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Jaundice among Hospitalized Newborn Infants in Sagamu: Observations on Aetiology and Clinical Course

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Abstract

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Background: Neonatal jaundice may be caused by physiological events and/or as specific disease conditions, while the clinical course may be related to the aetiology.
Objective: To determine the spectrum of identifiable causes as well as the clinical course of jaundice among hospitalized babies.
Methods: Babies hospitalized with jaundice requiring therapy in a tertiary hospital were prospectively studied for the aetiology and the pattern of total serum bilirubin (TSB). Babies with unexplained jaundice were compared with babies in whom the aetiology was known.
Results: Jaundice was unexplained in 51 (20.6 percent) of 248 babies aged 0 to 240 hours, while 50 (20.2 percent) had various combinations of prematurity, blood group incompatibilities, Glucose-6-phosphate dehydrogenase (G6PD) deficiency and septicaemia. Babies with G6PD deficiency had the highest mean peak TSB (26.3 ± 9.0mg/dl), those with Rhesus incompatibility had their peak TSB earliest (5.7 ± 0.8 days), while the mean duration of phototherapy was longest in babies whose jaundice was due to prematurity (10.4 ± 0.9 days). Exchange blood transfusion (EBT) rate was highest among babies with Rhesus incompatibility (100.0 percent) and G6PD deficiency (70.3 percent). Preterm infants tended to have multiple EBT sessions compared to term infants ($p < 0.001$). Bilirubin encephalopathy was most frequent among babies with G6PD deficiency (62.1 percent).
Conclusion: There appears to be a pattern of clinical events which are peculiar to the specific aetiology of newborn jaundice.

Key words: Exchange transfusion, Hyperbilirubinaemia, Newborn, Serum bilirubin

Introduction

JAUNDICE is common in the newborn period, and is reported to be one of the leading causes of neonatal admissions in Nigeria.[1] Similarly, a significant proportion of neonatal deaths in Nigeria has been attributed to jaundice.[2] Studies within and outside Nigeria have also described the aetiological roles of blood group incompatibilities (ABO and Rhesus), Glucose-6-phosphate dehydrogenase (G6PD) deficiency, septicaemia and prematurity in newborn jaundice.[3,4]

Bilirubin encephalopathy (BE) is the most important morbidity associated with severe cases of jaundice particularly among babies delivered outside hospitals. This condition is known to cause death in the newborn period as well as various neurological deficits later in life.[5] Encephalopathy usually follows severe hyperbilirubinaemia and it is instructive that most studies have reported G6PD deficiency as the leading cause of severe hyperbilirubinaemia that results in encephalopathy in various parts of the world.[6,7] However, newborn jaundice is not pathological in all cases. Physiological jaundice may result from excessive haemolysis and increased bilirubin production in addition to poor activity of

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hepatic conjugating mechanisms. Physiological jaundice is defined by specific characteristics: the jaundice is not usually noticed until after the first 36 to 48 hours of life, serum bilirubin does not exceed 10mg/dl in term babies or 15mg/dl in preterm babies and clears by the 7th and 14th day in term and preterm babies, respectively.[8]

From the aforementioned, it is possible that other pathological types of jaundice may have peculiar or distinctive characteriistics as defined for physiologic jaundice since different disease conditions associated with jaundice may cause hyperbilirubinaemia to varying extents. Obviously, the pathological mechanisms by which these different conditions cause jaundice and its complications vary and may determine the clinical events which characterize each disease condition.

The present study is aimed at documenting our observations on the aetiology as well as clinical course of jaundice among hospitalized babies.

Patients and Methods

Babies hospitalized at the Neonatal Ward of Olabisi Onabanjo University Teaching Hospital, Sagamu, between January 2008 and February 2010, were prospectively studied. This tertiary hospital provides specialized neonatal care for babies delivered in the maternity unit of the hospital as well as those referred from other government-owned and private hospitals in Ogun State and neighbouring states of the federation.

The subjects were consecutive term and preterm babies requiring phototherapy or exchange blood transfusion (EBT). Babies primarily admitted with jaundice and those who developed jaundice following hospitalization for other reasons were included. Institutional ethical approval was obtained and only babies whose parents consented were recruited.

In the unit, all babies are routinely examined for jaundice on admission and are subsequently monitored for the appearance of jaundice. Babies with significant hyperbilirubinaemia (TSB > 10mg/dl in term babies or > 5mg/dl/kg in preterm babies) are managed with conventional phototherapy (using blue or white light), while those with severe hyperbilirubinaemia (defined as TSB > 20mg/dl for term babies and > 10mg/dl/kg for preterm babies) are managed with both phototherapy and exchange blood transfusion (EBT). Serum bilirubin levels are monitored at least once daily. Phototherapy is discontinued when TSB is < 50 percent of the level at which phototherapy was commenced or when conjugated bilirubin is > 20 percent of the TSB.

Routine investigations include blood typing for baby and mother, direct Coombs' test (DCT), blood culture, G6PD assay (using spectrophotometer) and full blood count. Blood group incompatibility is usually suspected when the mother belongs to group O or is Rhesus D negative, while the baby belongs to either group A or B or is Rhesus D positive. Iso-immunization is further corroborated with positive DCT. In situations where the mothers are not available, and their blood groups could therefore not be tested, babies who belonged to groups O or Rhesus D-negative were not considered at risk of blood group incompatibility. Rather, babies in groups A, B or Rhesus D-positive in such instances were excluded from the study. Serum G6PD level less than 245mU/10^9Erythrocytes (reference range using *Janeway® Spectrophotometer*: 245 to 299mU/10^9 Erythrocytes) suggests deficient state. Facilities for thyroid function tests and metabolic screening are not available in the centre. Furthermore, facilities for blood culture are not always available, hence clinical details are used in such instances by the consultants supervising the unit in arriving at the diagnosis of probable septicaemia. Jaundice in term babies with normal G6PD status, no septicaemia and no blood group incompatibility is regarded as unexplained. Similarly, jaundice in preterm infants with no other aetiology is attributed to prematurity. Jaundice is also ascribed to multiple aetiology when two or more likely causes are present in the same infant. Bilirubin encephalopathy is diagnosed from clinical features such as poor sucking, tone abnormalities, high-pitched cry, setting-sun appearance or seizures.

Data collection and analysis

The data collected included age on admission, sex, weight, peak TSB, age at which the peak TSB was recorded, type and duration of therapy for jaundice. These data were processed with SPSS 15.0 software using only univariate and bivariate analysis. Babies with unexplained jaundice were compared with babies with specific causes of jaundice in terms of peak TSB, age at which peak TSB was recorded, duration of therapy, EBT rates and prevalence of BE.[9] Proportions were compared with chi-squared test while Student t-test compared means and standard deviations. Statistical significance was established when *P* value was less than 0.05.

Results

General description of subjects

The 248 babies studied were aged 0 to 240 hours with a mean of 70.9 ± 86.9 hours. One hundred and thirty-six (54.8 percent) were aged ≤48 hours, while 95 (38.3 percent) and 17 (6.9 percent) were aged 73 to 168 hours and > 168 hours respectively, on admission. There were 152 (61.3 percent) males and

96 (38.7 percent) females with a male-to-female ratio of 1.6:1. There were 70 (28.2 percent) in-born babies, while 178 (71.8 percent) were out-born. One hundred and seven (43.2 percent) were preterm and 141 (56.8 percent) term babies. Distribution according to bodyweight on admission showed that 41 (16.5 percent), 83 (33.5 percent) and 124 (50.0 percent) weighed < 1.5kg, 1.5 to 2.49kg and ≥2.5kg, respectively.

Description of jaundice

Age at onset of jaundice was reliably assessed in only 165 babies (64 in-born and 101 out-born). Jaundice was noticed within 24 hours of life in 17 (10.3 percent) of the 165, between 24 and 48 hours in 40 (24.2 percent), between 49 and 72 hours among 68 (41.2 percent) and after 72 hours in the remaining 40 (24.2 percent) babies. Two hundred and thirty-five (94.8 percent) had unconjugated hyperbilirubinaemia while 13 (5.2 percent) had conjugated hyperbilirubinaemia.

Aetiology

Blood typing was carried out in respect of 232 mother-infant pairs while 16 mothers were not available for this test. Direct Coombs test (DCT) was carried out on only 215 babies and the test was negative in all the cases. Blood culture was carried out in 136 babies and only 53 (38.9 percent) were positive. Another 28 babies were clinically adjudged to have septicaemia without blood culture. Similarly, 154 babies had G6PD assay and 59 (38.3 percent) of these were deficient.

The 13 babies with conjugated hyperbilirubinaemia had bacterial sepsis (10; 76.9 percent) and Down syndrome (3; 23.1 percent). All the 13 babies had normal hepatic enzyme levels and were negative for the Hepatitis B surface antigen. Seven of these babies had hepatic ultrasonographic scan and the features were reported to be normal in all of them.

Jaundice was unexplained in 51 (20.6 percent) term babies while 197 (79.4 percent) had various identified causes. Prematurity was the only identifiable aetiology of jaundice in 48 (19.3 percent) babies. Other identified causes included ABO incompatibility, G6PD deficiency, septicaemia, cephalhaematoma and Rhesus incompatibility in 39 (15.7 percent), 37 (14.9 percent), 15 (6.0 percent), four (1.6 percent) and four (1.6 percent) cases, respectively. The remaining 50 (20.2 percent) had various combinations of prematurity, ABO incompatibility, G6PD deficiency and septicaemia.

Comparison of mean peak SB values (mg/dl)

Table I shows that babies with unexplained jaundice had significantly less mean peak SB values compared with babies with ABO incompatibility ($P < 0.0001$), G6PD deficiency ($P < 0.0001$), Rhesus incompatibility ($P = 0.02$) and babies with multiple causes ($P < 0.001$). Babies with Rhesus incompatibility and G6PD deficiency had the highest peak SB values, while babies with unexplained jaundice had the lowest.

Comparison of age (days) at which Peak SB occurred

Babies with prematurity, ABO incompatibility, septicaemia and G6PD deficiencywere significantly older than babies with unexplained jaundice when peak SB values were recorded ($P < 0.0001$, $P = 0.011$, $P < 0.0001$ and $P = 0.0002$, respectively; Table II). The mean age at which SB levels peaked was lowest

Table I

Comparison of the Mean Peak Total Serum Bilirubin (TSB) levels among Babies with Jaundice

Aetiology	*Mean Peak TSB ± SD (mg/dl)*	*t*	*P*
Prematurity (n = 48)	15.8 ± 3.5	0.64	0.522
ABO incompatibility (n = 39)	23.5 ± 10.2	4.22	<0.0001
G6PD deficiency (n = 37)	26.3 ± 9.0	5.78	<0.0001
Septicaemia (n = 15)	18.7 ± 6.1	1.52	0.134
Rhesus incompatibility (n = 4)	26.3 ± 9.8	2.40	0.020
Cephalhaematoma (n = 4)	16.3 ± 8.9	0.30	0.768
Mixed aetiology (n = 50)	22.2 ± 4.6	5.07	<0.001
*Unexplained (n = 51)	14.9 ± 9.1		

* Comparison Group

in babies with Rhesus incompatibility while it was highest among babies with prematurity.

Comparison of the mean duration (days) of phototherapy

As shown in Table III, the mean duration of phototherapy was significantly longer in premature babies ($P < 0.0001$), septicaemia ($P < 0.0001$), G6PD deficiency ($P < 0.0001$) and multiple aetiology ($P < 0.001$) compared to its duration in those with unexplained jaundice. The mean duration of phototherapy was longest in babies with jaundice due to prematurity while it was shortest in babies with unexplained jaundice.

Comparison of the mean packed cell volume (PCV %)

Table IV shows that the mean PCV of babies with unexplained jaundice was significantly higher than that of babies with jaundice due to G6PD deficiency ($P = 0.001$), and multiple aetiology ($P < 0.001$), respectively. The mean PCV was highest among babies with prematurity but lowest in babies with G6PD deficiency.

Details of therapy

Two hundred and thirty-five babies had phototherapy. This number was made up of 128 (51.7 percent) who had EBT with phototherapy, while 107 (43.1 percent) had only phototherapy. The remaining 13 (5.2 percent) with conjugated jaundice did not require either procedure.

Eighty-two (64.1 percent) of 128 babies had EBT within 24 hours of admission, while 39 (30.5 percent) and seven (5.5 percent) had EBT between 25 and 72 hours and after 72 hours of admission, respectively. Sixty-six babies (51.6 percent) had single sessions of EBT while 62 (48.4 percent) had at least two sessions. A significantly higher proportion of babies who had multiple EBT were preterm compared to those who had one EBT session {49/62 (79.0 percent) Vs 32/66 (48.5 percent); $X^2 = 12.838$, $P = 0.0003$}. Furthermore, EBT rate was also inversely related to body weight; 87.8 percent (36/41) of the babies weighing <1.5kg, 50.6 percent (42/83) of those weighing 1.5 to 2.49kg and 41.9 percent (52/124) of the babies weighing ≥2.5kg had EBT.

Significantly higher proportions of premature babies ($P = 0.02$), those with Rhesus incompatibility ($P = 0.022$), septicaemia ($P = 0.009$), G6PD deficiency ($P < 0.0001$) and multiple aetiology ($P < 0.001$) had EBT compared to those with unexplained jaundice (Table V). The EBT rate was highest among babies with Rhesus incompatibility and lowest in babies with ABO incompatibility.

Prevalence of bilirubin encephalopathy (BE)

As shown in Table VI, BE occurred more frequently among babies with G6PD deficiency ($P < 0.0001$), prematurity ($P = 0.008$) and ABO incompatibility ($P = 0.001$) compared to babies with unexplained jaundice. The prevalence of BE was higher among

Table II

Mean Age at which Peak Total Serum Bilirubin was recorded

Aetiology	*Mean Age ± SD (Days)*	*t*	*P*
Prematurity (n = 48)	10.9 ± 2.3	11.31	<0.0001
ABO incompatibility (n = 39)	7.4 ± 0.9	2.61	0.011
G6PD deficiency (n = 37)	7.8 ± 1.2	3.83	0.0002
Septicaemia (n = 15)	8.6 ± 1.4	4.92	<0.0001
Rhesus incompatibility (n = 4)	5.7 ± 0.8	1.27	0.208
Cephalhaematoma (n = 4)	6.3 ± 1.4	0.79	0.431
Mixed aetiology (n = 50)	6.1 ± 1.1	3.05	0.003
*Unexplained (n = 51)	6.8 ± 1.2		

* Comparison Group

Table III

Mean Duration of Phototherapy in Babies with Jaundice

Aetiology	*Mean Duration ± SD (Days)*	*t*	*P*
Prematurity (n = 48)	10.4 ± 0.9	17.96	<0.0001
ABO incompatibility (n = 39)	6.0 ± 2.2	0.97	0.333
G6PD deficiency (n = 37)	8.1 ± 1.8	6.59	<0.0001
Septicaemia (n = 15)	8.8 ±1.7	6.41	<0.0001
Rhesus incompatibility (n = 4)	7.3 ± 2.1	1.90	0.063
Cephalhaematoma (n = 4)	6.2 ± 2.1	0.67	0.506
Mixed aetiology (n = 50)	7.9 ± 2.2	5.89	<0.001
Unexplained (n = 51)	5.6 ± 1.7		

* Comparison Group

Table IV

Mean Packed Cell Volume in Babies with Jaundice

Aetiology	*Mean Peak PCV ± SD*	*t*	*P*
Prematurity (n = 48)	40.1 ± 7.9	1.44	0.153
ABO incompatibility (n = 39)	34.3 ± 9.9	1.70	0.093
G6PD deficiency (n = 37)	30.1 ± 12.0	3.38	0.001
Septicaemia (n = 15)	34.6 ± 1.7	1.26	0.213
Rhesus incompatibility (n = 4)	30.8 ± 0.7	1.92	0.134
Cephalhaematoma (n = 4)	32.3 ± 7.6	1.17	0.249
Mixed aetiology (n = 50)	31.4 ± 3.7	4.58	<0.001
Unexplained (n = 51)	37.7 ± 9.0		

* Comparison Group

Table V

Exchange Blood Transfusion (EBT) Rates among Babies with Jaundice

Aetiology	*No (%) of Babies who had EBT*	X^2	*P*
Prematurity (n = 48)	27 (56.3)	5.40	0.020
ABO incompatibility (n = 39)	11 (28.2)	0.01	0.900
G6PD deficiency (n = 37)	26 (70.3)	15.52	<0.0001
Septicaemia (n = 15)	10 (66.7)	6.837	0.009
Rhesus incompatibility (n = 4)	4 (100.0)	5.24	0.022
Cephalhaematoma (n = 4)	1 (25.0)	0.035	0.852
Mixed aetiology (n = 50)	35 (70.0)	16.63	<0.001
Unexplained (n = 51)	15 (29.4)		

* Comparison Group

Table VI

Comparison of the Prevalence of Bilirubin Encephalopathy (BE) in Babies with Jaundice

Aetiology	*No (%) of Babies with BE*	X^2	*P*
Prematurity (n = 48)	16 (33.3)	6.92	0.008
ABO incompatibility (n = 39)	15 (38.5)	10.50	0.001
G6PD deficiency (n = 37)	23 (62.2)	28.28	<0.0001
Septicaemia (n = 15)	3 (20.0)	0.518	0.472
Rhesus incompatibility (n = 4)	1 (25.0)	0.03	0.852
Cephalhaematoma (n = 4)	0 (0)	0.00	1.000
Mixed aetiology (n = 50)	10 (20.0)	1.20	0.273
Unexplained (n = 51)	5 (9.8)		

babies with G6PD deficiency (62.1 percent) and ABO incompatibility (38.5 percent).

Discussion

Most of the babies with reliable data on age of onset of jaundice in the present study were jaundiced between the second and third day of life as previously reported by others.[10] This carries the risk of being lumped together with physiological jaundice which is typically noticed at about same age.[8] It highlights the need to monitor serum bilirubin levels in order to differentiate between physiological and pathological jaundice. In addition, about one in ten babies had early-onset jaundice and these were mainly preterm babies with ABO incompatibility. This group of babies is particularly important because seemingly mild hyperbilirubinaemia may progress to severe levels in a short time thus predisposing these 'at-risk' babies to encephalopathy. This justifies the use of prophylactic phototherapy for preterm infants and other infants at risk of severe haemolysis.

Although we were limited in our capability to extensively investigate jaundiced babies, four-fifth of the babies studied had one or more of the known aetiology of newborn jaundice. A quarter of the 197 babies with identified aetiology had multiple aetiology while the remaining three-quarters had single probable aetiology. Interestingly, the remaining one-fifth had no identifiable aetiology. This observation concurs with the finding in an Indian study[11] where 20 percent of newborn jaundice was unexplained. Another study from the West Indies reported that 71 percent of newborn jaundice was unexplained.[12] The bottom line in these observations is that the extent to which jaundice is investigated determines what proportion is truly unexplained. Studies have also shown that some cases of unexplained jaundice in the newborn may be due to aflatoxicosis or breast milk jaundice.[13,14] Although we did not have the facilities to detect aflatoxicosis, none of the babies studied fitted into the clinical picture of breast milk jaundice.

The group of babies with unexplained jaundice poses great diagnostic challenge to practitioners in the developing world. In our study, we entertained the possibility of missed diagnosis in some babies due to inadequate investigation. Even now, we lack facilities to investigate endocrine, metabolic or genetic disorders in our centre. Rapid reduction of serum bilirubin is definitely not enough in the management of jaundiced infants. It is equally important to make conclusive diagnosis of the aetiology since this may also be associated with serious morbidity and mortality.

The entire spectrum of the aetiology of newborn jaundice recorded in the present study is not different from previous reports from other parts of the country[3,15,16] or from other parts of the world.[17,18] Of importance is the leading role of ABO incompatibility and G6PD deficiency as earlier reported by others.[18,19] In spite of the inability to assay G6PD in all the babies in the present study, 35.9 percent of the babies so investigated had G6PD deficiency. This is similar to the 38.3 percent and 40 percent reported from Calabar,[20] and Zaria,[16] respectively.

Iso-immunization was not conclusively established among babies with blood group incompatibility as DCT was negative in all the cases. This was contrary to previous reports that about 36 percent of Nigerian babies with ABO incompatibility may have evidence of iso-immunization.[21] Nevertheless, some of the

babies with ABO incompatibility in the present study had severe hyperbilirubinaemia requiring EBT, thus justifying the likelihood of iso-immunization in them. However, anecdotal reports suggest that DCT has low sensitivity and may not be very useful in identifying significant haemolysis.[22] This may explain our inability to confirm iso-immunization in babies at risk of blood group incompatibility. End-tidal carbon monoxide estimation has been reported to be superior to DCT in identifying infants at risk of significant hyperbilirubinaemia.[23] This non-invasive method should be recommended for routine use.

The relatively higher mean peak serum bilirubin levels in babies with G6PD deficiency and blood group incompatibilities compared to babies with unexplained jaundice, may reflect the occurrence of haemolysis in the former conditions. This may also explain the relatively lower mean haematocrit levels in babies with the aforementioned conditions. Thus, babies with G6PD deficiency and blood group incompatibility are most at risk of severe hyperbilirubinaemia as well as anaemia. Babies with jaundice due to prematurity, G6PD deficiency, septicaemia and ABO incompatibility were also relatively older than babies with unexplained jaundice at the time their serum bilirubin levels peaked presumably because of prolonged and persistent hyperbilirubinaemia. This may be related to delay in bilirubin clearance either as a result of higher bilirubin load or immaturity of hepatic enzymes. The high EBT rate among babies with G6PD deficiency and Rhesus incompatibility is most probably related to the relatively high peak serum bilirubin in these babies.[24] All the babies with Rhesus incompatibility had EBT whereas most babies with ABO incompatibility did not require EBT as previously reported by others.[9]

It is instructive that babies with jaundice due to prematurity required phototherapy for longer periods and also required multiple EBT compared to term babies.[25] This difference may be related to gestational age-related differences in the production of bilirubin as well as the efficiency of the mechanisms of phototherapy such as photo-isomerization and photo-oxidation.[8] Further studies are required on this aspect of bilirubin metabolism.

The relatively high prevalence rate of encephalopathy among babies with jaundice due to G6PD deficiency and ABO incompatibility may also be a reflection of their relatively higher serum bilirubin levels.[26] It is attractive to postulate that early diagnosis of these conditions would allow the prediction of the probable clinical course and also facilitate more pro-active management of hyperbilirubinaemia in babies with such conditions.

We acknowledge, as a limitation, our inability to conduct extensive investigation of our subjects. To this end, it is essential to institute advocacies that would ensure the provision of diagnostic facilities for endocrine, metabolic and genetic disorders at least in the major referral hospitals in the country. The clinical course of newborn jaundice can also be modified by making use of effective therapeutic options like intensive phototherapy with blue light and use of the metallo-porphyrins both of which should reduce the requirement for EBT. This is important as studies have also documented morbidities and mortality associated with EBT.[27]

In conclusion, the present study has presented some evidence that the clinical course of newborn jaundice may be related to the cause of hyperbilirubinaemia. The implication of this is that, with early diagnosis of the cause, practitioners could reliably predict the likely clinical events in jaundiced infants and prepare appropriately for the likely associated morbidities.

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