Consecutive neonates presenting with jaundice or who developed jaundice while on admission at the special care baby unit were enrolled. A total of 401 neonates were admitted into the unit during the study period, of these 115 (28.7%) had jaundice. Of these 100 met the inclusion criteria and were enrolled.
Neonates that had blood transfusion or whose parents declined consent were excluded.
For every neonate, prenatal history was obtained; history suggestive of birth asphyxia, history of the time when jaundice was noticed was also obtained. Exposure to possible Icterogenic agents, such as naphthalene balls, henna, dusting powder. The enrolled neonates were closely monitored for morbidities like anaemia, haemoglobinuria, seizure, hypertonia, hypotonia, high pitched cry, windmill like movement of the limbs, retrocolis, opistothonus feature s of Bilirubin Induced Neurological Dysfunction (BIND) Score[15] were noted. The outcome discharge home, survival with Acute Bilirubin Encephalopathy ABE were noted. Phototherapy or exchange blood transfusion was carried out according to the protocol of the unit.

Laboratory investigations on all the jaundiced neonates were as follows; Blood typing (ABO and Rhesus groups) for mothers and the babies, blood cultures when indicated. Total and direct reacting serum bilirubin (SB) using the modified method of Winsten and Cehelyk[13] Using an auto analyzer (Express Plus Chiron/ Diagnostics Bio-Rad® California USA). Complete blood count with supra-vital staining for reticulocyte count was done on each sample. Smears for malarial parasites were done when indicated.
Quantitative spectrophotometric method of Kornberg[14] was used to assay the G-6-PD activity, with G-6-PDH kit procedure No. 345-UV Trinity biotech Wiclow, Ireland. Using Spectrulab spectrometer, Surgifield Middlesex London. The cut off point for enzyme deficiency is any value less than 4.6 U/gHb

Statistical analysis

Statistical analysis was done with the aid of the EPI info 2000 version 1.1.2 statistical software. Statistical tests Student's t test for continuous variables; Fisher's exact test, Analysis of Variance (ANOVA) and the chi-squared test for discrete variables were employed where appropriate. Probability (p) value less than 0.05 were accepted as significant. Data on G-6-PD deficient neonates were compared to sufficient neonates.

Results

There were 55 (55%) males and 45(45%) females' neonates. Thirty-three (33%) of the babies were delivered at AKTH and 67 (67%) were referred. Eighty (80%) neonates were born at term and twenty (20%) were born preterm. Half of the preterm neonates were born at AKTH.
Forty-six of 100 neonates studied had G-6-PD deficiency, giving an incidence of 46% with 95% confidence interval of 36% to 56.3%. Of the 46 G-6-PD deficient neonates, 35 (76%) were males and 11 (24%) were females. The male: female ratio was 3:1. The sex difference was statistically significant Table I (X^2 = 15, p = 0.001).The mean G-6-PD activity in the whole study population of 100 neonates was 5.04 U/gHb. The mean G-6-PD enzyme activity in the deficient neonates was 3.1, SD = 1.0 U/gHb Table I shows Jaundice was noticed significantly earlier in the G-6-PD deficient neonates compared with the G-6-PD sufficient neonates
Inborn neonates were younger at presentation mean age of 2.88 ± 2.3 days, range 1-9 days, compared with the mean age of 5.6 ± 4.8 days, range 2-21 days in neonates delivered at other hospitals and at home with the mean age of 5.59 ± 2.9 days, range1-14 days. The difference was statistically significant (F = 3.7 P = 0.013).
Birth weight was recorded in only 39 neonates (all the 33 AKTH born babies and 6 babies born in other hospitals). This is because some jaundiced neonates were not seen until they were several days old, and there was no record of their birth weight as they were delivered at home or other hospitals. The mean birth weight of the 39 neonates was 2925.4, SD = 752.6 g, the range 900-5100g. The mean admission weight of all the neonates was 2663.5, SD = 798.0g.
A total of 94 of the 100 (94%) neonates were breast-feeding.

Table 1: Comparison the mean age at presentation, mean age at the onset of jaundice and mean total serum bilirubin of the neonates withG-6-PD deficiency compared with neonate with sufficient enzyme activity

	G-6-PD ACTIVITY					
	Deficient(n = 46)		Sufficient(n = 44)			
	Mean	SD	Mean	SD	t	p
Peak TSB	227.4	97.6	225.5	108.6	- 0.02	0.92
Age at presentation (days)	4.6	4.1	4.8	3.9	0.29	0.29
Age Jaundice Was noticed (days)	2.0	1.0	2.7	1.6	2.3	0.02

Table 2: Comparison of the mean Total serum bilirubin, Haemoglobin and Reticulocyte count of the jaundiced neonates. G-6-PD deficient compared with G-6-PD sufficient neonates

Mean ± SD	G-6-PD Status			
G-6-PD deficient	G-6-PDsufficient			
	n= 46	n= 54	p	
Parameter				
TSB µmol/l	227.5 ± 96.3 (81.6-517.0)	225.5 ± 106 (87.4-609.9)	0.90	NS
Hb g/dl	13.25±2.9 (4-18)	12.91±3.03 (4-18)	0.57*	NS
*R*etic count %	2.5 ± 2.6 (0.2-15.1)	2.6± 2.1 (0.1-10.0)	0.70*	NS

There was no statistically significant difference in the mean TSB, haemoglobin levels, reticulocyte count Table 2

Table 3: The mean total serum bilirubin and Haemoglobin levels by the age of baby when jaundice was noticed. G-6-PD deficient compared with G-6-PD sufficient neonates

	G-6-PD Status					
	Deficient			Sufficient		
Age of onset		TSB µ/ mol	Hb g/ dl		TSB µ/ mol	Hb g/ dl
	n=46 [%]			n=54 [%]		
0-1	7[15]	218.6+_159 (81-547)	14.7±2.3 (9-17)	5[9.3]	237.3±175 (130-547)	12 ±2.5 (9-15)
2-3	12[6]	166+_54 (89.6-265.2)	14.2±2.3 (9-17)	21 [38]	208.5 ± 77 (87.4-359.)	14.4± 2.0 (9-18)
4-7	21 [46]	260.7+_98 (110-609)	12.4 ± 3.3 (4-18)	18 [33]	243.7 ±121 (110-611)	12.6 ±2 (8-18)
>7	6[13]	250.3+_100 (100.1-394)	12.7±3.0 (8-16)	10 [19]	230 ±103 (121-436)	10.9 ±3.9 (4-15)
F		2.9	1.6		0.3	3.7
P		0.04 S	0.20 NS		0.77 NS	0.17 NS

Data in parenthesis denote percentage [ ] or range ( ) of values recorded where appropriate. n is the total number of neonates in the group. F = test value for ANOVA

EBT

Exchange blood transfusion was done in 26% (26 of 100) neonates. Proportionally there was higher frequency of EBT 60% (15 of 26) among the G-6-PD deficient compared to G-6PD sufficient neonates this was not statistically significant. (c^2 = 1.9, p = 0.16).

Other causes of jaundice singly or in combinations are shown in table V. Two neonates had cephalohaematoma in association with G-6-PD deficiency. And 20 neonates were preterm; of these 7 have G-6-PD deficiency. Clinical diagnosis of sepsis was made in 25 neonates, of these 12 had G-6-PD deficiency. Only two (8%) had bacteriologically proven sepsis. In one G-6-PD deficient baby *Staphylococcus aureus* was grown, and *Proteus* was grown in another baby with no G-6-PD deficiency.

The mean duration of hospital stay was 6.38, SD 5.5 days. There was no statistically significant difference the length of hospitalization between G-6-PD deficient and sufficient neonates t (t = 0.78, df 98, p = 0.44).

The mean weight at presentation in the neonates that died was significantly lower (both G-6-PDdeficient and sufficient neonates) than the mean weight at presentation of neonates that survive as shown in Table 5 (Anova F= 5.6, p = 0.001).

Exposure to Icterogenic substances;

For the majority of the neonates methylated spirit was applied to the umbilical cord. Application of heat with a piece cloth or a piece of clay pot was also commonly used in both groups of neonates. Mentholatum ointment was applied to the umbilicus in one G-6-PD deficient baby . Five (5%) of the total 100 neonates in the study were exposed to naphthalene balls, of which 3 were G-6 -PD deficient. None of the deficient neonates was exposed to henna dye. Five (5%) of the neonates in the study were given traditional medicine. Of the drugs known to trigger haemolysis in G-6-PD deficient subjects, Chloramphenicol eye ointment was used in one neonate with enzyme deficiency.

Table 4: Causes of jaundice among the 100 babies in the study

Aetiology	n	%
G-6-PD deficiency alone	17	17
Sepsis alone	13	13
ABO incompatibility alone	6	6
Weight < 2500g	12	12
G-6-PD deficiency+ weight < 2500g + ABO incompatibility	4	4
G-6-PD deficiency weight < 2500g + sepsis	4	4
G-6-PD deficiency + Sepsis	8	8
G-6-PD deficiency + ABO incompatibility,	8	8
ABO incompatibility + weight < 2500g	6	6
G-6-PD deficiency + weight < 2500g	5	5
Unknown	17	17
Total	100	100

n denote number of neonates

Table 5: The weight by the outcome among the jaundiced neonates. G-6-PD deficient compared with the G-6-PD sufficient neonate

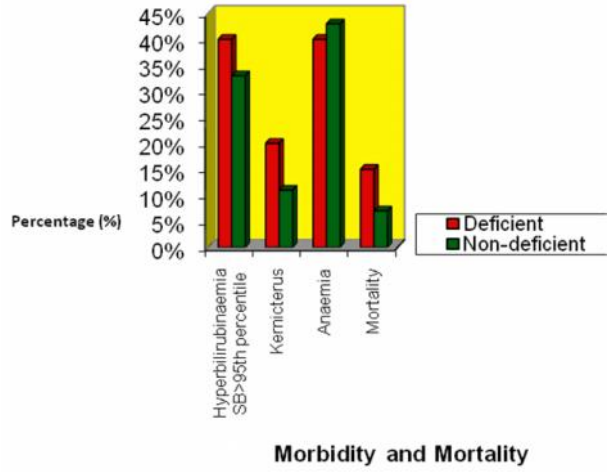
Outcome	G-6-PD status							
	Deficient Weight (g)			Sufficient Weight (g)				
	n=46	Mean	SD	n=54	Mean	SD	F	P
No ABE *Survived*	29	2768.7	711.0	44	2788.1	689.0	5.6	0.001
ABE	10	2788.1	689.0	6	3280.0	554.0		
ABE/Died	7	2192.0	749.0	4	1560.0	563.9		

F = test values for Anova, n = number of patients. ABE = Acute Bilirubin Encephalopathy

A higher proportion of the G-6-PD deficient neonates 21% (10 of 46) had clinical features of ABE In contrast, 11.1% (4 of 54) of G-6-PD sufficient neonates developed ABE (c^2 = 2.1, p = 0.15) as shown in figure1.

A total of 11 neonates died giving an overall mortality rate of 11%. Five (45.5%) of these were preterm with low weigh. The mortality rate among the G-6-PD deficient neonates was proportionately higher 15.2% (7 of 46 neonates) than the mortality of 7.4% (4 of 54) in the G-6-PD sufficient neonates. All the G-6-PD sufficient neonates that died were preterm low birth weight.

Fig 1: Morbidity and mortality pattern among the jaundiced neonates:G-6-PD deficient compared with G-6-PD sufficient neonates



Discussion

The incidence of G-6-PD deficiency in the present study was found to be high in the order of 46% is in keeping with previous reports from Nigeria 34%, 25%, 62.1% [7,8,11]The male to female ratio of 3:1 in the present study is similar to what was previously reported from USA, Israel and Middle East [3,4,5]It is in keeping with what would be expected from the gene distribution, and the X linked mode of inheritance of the enzyme deficiency.
The mean TSB in the G-6-PD deficient babies was similar to the mean TSB in the G-6-PD sufficient neonates. This finding is similar to the findings of Kaplan and co-workers, who demonstrated poor correlation between quantitative values of enzyme activity and peak TSB values. Jaundice in the G-6-PD deficient neonates in the present study was noticed earlier than in those neonates with sufficient enzyme activity ($p = 0.02$). This finding is in keeping what has been reported previously. There is some evidence that jaundice in the G-6-PD deficient neonates may have its origin in-utero.[16]However, the age of presentation was similar between G-6-PD deficient and sufficient neonates. This may suggest a significant delay (average of 2 days) from the time jaundice was noticed and the time of presentation in these babies. This could be the reason why greater proportion (32%) of the G-6-PD deficient babies in the study had EBT, also 21.1% developed kernicterus compared with 20% and 11% of the sufficient respectively.

The mean Hb level in the G-6-PD deficient neonate in the study was slightly low but comparable to what was found in the sufficient neonates. Similarly the mean reticulocyte count in the G-6-PD deficient was similar to that of the sufficient neonates. These findings may imply that G-6-PD deficiency does not show association with decrease in Hb or reticulocyte count This could be because the G-6-PD sufficient neonates might be experiencing haemolysis from other causes like blood group incompatibility, sepsis and so on. Therefore, their haemoglobin and reticulocyte responses would be similar to those of G-6-PD deficient neonates. Other workers have reported similar findings.[18] On the other hand, Slusher and co-worker's[8] reported significantly lower values of haematocrit in jaundiced G-6-PD deficient babies compared with G-6-PD sufficient neonates. They concluded that haemolysis was the cause of hyperbilirubinaemia in the G-6-PD deficient neonate.

The frequency of G-6-PD deficiency was proportionately higher among the jaundiced neonates inborn compared with the out born babies. This finding is similar to what was reported by other workers from Zaria[15] Exposureto yet to be identified substances e.g cleaning chemicals in all babies born at AKTH might have contributed to the jaundice in the G-6-PD deficient neonates. The AKTH babies constitute a 'homogeneous' group or cohort. The out born neonates constituted a wider group with a less well-defined denominator. The babies would have been taken to any other health facility or may have indeed been left at home. These factors would conceivably reduce the number of out-born babies presenting to AKTH.
Nevertheless, significant hyperbilirubinaemia in the present study was observed among relatively higher number of the out born neonates compared with the inborn neonates, in agreement with previous reports from Zaria[15] Late detection of jaundice and delay at presentation to hospital observed in the out-born babies might have contributed to the greater severity of jaundice in these neonates.

The jaundiced inborn neonates were significantly younger at presentation, compared with the out born neonates ($P = 0.013$). This could be ascribed to a higher level of vigilance for jaundice by trained hospital caregivers at AKTH, compared with staff of basic or secondary health care facilities and mothers at home.
There was a high frequency of Acute Bilirubin Encephalopathy in the present study, 16% (16 of 100). Glucose-6 -phosphate dehydrogenase deficiency was found in 63% of the kernicteric babies (10 of 16). . This is similar to what was reported by other workers in developing countries. [4,6,7,8]Even in developed countries a resurgence of kernicterus is being observed in places where ABE was previously less frequently observed. [19-21]

A combination of late presentation and genetic predisposition (G-6PD deficiency)appear to play a great role in the high incidence of ABE observed. The present practice of early discharge of sufficient neonates from our hospital after delivery (within 24 hour of birth) might have contributed to late identification of jaundice in some of the neonates with consequent hyperbilirubinaemia and kernicterus. The late recognition of jaundice by mother's and/ or health care providers and delay in referral of jaundiced neonates to tertiary health centers might have contributed to the higher frequency of kernicterus in the present study.
Exchange blood transfusion was done proportionately more often in the G-6-PD deficient neonates than in sufficient neonates. The mean TSB in the neonates that had EBT was higher than the mean TSB in the neonates

with no EBT (Anova F= 32 p = 0.001) and in line with what was previously reported.[7] In keeping with the fact that severe hyperbilirubinaemia was the main indication for EBT in the neonates.

The high mortality rate of 15% (7 of 46) among G-6-PD deficient jaundiced newborns in the present study is similar to previous reports[6, 8] Late identification of jaundice and delay in presentation to the hospital observed in the present study could account for this pattern of mortality. Preterm neonates contributed significantly to the mortality. Low weight on admission significantly contributed to the mortality in both the G-6-PD deficient and sufficient neonates. This is because of the relatively high number of premature neonate in the mortality.

Exposure to naphthalene balls and Menthol containing balm and powder among the G-6-PD deficient neonates in the present study was not common and was seen only in 8.7% (4 of 46). In contrast, reports from southern part of Nigeria found exposure rate to Icterogenic agents to be as high as 73.5%, and thus clearly demonstrated the association between exposure to Icterogenic agents and jaundice in the G-6-PD deficient neonate.[22] The observed variation in the exposure rate could be ascribed to cultural differences in the care of the newborn between Kano in the north and the southern parts of the country. It is probable that naphthalene-containing substances were not commonly used in households in Kano. Only two neonates were exposed to Mentholatum in the present study, (one dusting powder, one mentholated balm), both had G-6-PD deficiency.

Henna dye was applied to one baby only, who had sufficient enzyme activity. Even though women in the northern part of Nigeria use henna for skin decoration, it appears that its use in the newborn is not common.

It was difficult to evaluate the role of breast-feeding in the etiology of jaundice in the present study, as 94% of all the babies were breast-feeding at the time of presentation. If breast-feeding contributed to neonatal jaundice it is possible that it did so in association with other factors in these neonates.

Other common causes of jaundice in the study included, low admission weight being the second most frequent cause of jaundice, similar to a previous report. And twenty percent of the babies were born preterm. This may be a reflection of low standard of living and poor antenatal care in the environment. The setting for ABO incompatibility was present in about a quarter of the neonates.

Sepsis did not seem to contribute significantly to hyperbilirubinaemia in the study. Only 2 neonates had bacteriologically proven sepsis. This could be because a high proportion of the neonates were delivered at AKTH where standard antiseptic procedures are available, which significantly reduced the likelihood of sepsis among them. And the out born neonates might have had antibiotics before presentation, which might affect bacterial culture. This finding agrees with findings of other researchers that infection does not play a significant role in the hyperbilirubinaemia associated with G-6-PD deficiency.[23, 24]

The most common factor associated with jaundice in the present study was G-6-PD deficiency, which was associated with early onset of jaundice, and relative delay of presentation to the hospital. There was a higher frequency of kernicterus among the G-6-PD deficient neonates, and the neonates with G-6-PD deficiency had a higher mortality rate.

The findings of the present study are indications that G-6-PD deficiency was an important factor in jaundice related morbidity, and it contributes significantly to the cost of management of jaundice in the study.

Conclusion

There is a high incidence of Glucose–6-phosphate dehydrogenase deficiency among jaundiced neonates in Kano, and it was the single most important aetiological factor with respect to neonatal jaundice.

It is recommended that neonatal screening for G-6-PD deficiency should be done with the use of hour specific normogram to monitor the rate of rise of TSB in the deficient babies There is a need for public heath campaign on neonatal jaundice and G-6-PD deficiency.

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