Clinico-demographic profile of hyperbilirubinemia in neonates admitted to a tertiary care hospital

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ABSTRACT

Background: The purpose of this study was to find etiological and other associated factors of neonatal hyperbilirubinemia at a tertiary care hospital SGRRIM&HS Patel Nagar Dehradun Uttrakhand, India. Jaundice is a common problem in neonatology. Early recognition of the cause of jaundice is very important as delay in management may lead to serious complications or even death.

Methods: In present study, newborns with jaundice were evaluated during a 12 months period between January 2015 – December 2015. 195 newborns with jaundice were enrolled in the study. Data regarding demographic profile of new born, physical examination and laboratory investigations were gathered and analyzed to interpret the common etiologies giving rise to neonatal hyperbilirubinemia.

Results: Out of 195 cases of neonatal hyperbilirubinemia, 40 cases belonged to physiological jaundice. Breast feeding jaundice-121 cases, breast milk jaundice-5 cases, jaundice due to prematurity-8 cases and pathological jaundice-21 cases (6 were of ABO incompatibility, 4 neonatal sepsis, 4 Rh incompatibility, 4 G6PD deficiencies, 2 neonatal hypothyroidism and 1 congenital biliary atresia).

Conclusions: Present study concludes that breast feeding jaundice forms the bulk of cases of neonatal hyperbilirubinemia in our hospital, followed by physiological jaundice, jaundice of prematurity, ABO Incompatibility, breast milk jaundice, neonatal sepsis, Rh incompatibility, G6PD Deficiency, neonatal hypothyroidism and congenital biliary atresia.

Keywords: Neonatal hyperbilirubinemia, Breast feeding, Breast milk, Physiologic jaundice, G6PD

INTRODUCTION

Hyperbilirubinemia is a common problem during the neonatal period occurring in upto 60% of term and 80% of preterm babies in the first week of life.1,2 Even though extreme hyperbilirubinaemia is rare in developed countries it is still quite rife in developing countries often resulting in kernicterus with its attendant medical, economic and social burden on the patient, family and society at large.3,4 The incidence, aetiological and contributory factors to neonatal jaundice vary according to ethnic and geographical differences.5 Unlike the developed countries where feto maternal blood group incompatibilities are the main causes of severe neonatal jaundice, it is mostly prematurity, G6PD deficiency, infective causes as well as effects of negative traditional and social practices such as consumption of herbal medications in pregnancy, application of dusting powder on baby, use of camphor balls to store baby’s clothes that mainly constitute the aetiology in developing countries.6,8 Severe neonatal jaundice can therefore be said to have modifiable risk factors particularly in developing countries.9 Some of the most common causes of neonatal jaundice include physiological jaundice, breast feeding jaundice, breast milk jaundice, prematurity leading to jaundice and various pathological causes like haemolytic
disease, liver dysfunction, neonatal sepsis, deficiency of G6PD enzyme, hypothyroidism and rare conditions such as Gilbert's syndrome etc.\textsuperscript{10,11} Physiological jaundice is attributable to physiological immaturity of neonates to handle increased bilirubin production. Visible jaundice usually appears between 24-72 hours of age. Total serum bilirubin (TSB) level usually rises in full-term infants to a peak of 12 to 15 mg/dL by 3 days of age and then falls. In premature infants, the peak may be 10 to 12 mg/dL on the fifth day of life, possibly rising over 15 mg/dL without any specific abnormality of bilirubin metabolism. Levels under 2 mg/dL may not be seen until one month of age in both full term and premature infants. TSB concentrations have been defined as non-physiologic if concentration exceeds 5 mg/dL on first day of life in term neonate, 10 mg/dL on second day, or 12-13 thereafter. Any TSB elevation exceeding 17 mg/dL should be presumed pathologic. Appearance of jaundice within 24 hours, peak TSB levels above the expected normal range, presence of clinical jaundice beyond 3 weeks and conjugated bilirubin (dark urine staining the clothes and light colored stool) would be categorized under pathological jaundice.\textsuperscript{12}

Neonatal jaundice is related to breast feeding in two primary clinical situations: firstly, new-borns who are exclusively breast fed and experience prolonged unconjugated hyperbilirubinemia are considered as patients of breast milk jaundice, approximately 2-4% of exclusively breast-fed term babies experience jaundice in excess of 10 mg/dL in the third week of life, diagnosis of breast milk jaundice should be considered if the TSB is predominantly unconjugated, other causes of prolonged jaundice have been excluded and the infant is in good health.\textsuperscript{12,13} Secondly, those patients who receive inadequate breast feeding and have high concentration of indirect bilirubin during the first post natal week are patients of breast feeding jaundice, jaundice in these babies usually appears between 24-72 hours of age, peaks by 5-15 days of life and disappears by the third week of life.\textsuperscript{12,13} Rise in indirect bilirubin in this type is due to enhancement of enterohepatic circulation. Moreover, presence of large amounts of bilirubin in meconium and delay in emptying of meconium have been shown to contribute to an increase in serum bilirubin levels in early days of life further increasing intestinal biliary absorption.\textsuperscript{14,15} The jaundice in this case can usually be ameliorated by frequent breast feeding sessions of sufficient duration to stimulate adequate milk production.\textsuperscript{16} Several hypotheses have been proposed for breast milk jaundice, including the presence of UDP glucuronosyltransferase inhibitor, β glucuronidase or yet unidentified factor in human milk that could inhibit excretion of bilirubin and results in hyperbilirubinemia. There is increase in enterohepatic circulation of bilirubin in this type and also may be attributed to increased levels of epidermal growth factor (EGF) in breast milk.\textsuperscript{17}

NNJ (Neonatal Jaundice) in less than 35 week gestation has similar pathogenesis to that of term and borderline preterm neonates, but hyperbilirubinemia in preterm infants less than 35 week is more prevalent, severe, and proctated than that in term infants because of increased immaturity of RBCs, liver, gastrointestinal tract in preterm infants, also there is often delay in enteral feeds, which may limit intestinal flow and bacterial colonization, resulting in further enhancement of enterohepatic circulation, so, patients less than 35 week having exaggerated physiological jaundice were taken as patients with NNJ of prematurity.\textsuperscript{18} Consideration of all these etiologies is essential in evaluating neonates with jaundice. Complete history of newborn, family history, sibling history, complete physical examination and laboratory investigations are key points in managing these patients. The aim of our study is to determine the underlying aetiologies of neonatal hyperbilirubinemia and to explore most common cause of neonatal jaundice in areas adjoining this tertiary care teaching hospital.

**METHODS**

Prospective observational study was done for 12 months period between January 2015–December 2015. Total patients admitted to the nursery of tertiary care hospital during this time period was 1272, only patients admitted to our unit with features of neonatal jaundice were included into our study, so we contained our study in 195 neonates. Only patients characteristics and general data were documented including age, birth weight, age at onset, type of feeding, history of jaundice in sibling. All cases were thoroughly examined on admission. Various investigations were carried out including serum bilirubin total and conjugated by Jendraski and Graf method, liver function tests (aspartate aminotransferase, alkaline phosphatases) by IFCC method by fully automatic chemistry analyzer, peripheral blood film for hemolysis and cell morphology, Coomb's test, reticuloocyte count, G6PD (glucose-6-phosphate dehydrogenase) activity in erythrocytes by semiquantitative SPOTCHECK MicroFlow Automatic Analyzer, full blood count by automated cell analyzer (Sysmex KX-21), septic screen, blood cultures monitored by an automated system (Bac T/ALERT 3D), thyroid function tests by automated immunoassay by TOSOH machine and urine test for reducing substances. A conjugated bilirubin of greater than 20% of total bilirubin was considered to be abnormal.

The hemolytic causes of jaundice include Rh hemolytic disease, ABO incompatibility, hereditary spherocytosis, G-6-PD deficiency and minor blood group incompatibilities. A baby born to an Rh-negative mother (and Rh-positive father) should have Rh typing, Direct Coomb's test (DCT), reticuloocyte count and serum bilirubin on cord blood. Babies born with maternal blood group 0 and Rh-positive, were an option to test the cord blood for the infant's blood type and other investigations for confirmation of hemolytic cause of jaundice accordingly. In case of G6PD deficiency, hereditary spherocytosis, minor group incompatibilities.
Investigations for G-6-PD deficiency should be considered in all term and near-term infants with jaundice requiring phototherapy, with a family history of significant jaundice or a geographic origin associated with G6PD deficiency. Urinary tract infection was defined as growth of single known pathogen on urine culture with ≥100,000 cfu/mL of urine obtained by urethral catheterization. Statistical analysis was made using graph pad prism. Data are shown as mean (S.D.).

RESULTS

According to history, clinical features and hematological investigations of the new borns, patients were grouped into ten classes. Demographic pattern and general data are summarized in Table 1. Laboratory results are summarized in Table 2. 40 cases belonged to physiological jaundice. Breast feeding jaundice-121 cases, breast milk jaundice-5 cases, jaundice due to prematurity-8 cases and pathological jaundice-21 cases (6 of ABO incompatibility, 4 of neonatal sepsis, 4 of Rh incompatibility, 4 of G6PD deficiency, 2 of neonatal hypothyroidism and 1 of congenital biliary atresia). The mean age of onset of jaundice in these patients was different in different groups (Table 1). Two E. coli, one Klebsiella and one Pseudomonas were detected in blood culture of four cases confirming the diagnosis of neonatal sepsis. There was no case of urinary tract infection and galactosemia in our study. TSH and T4 levels in neonatal hypothyroidism were highly abnormal, they were two in number. Reticulocyte count was raised in hemolytic causes like ABO, Rh incompatibilities and G6PD deficiency. Conjuncted bilirubin level and liver function tests were highly abnormal in case of congenital biliary atresia. 2 patients expired one was suffering from pseudomonas sepsis with NNJ and other one from ABO incompatibility both patients were born outside the hospital and were admitted in very sick condition with bilirubin encephalopathy. 3 patients suffered from kernicterus all were born outside the hospital one was suffering from ABO incompatibility, second was suffering from G6PD deficiency and third from Rh incompatibility, all the three were hospitalized late, in the state of bilirubin encephalopathy to the hospital.

Table 1: Demographic profile and general data of newborns.

<table>
<thead>
<tr>
<th>Type of jaundice</th>
<th>Cases total (195)</th>
<th>Sex</th>
<th>Age (Days) (SD)</th>
<th>Age of onset (Days) (SD)</th>
<th>Birth W (Gram) (SD) eight</th>
<th>Feeding method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast feeding</td>
<td>121</td>
<td>M-84 F-37</td>
<td>5.6 (1.69)</td>
<td>4.19 (0.76)</td>
<td>2648 (160)</td>
<td>BF-27.7% Bot-33.3% MF-39%</td>
</tr>
<tr>
<td>Physiological</td>
<td>40</td>
<td>M-23 F-17</td>
<td>4.22 (1.049)</td>
<td>2.98 (0.82)</td>
<td>2670 (188.26)</td>
<td>BF-81.66% Bot-18.34%</td>
</tr>
<tr>
<td>Prematurity</td>
<td>8</td>
<td>M-5 F-3</td>
<td>4.5 (0.84)</td>
<td>3.00 (0.71)</td>
<td>2022 (86.03)</td>
<td>BF-20% Bot-25% MF-55%</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>6</td>
<td>M-4 F-2</td>
<td>3.5 (1.80)</td>
<td>1.89 (0.86)</td>
<td>2568 (140)</td>
<td>BF-60% MF-40%</td>
</tr>
<tr>
<td>Breast Milk</td>
<td>5</td>
<td>M-4 F-1</td>
<td>23.4 (2.52)</td>
<td>16 (0.89)</td>
<td>2705 (150)</td>
<td>BF-100%</td>
</tr>
<tr>
<td>Rh incompatibility</td>
<td>4</td>
<td>M-3 F-1</td>
<td>3.8 (1.82)</td>
<td>1.62 (0.99)</td>
<td>2568 (130)</td>
<td>BF-70% MF-30%</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>4</td>
<td>M-4</td>
<td>6.8 (1.82)</td>
<td>6.22 (0.86)</td>
<td>2566 (150)</td>
<td>BF-50% MF-50%</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>4</td>
<td>M-2 F-2</td>
<td>7.5 (1.71)</td>
<td>1.50 (0.71)</td>
<td>2295 (146.49)</td>
<td>BF-50% MF-50%</td>
</tr>
<tr>
<td>Neonatal hypothyroidism</td>
<td>2</td>
<td>M-2</td>
<td>36.5 (12.61)</td>
<td>5.02 (1.41)</td>
<td>2922 (133)</td>
<td>BF-100%</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>1</td>
<td>M-1</td>
<td>8</td>
<td>1</td>
<td>2430</td>
<td>BF-100%</td>
</tr>
</tbody>
</table>

DISCUSSION

In our study, breast feeding jaundice emerged as the most common aetiology of neonatal jaundice with 121 patients followed by physiological jaundice, jaundice of prematurity, ABO incompatibility, breast milk jaundice, neonatal sepsis, Rh incompatibility, G6PD Deficiency, neonatal hypothyroidism and congenital biliary atresia. Bilirubin level regressed after increasing the frequency and improving the method of breast feeding. Najati, et al also concluded that majority of patients had an unconjugated hyperbilirubinemia probably due to inadequate breast feeding. Other causes in their study were G6PD deficiency, hypothyroidism, UTI,
septicaemia, Down syndrome and ABO incompatibility, but here in our study there was no case of UTI responsible for neonatal hyperbilirubinemia. Another study by Bertini stated that fasting plays an important role in pathogenesis of neonatal hyperbilirubinemia and forms bulk of the cases.\textsuperscript{21}

All 5 newborns were exclusively breast fed in case of breast milk jaundice. Icterus started developing after 1st week of life and peak occurred at 3rd week (13.3-17.12 mg/dl) and thereafter it regressed by its own requiring no treatment. This type is not a clinical disorder but recognized to be a normally occurring extension of physiological jaundice of new born and breast feeding should not be interrupted. Breast milk jaundice was the diagnosis of exclusion as also stated by Prashant.\textsuperscript{22}

\textbf{Table 2: Laboratory investigations of newborns.}

<table>
<thead>
<tr>
<th>Type of jaundice</th>
<th>Hb%</th>
<th>Reticulocyte Count</th>
<th>Highest total bilirubin (mg%)</th>
<th>Conjugated bilirubin (µg/dl)</th>
<th>TSH µIU/ml</th>
<th>T4 µg/dl</th>
<th>ALT µ/l</th>
<th>AST µ/l</th>
<th>ALP µ/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>13.54 (1.25)</td>
<td>1.9 (0.42)</td>
<td>6.917 (0.67)</td>
<td>0.158 (0.072)</td>
<td>2.5 (0.41)</td>
<td>14.0 (1.38)</td>
<td>15.88 (4.07)</td>
<td>24 (6.7)</td>
<td>166.13 (53.28)</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>13.78 (1.25)</td>
<td>2.010 (0.30)</td>
<td>14.908 (1.96)</td>
<td>1.38 (0.22)</td>
<td>2.8 (0.34)</td>
<td>12.35 (0.88)</td>
<td>19.70 (4.41)</td>
<td>21.43 (7.16)</td>
<td>152.08 (50.41)</td>
</tr>
<tr>
<td>Breast milk</td>
<td>11.40 (2.07)</td>
<td>1.48 (0.47)</td>
<td>15.20(1.92)</td>
<td>1.88 (0.497)</td>
<td>2.72 (0.26)</td>
<td>11.6 (1.14)</td>
<td>21.6 (4.28)</td>
<td>25.6 (2.3)</td>
<td>92.6 (17.34)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>10.00 (0.71)</td>
<td>1.14 (0.27)</td>
<td>7.6 (1.14)</td>
<td>0.66 (0.13)</td>
<td>1.32 (0.37)</td>
<td>12.2 (0.84)</td>
<td>14.8 (2.77)</td>
<td>19.6 (2.3)</td>
<td>58.2 (3.19)</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>8.5 (0.71)</td>
<td>5.00 (1.41)</td>
<td>17.00 (1.41)</td>
<td>0.35 (0.07)</td>
<td>0.9 (0.14)</td>
<td>8.5 (0.71)</td>
<td>41 (1.41)</td>
<td>49 (1.41)</td>
<td>67 (4.24)</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>13.00</td>
<td>3.00</td>
<td>18.00</td>
<td>16.00</td>
<td>3.00</td>
<td>13.00</td>
<td>50.00</td>
<td>63.00</td>
<td>4000</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>14</td>
<td>9.00 (1.48)</td>
<td>23.00 (1.22)</td>
<td>2.40</td>
<td>3.00</td>
<td>13.00</td>
<td>15.00</td>
<td>29.00</td>
<td>160</td>
</tr>
<tr>
<td>Neonatal Hypothyroidism</td>
<td>12</td>
<td>0.95 (0.07)</td>
<td>17.00 (1.41)</td>
<td>2.05 (0.21)</td>
<td>47 (9.90)</td>
<td>1.57 (0.18)</td>
<td>16.5 (0.71)</td>
<td>28 (2.8)</td>
<td>120 (7.1)</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>4.00 (1.88)</td>
<td>10.00 (0.56)</td>
<td>17.44 (0.22)</td>
<td>1.22 (0.22)</td>
<td>2.72 (0.24)</td>
<td>14.35 (0.88)</td>
<td>14.88 (4.07)</td>
<td>21.6 (2.3)</td>
<td>48.2 (3.19)</td>
</tr>
<tr>
<td>Rh incompatibility</td>
<td>12.00 (1.34)</td>
<td>10.20 (0.88)</td>
<td>17.88 (0.20)</td>
<td>1.44 (0.22)</td>
<td>3.72 (0.26)</td>
<td>13.35 (0.88)</td>
<td>16.88 (4.07)</td>
<td>22.6 (2.3)</td>
<td>68.2 (3.19)</td>
</tr>
</tbody>
</table>

In our study there were 6 cases of ABO incompatibility and 4 cases each of sepsis, RH incompatibility and G6PD deficiency related neonatal hyper bilirubinemia. While Ahmed, et al from northern Nigeria and Owa and Ogunlesi from Ile-Ife, southern Nigeria reported septicaemia and G6PD deficiency as well as prematurity and G6PD deficiency as leading causes of NNJ respectively, Ho NK from Asia documented ABO incompatibility and G6PD deficiency as the leading causes, so ABO incompatibility was 4\textsuperscript{th} most common cause of neonatal hyper bilirubinemia followed by, RH incompatibility, sepsis and G6PD deficiency at sixth position in our study.\textsuperscript{4,25}

Prematurity was another reason for neonatal hyperbilirubinemia. 8 cases out of 195, which was third most common cause in our study. Preterm new borns are prone to developing jaundice due to immaturity of bilirubin conjugating system, higher rate of hemolysis, increased enterohepatic circulation, decreased caloric intake Chan.\textsuperscript{23} Onyearugha, et al concluded prematurity as the second leading cause of neonatal jaundice.\textsuperscript{24} Four cases of neonatal sepsis were reported. Blood culture showed two cases of E. coli and one each of Klebsiella and Pseudomonas, sepsis was sixth most common cause of neonatal jaundice in our study. Onyearugha, et al found sepsis as the second leading cause of jaundice in neonates in Nigeria.\textsuperscript{24} 2 patients expired one was suffering from pseudomonas sepsis with NNJ and other one from ABO incompatibility both patients were born outside the hospital and were admitted in very sick condition with bilirubin encephalopathy, study by C. N. Onyearugha had shown of the eight deaths recorded in this study, 6 occurred in outborn babies.\textsuperscript{24} This was because the outborn babies presented in a more severely ill state with higher SB levels and relatively late. This further infers that delivery to be conducted in an appropriate healthcare facilities where they receive proper pregnancy management and counselling on the
care of their yet to be born baby with delivery under skilled supervision and hygienic circumstances.

3 patients suffered from kernicterus all were born outside the hospital one was suffering from ABO incompatibility, second was suffering from G6PD deficiency and third from RH incompatibility, all the three were hospitalized late, in the state of bilirubin encephalopathy to the hospital. There is one study by C. N. Onyearugha which had shown fifteen of the overall subjects (9.7%) comprising 14 outborn babies (19.7%) and 1 inborn (1.2%) developed kernicterus which is higher in comparison to our study. Another study by Ahmed, et al from Zaire which had shown kernicterus 20.3% and 9.6% in outborn and inborn babies respectively which is also quite high in comparison to our study.

Two cases of neonatal hypothyroidism were noted in our study. Scott, et al concluded in his study that hypothyroidism can also lead to neonatal hyperbilirubinemia. Congenital biliary atresia also contributed as one of etiology of hyperbilirubinemia in neonates. Careful education about breast feeding and monitoring of mothers as well as assessment of newborns for the risk of developing hyperbilirubinemia can aid in preventing neonatal jaundice. Treatment is based on total serum bilirubin concentration 6 hourly during phototherapy and exchange transfusion.

CONCLUSION

The present study concludes that breast feeding is the most common cause of neonatal hyperbilirubinemia, followed by physiological jaundice, jaundice of prematurity, ABO Incompatibility, breast milk jaundice, neonatal sepsis, Rh incompatibility, G6PD Deficiency, neonatal hypothyroidism and congenital biliary atresia.

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