

Neonatal Jaundice in Ibadan: A Study of Cases seen in the Out-Patient Clinic

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Summary

Effiong, C. E. and Laditan, A. A. O. (1976). *Nigerian Journal of Paediatrics*, 3 (1), 1. **Neonatal Jaundice in Ibadan: A study of cases seen in the Out-Patients Clinic.** The results of a prospective study of the frequency, aetiological factors, immediate prognosis and management of neonatal jaundice in Nigerian babies admitted into the Children's Emergency Room, University College Hospital, Ibadan, are reported. There were 195 cases during a six-month period. Jaundice was of late onset, and it occurred nearly twice as frequently in the male as in the female. In the female, jaundice was associated not only with the homozygous G-6-PD deficiency, but also with the heterozygous. G-6-PD deficiency, ABO incompatibility, low birthweight and infection were the main aetiological factors. Infection in association with G-6-PD occurred in 54 per cent of cases while in association with ABO incompatibility it occurred in 23 per cent of the babies.

Thirty-two per cent of the cases were kernicteric on admission; 6.2 per cent of all the cases died within 24 hours of admission. The severity of the jaundice was directly proportional to the level of unconjugated bilirubin which, in turn, was related to the aetiological factor(s), the most important of these being G-6-PD deficiency and infection.

IN a previous study undertaken to determine the incidence and aetiology of neonatal jaundice in two hospitals in Ibadan, Effiong *et al.*, (1975), have shown that:

1. neonatal jaundice is a major paediatric problem,
2. glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, ABO blood group incompatibility and low birthweight are common aetiological factors and
3. no aetiological factor could be identified in a significant proportion of the cases.

In another study carried out to determine the possible aetiological role of other red cell enzymes in neonatal jaundice, Bienzle *et al.*, (1975) have found that glutathione reductase level is significantly lower in jaundiced babies with normal G-6-PD activity than in both normal and G-6-PD deficient jaundiced babies. This finding suggests that some of the cases of neonatal jaundice hitherto classified as of unknown cause may be due to low levels of this enzyme.

The present study concerns cases of neonatal jaundice referred to the Children's Emergency

Room, University College Hospital (UCH), Ibadan. Our objectives were:

- (a) to determine the aetiological factors of jaundice in neonates delivered at home and those discharged home from other hospitals soon after birth, and
- (b) to identify the factors responsible for the poor prognosis of jaundice in such babies.

It was hoped that by supplementing our previous data with those from the present study, a more comprehensive picture of the disease in Ibadan will be obtained.

Materials and Methods

All infants with neonatal jaundice referred to the Children's Emergency Room, UCH, Ibadan, over a period of six months, (March–May 1971 and September–November 1972) were studied.

Clinical history on each child included:

- (a) duration of labour,
- (b) type of delivery,
- (c) drugs taken by or administered to the mother during the last few weeks of pregnancy, labour and puerperium,
- (d) drugs administered to the baby since birth, and
- (e) the age of baby at the onset of jaundice.

In the physical examination, particular attention was paid to the admission weight of the child, and to any evidence of trauma, infection or kernicterus.

The following investigations were carried out on most of the patients: packed cell volume (PCV), total and conjugated serum bilirubin, and ABO and Rh blood groups of the baby and its mother. G-6-PD screening test was done using the method of Motulsky and Campbell-Kraut (1961). Blood and umbilical cord swabs were cultured for pathogens. Direct Coombs' test was performed if this was indicated

by the existence of the set-up for ABO or Rh incompatibility. The haemolysin test, (Boorman and Dodd, 1970) was undertaken in twenty-four cases with ABO incompatibility set-up.

Exchange blood transfusion was indicated by the following criteria:

- (a) baby's weight of 2,500 gm and above, plus unconjugated serum bilirubin level of 20 mg per 100 ml and above;
- (b) baby's weight of less than 2,500 gm and level of unconjugated serum bilirubin of 15–19 mg per 100 ml depending on the weight of the baby.

These criteria also applied to babies with doubtful or mild evidence of bilirubin encephalopathy.

Results

There were 195 patients; 121 were males and 74 were females (male: female ratio of 1.6 : 1). Bilirubin results were not available in 15 cases either because of death occurring soon after arrival (10 babies), or withdrawal of the children from hospital before bilirubin determination (5 cases). In 20 (11 per cent) of 180 babies the total serum bilirubin was less than 15 mg per 100 ml., and in 160 (89 per cent) it was 15 mg per 100 ml. or above. Thus, jaundice was severe (total serum bilirubin 15 mg per 100 ml. or above) in a majority of the cases.

Age on Admission

The age at the onset of jaundice could not be reliably determined in most cases because many mothers did not recognize jaundice in their babies until it was very deep. The age on admission (Fig. 1) rather than age of onset of jaundice in 140 cases were therefore analysed. It will be seen that 92 out of 140 babies (65.7 per cent) were admitted between the ages of three and six days, 9 (6.4 per cent) at the age of two days and only 6 (4.3 per cent) during the first 24 hours. The remaining 33 cases

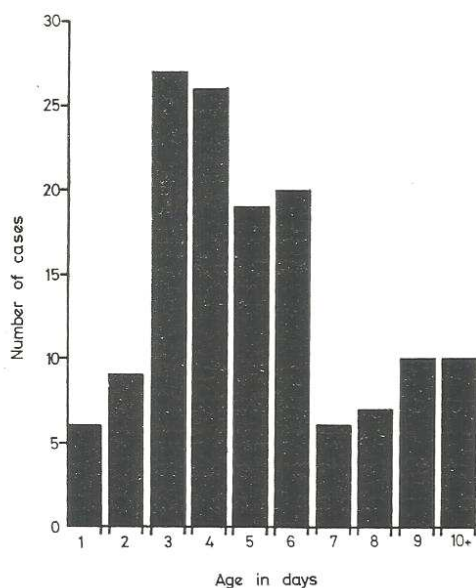


Fig. 1. Age at admission of 140 babies with neonatal jaundice.

(23.6 per cent) were admitted between the ages of 7 and 14 days.

Aetiological Factors

Data were available for analysis of possible aetiological factors in 175 cases (Table 1). In 75 males (69.4 per cent) and 28 females (42 per cent) the jaundice was associated with G-6-PD deficiency either alone or in combination with infection or the set-up for ABO incompatibility. In 16 males (15 per cent) and 14 females (21 per cent) the only possible aetiological factor detected was ABO incompatibility. Infection, in some cases associated with ABO incompatibility, or G-6-PD deficiency was responsible for the jaundice in 14 males (13 per cent) and 12 females (18 per cent).

The admission weights of the 195 babies ranged between 1,500 gm and 4,500 gm, being 2,500 gm or less in 26 per cent of the cases. The incidence of low birthweight (2,500 gm or less) in Ibadan is 15.5 per cent (Effiong *et al.*, 1975 unpublished data). Thus, there was a much higher proportion of low birthweight babies in this series than in normal population of

TABLE I

Possible Aetiological Factors in 175 cases of Neonatal Jaundice admitted into the Children's Emergency Room

Factor	Number of Cases	
	Male	Female
G-6-PD Deficiency	48 (44.4)	23 (34.3)
G-6-PD Deficiency + ABO Incompatibility	18 (16.7)	—
Infection + G-6-PD Deficiency	9 (8.3)	5 (7.5)
Infection + ABO Incompatibility	3 (2.8)	3 (4.5)
Infection without other factors	2 (1.9)	4 (6.0)
ABO Incompatibility without other factors	13 (12.0)	11 (16.4)
Low Birthweight	11 (10.2)	9 (13.4)
Unknown Aetiological Factors	4 (3.7)	12 (17.9)
Total	108 (100)	67 (100)

Per cent of total in parenthesis.

Nigerian neonates. In 20 patients (11 males and 9 females) there were no other identifiable aetiological factors except low birthweight. It was not possible to determine reliably the maturity, by gestation period, in these babies. No aetiological factor was identified in four males (3.7 per cent) and 12 females (17.9 per cent); nor was there any evidence of Rhesus iso-immunisation in the series.

In many patients, there were multiple aetiological or precipitating factors. Eighteen (24 per cent) of 75 males with G-6-PD deficiency also had different ABO blood groups from their mothers. The results of blood culture were available in 44 patients and of these, organisms were isolated in 26 (59 per cent). The pathogens included *E. coli* 10; *Staph. aureus* 5; *Staph. albus* 6; coliforms 3; *Ps. aeruginosa* 2; *Klebsiella* species 3; non-haemolytic streptococci 2; and *Strept. faecalis* 2. Of the 26 positive blood cultures, 12 yielded a mixture of 2 organisms. Fourteen (54 per cent) of the 26 patients with positive blood cultures were G-6-PD deficient, 6 (23 per cent) were

ABO incompatible with their mothers, and no other associated factors were found in the remaining 6 cases.

Table II shows the distribution of G-6-PD activity in 175 cases, while Table III shows the distribution of ABO blood groups in 56 cases of jaundice not associated with G-6-PD deficiency or infection. Blood groups: A and B occurred equally at a frequency of 28.6 per cent in jaundiced babies, compared with a frequency of 21.3 per cent and 23.3 per cent respectively in the normal Yoruba population (Worlledge *et al.*, 1974). Direct Coombs' test was weakly positive in 3 cases, and the haemolysin test was positive in 16 (66.6 per cent) of 24 cases tested. In four of 12 males with positive haemolysin test, G-6-PD was also deficient.

TABLE II

G-6-PD Activity in 175 Infants with Neonatal Jaundice Admitted into the Children's Emergency Room

G-6-PD Activity	Sex	
	Male	Female
Deficient	75 (69)	28 (42)
Heterozygous	-	16 (24)
Normal	33 (31)	23 (34)
Total	108 (100)	67 (100)

Per cent of total in parenthesis.

TABLE III

ABO Blood Group Distribution in 56 Cases with Neonatal Jaundice of unknown Aetiology and in Control

Blood Group	No. of Cases	Per cent of total
A	16	28.6 (21.3)*
B	16	28.6 (23.3)*
AB	2	3.5 (3.9)*
O	22	39.3 (51.5)*
Total	56	100.0 (100.0)*

* Normal Distribution among the Yorubas (Worlledge *et al.*, 1974).

All the 128 mothers who received ante-natal care, had pyrimethamine and folic acid throughout pregnancy, and 20 of these had ferrous sulphate as well. There were seven cases of chloroquine, five of aspirin, seven of naphthalene and one of vitamin K₁ exposure in the babies before the onset of jaundice. Fourteen of these 20 patients were G-6-PD deficient.

Immediate Prognosis

Of 161 cases adequately assessed, 107 patients (66 per cent) were discharged home well; 51 (32 per cent) were kernicteric on admission and 10 (6.2 per cent) of these died within 24 hours of admission. Three (1.8 per cent) non-kernicteric babies died, 1 from severe septicaemia and meningitis, 1 from persistent diarrhoea and dehydration, and another one had multiple congenital malformations with terminal uraemia. All the kernicteric babies who died were admitted at the age of 3-4 days, the jaundice having started only one day previously. Their serum bilirubin ranged from 30.2 to 53 mg per 100 ml (mean 42.1 mg).

Frequency of Kernicterus in Relation to (a) Levels of Bilirubin and (b) Aetiology of Jaundice

Figure 2 shows the frequency of kernicterus in relation to the initial level of unconjugated serum bilirubin. There was one case (2 per cent) of kernicterus out of 48 cases with unconjugated serum bilirubin level of 10-20 mg per 100 ml. Kernicterus occurred in all the 15 cases with unconjugated serum bilirubin of 50 mg per 100 ml and above. Thus, the occurrence of kernicterus was directly proportional to the level of unconjugated bilirubin. Figure 3 shows the frequency of kernicterus in relation to possible aetiological factors. Of 66 patients with G-6-PD deficiency, 23 (35 per cent) were kernicteric, compared with 5 (25 per cent) out of 20 cases with ABO incompatibility, and one case (7 per cent) among 15 cases with low birthweight.

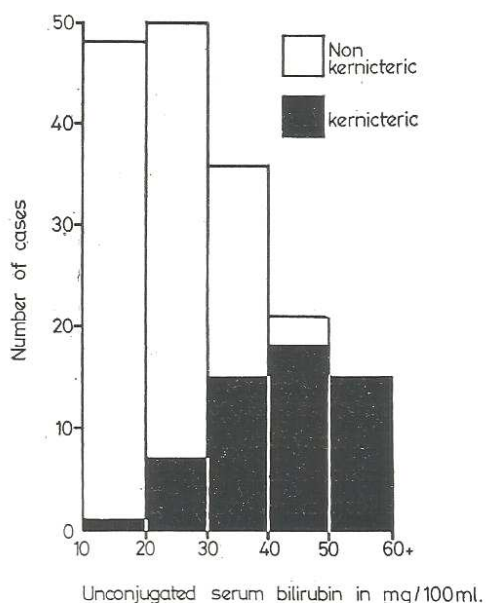


Fig. 2. Frequency of kernicterus in relation to levels of unconjugated bilirubin in 161 cases of neonatal jaundice.

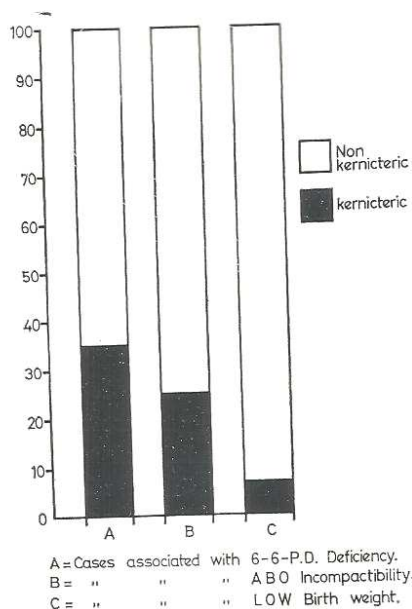


Fig. 3. Frequency of kernicterus in relation to aetiological factors. Note the higher frequency of kernicterus in relation to G-6-PD deficiency.

Management

Exchange blood transfusion was undertaken in 72 (46 per cent) of 158 patients; once in 51 patients, twice in 17 and three times in 4 cases.

There were five severely anaemic patients who required only simple blood transfusion with packed red cells.

Discussion

The present study has shown that jaundice is a major neonatal problem among infants seen in the outpatient clinic. The condition is associated with high morbidity and mortality. The study also shows that G-6-PD deficiency is the most important aetiological factor in neonatal jaundice. Smith and Vella (1960) first reported the aetiological relationship between neonatal jaundice and G-6-PD deficiency and other workers have confirmed this relationship in different parts of the world: Greece, (Doxiadis *et al.*, 1960 and 1961); Italy, (Panizon, 1960); Senegal, (Oudart *et al.*, 1971); Hong Kong, (Yeu and Strickland, 1965; Lee *et al.*, 1970); Nigeria, (Gilles and Arthur, 1960; Gilles and Taylor, 1961; Capps *et al.*, 1963; Ifekwunigwe and Luzzatto, 1966; Hendrickse, 1972; Ransome-Kuti, 1972; Effiong *et al.*, 1975).

In the present series, jaundice was more common in the male than in the female. This preponderance of males over females with neonatal jaundice has been reported in Lagos, Nigeria, (Ransome-Kuti, 1972) and in Hong Kong (Lee *et al.*, 1970). Since G-6-PD deficiency is more common among males than in females in Nigeria and Hong Kong, and is also an important aetiological factor in neonatal jaundice, the male preponderance in the present as well as in other studies may be expected.

Our findings with regards to severity of jaundice in G-6-PD deficient neonates agree with those of Ransome-Kuti (1972). In contrast, Capps *et al.*, (1963) reported that severe complications of G-6-PD deficiency were rare in Nigeria. Their conclusion was based on a study of a small number of babies delivered at the UCH, Ibadan. These babies were not therefore exposed to precipitating factors such as infection, drugs and other substances which commonly operate in the environment of

patients born at home. Similarly, the conclusion by Valaes (1969), which was based partly on the report by Capps and his co-workers, that Nigerian G-6-PD deficient neonates belonged to a population with a milder type of G-6-PD deficiency, and therefore very little associated jaundice, is at variance with the present findings.

The frequency of G-6-PD deficiency among the males in this study was $3\frac{1}{2}$ times the incidence of the condition in the Nigerian male population, while among the females, the incidence was about 10 times. Since the proportion of female heterozygote (24 per cent) in our series is much less than the expected 36 per cent (Luzzatto, 1972), it is suggested that some of the deficient females are indeed heterozygotes. Severe neonatal jaundice has been reported in G-6-PD heterozygous female neonates in Greece (Fessas *et al.*, 1962). Valaes *et al.*, (1969) and Zannos-Mariolea *et al.*, (1968) using a variety of methods in estimating G-6-PD activity, have, in addition, emphasised the difficulty in distinguishing biochemically the heterozygote from homozygote deficient female neonate with jaundice. This strong association of neonatal jaundice and G-6-PD heterozygous state has not, to our knowledge, been reported in Nigeria before.

ABO incompatibility was the next most common factor. Alone, it accounted for jaundice in 12 per cent of the males and 16 per cent of the females. As in the cases with G-6-PD deficiency, there were some patients in whom ABO incompatibility and infection or ABO incompatibility and G-6-PD deficiency co-existed.

Absolute proof of ABO incompatibility being an aetiological factor in neonatal jaundice is a difficult problem. Unlike in Rh. iso-immunisation Coombs' test is only occasionally positive. The haemolysin test was positive in 66 per cent of the cases with the set-up for ABO incompatibility in which this test was performed. This number of patients with positive haemolysin test, is not significantly higher than that reported

among blood donors in Ibadan (Worlledge *et al.*, 1974). However, since the frequencies of A and B blood groups are significantly higher, and the frequency of the O blood group significantly lower than those in the normal Yoruba population (Worlledge *et al.*, 1974), it may be inferred that ABO incompatibility is aetiologically related to neonatal jaundice in at least, some of the babies in whom the set-up existed.

Low birthweight was the third common aetiological factor; there were 10 and 13 per cent of males and females respectively in whom jaundice was associated with low birthweight.

Infection alone was the least common possible causative factor accounting for 2 per cent of cases in males and 6 per cent in females. It must be emphasized however, that this low incidence of infection in the present series should be accepted with reservation since the results of only 44 blood cultures were available for analysis. The role of infection and drugs in causing haemolysis in G-6-PD deficient individuals has been emphasized by Larizza *et al.*, (1960), Panizon (1960) and Doxiadis *et al.*, (1961).

In the present study, it may be assumed that haemolysis was precipitated by infection in 54 per cent of the patients in whom G-6-PD deficiency and infection were associated. There were 14 per cent of the G-6-PD deficient babies who were exposed to known precipitating drugs and other substances (chloroquine, aspirin, naphthalene and Vitamin K). It is possible, as has been suggested by Ransome-Kuti (1972), that application of traditional medicine to the skin may have been the precipitating factor in some of the cases.

It must be admitted that it is difficult to assign precise aetiological roles to the different factors studied, since in some patients there were more than one possible factor. Indeed, two factors co-existed in 28 and 12 per cent of males and females respectively. However, of the aetiological factors examined in the present series, G-6-PD deficiency was not only the most frequent but also the most important. The

enzyme was deficient in 70 per cent of the males and 42 of the females. In some patients, however, other possible aetiological factors, (ABO incompatibility and infection) co-existed. In combination with other possible aetiological factors, particularly G-6-PD deficiency, infections played a highly significant aetiological role. In this series 54 per cent of the patients with positive blood culture were G-6-PD deficient. In our previous study (Effiong *et. al.*, 1975) of babies born in UCH, the incidence of infection was extremely low.

In the present study, the immediate prognosis of jaundice was grave; 32 per cent of the cases were admitted with kernicterus, 46 per cent required exchange blood transfusion and 6.2 per cent of the kernicteric neonates died. This contrasts with the findings in babies born in the hospital (Effiong, *et. al.*, 1975) where there was no case of kernicterus, and only 7.2 per cent of the cases required exchange transfusion. This difference in prognosis between the hospital and out-patient cases may be attributed to the numerous precipitating factors existing in the baby born at home as well as the delay in parents seeking medical attention. The incidence and severity of neonatal jaundice may be considerably reduced by prevention of neonatal infection and avoidance of exposure to drugs and other known precipitating substances during the first week of life. It is also suggested that in our environment where neonatal jaundice is common, phenobarbitone should be given either to the mothers during the last 2 weeks of pregnancy, or to the newborn infant during the first week of life as recommended by Yeung and Field, (1969), and Vest *et. al.*, (1971).

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