Clinical and Biochemical Profile of Neonates with Hyperbilirubinemia in a Tertiary Care Center

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ABSTRACT
Background: Neonatal hyperbilirubinemia, though of common occurrence, is a significant medical condition not only because of its impact on hospital discharge but more importantly because of its potential to cause serious long term neurological complications.

Method: In this retrospective study, data of 258 neonates treated for neonatal hyperbilirubinemia in the neonatal unit of MGM Medical College, Kishanganj, Bihar during the period January 2016 to December 2016 were analyzed and taken up for the study.

Results: In our study ABO incompatibility was the most common cause of neonatal hyperbilirubinemia followed by idiopathic, prematurity, Rh incompatibility and glucose 6 phosphate dehydrogenase deficiency, in addition to other minor causes. Male preponderance was seen. Unfortunately bilirubin encephalopathy (Kernicterus) was seen in a couple of cases.

Conclusion: ABO incompatibility is a very common cause of neonatal hyperbilirubinemia. Although historically Rh incompatibility has been accorded much importance, ABO incompatibility should alert the attending doctors about the impending risk of significant neonatal jaundice. If discharged early a written protocol should be followed where a revisit should be planned within 1 to 3 days for babies with any risk factor so that hyperbilirubinemia, if any, is detected and treated accordingly to prevent long term neurological morbidity.

Key Words: Neonates, Hyperbilirubinemia, ABO incompatibility, Prematurity, Jaundice, G6PD.

INTRODUCTION
Neonatal jaundice is observed during the first week of life in 60% of full term infants and 80% of preterm infants¹. It is one of the most common causes of readmission in neonates and also a case of ‘LAMA – Left Against Medical Advice’ because of delay in discharge.

Neonatal Jaundice is broadly classified as physiologic and non physiologic hyperbilirubinemia; in the former the level rises to 6 to 8 mg/dl by 3-5 days of age and may reach up to 12 mg/dl and then falls. Non physiologic hyperbilirubinemia is one in which onset of jaundice is before 24 hours of age or persists beyond 8 days. In fact any elevation of serum bilirubin that requires phototherapy is non physiologic².

This study was conducted to know the profile of neonatal hyperbilirubinemia in babies admitted in a...
tertiary care hospital in Bihar, India. Although there are innumerable studies on neonatal jaundice worldwide, there are hardly any studies from this region.

MATERIALS AND METHODS
This retrospective study was conducted in MGM Medical College and LSK Hospital, Kishanganj, Bihar. The data was collected from the medical record section of the college.

A total of two hundred and fifty eight neonates were taken up for the study. Those babies who were admitted in the neonatal unit (NICU) during the period January 2016 to December 2016 for the treatment of hyperbilirubinemia with bilirubin level of ≥14 mg/dl in case of term babies and ≥12 mg/dl in case of preterm babies were considered for the study.

All other details like history, physical examination, laboratory tests and those requiring phototherapy and /or exchange transfusion, were collected from the medical records and were thoroughly analyzed. Details of laboratory investigation done which included – total bilirubin (conjugated and unconjugated bilirubin), blood group of mother and neonate, Hb, TC, DC, and CRP (sepsis screening), G6PD status, TSH levels were collected and analyzed in our study.

RESULTS
After thoroughly analyzing the data, a total of 258 neonates with hyperbilirubinemia – with bilirubin level ≥14 mg/dl in case of term babies and ≥12 mg/dl in case of preterm babies were included in the study. It was seen that out of 258 neonates 144 (55.8%) were male and 114 (44.2%) were female and 195 (75.58%) were full term babies whereas 63 (24.42%) were preterm babies. (Table 1)

Out of 195 full term babies 109 (55.90%) had bilirubin level between 14 to 17 mg/dl, 67 (34.36%) had bilirubin level between >17 to 20 mg/dl whereas 19 (9.74%) neonates had bilirubin level more than 20 mg/dl.

Amongst the 63 preterm babies 31 (49.21%) had bilirubin level between 12 to 15 mg/dl whereas 25 (39.68 %) babies had bilirubin level between >15 to 19 mg/dl and 7 (11.11%) had bilirubin levels more than 19 mg/dl. (Table 2)

ABO incompatibility was observed in 68 (26.36%) babies, out of which 37 (54.41%) were male and 31 (45.59%) were female. RH incompatibility was observed in 20 (7.75%) babies with 12 (60%) male and 8 (40%) female.

In 50 (19.38%) babies the cause of hyperbilirubinemia was not known. Out of these 50 babies 26 (52%) were male and 24 (48%) were female.

Out of 63 premature babies, in 46 (17.83%) other causes of hyperbilirubinemia were ruled out and prematurity itself was assigned as a cause of hyperbilirubinemia. Out of these 46 babies 27 (58.75) were male and 19 (41.3%) were female.

Sepsis was the cause of hyperbilirubinemia in 26 (10.08%) babies among them 15 (57.7%) were male and 11(42.3%) with female.

G6PD deficiency was observed in 18 (6.98%) babies among them 10 (55.6%) were male and 8 (44.4%) were female.

There were 11 (4.26%) infant of diabetic mother who had hyperbilirubinemia out of which 6 (54.5%) were male and 5 (45.5%) were female.

Breast milk jaundice was seen in 8 (3.10%) babies out of which 5 (62.5%) were male and 3 (37.5%) were female.

Hyperbilirubinemia with cephalhematoma was observed in 4 (1.55%) babies with equal male 2 (50%) and female 2 (50%) distribution.

Hypothyroidism was the cause of neonatal hyperbilirubinemia in 3 cases with identical number seen in polycythemia as well. Gender distribution in case of hypothyroidism was 1(33.3%) male baby and 2(66.7%) female babies whereas it was just the opposite in case of polycythemia where 2 (66.7%) babies were male and 1 (33.3%) was female.

One (0.39%) baby with Down's syndrome also had hyperbilirubinemia. (Table 3)

Features of bilirubin encephalopathy (kernicterus) was seen in 2 neonates and both the babies had G6PD deficiency too.

Amongst the 258 neonates all the babies had received phototherapy as a part of the treatment for hyperbilirubinemia whereas only 21 babies had to undergo exchange transfusion.
**Table 1.** Gender distribution in neonates with hyperbilirubinemia

<table>
<thead>
<tr>
<th>Gender</th>
<th>No of Neonates</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>144</td>
<td>55.8</td>
</tr>
<tr>
<td>Female</td>
<td>114</td>
<td>44.2</td>
</tr>
</tbody>
</table>

**Figure 1.** Pie chart showing gender distribution in neonates with hyperbilirubinemia

**Table 2.** Serum bilirubin levels in Term and Preterm Neonates

<table>
<thead>
<tr>
<th>Serum Bilirubin</th>
<th>Full Term Neonates</th>
<th>Pre Term Neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of neonates</td>
<td>No of neonates</td>
</tr>
<tr>
<td>14 – 17 mg/dl</td>
<td>109</td>
<td>12 – 15 mg/dl</td>
</tr>
<tr>
<td>&gt; 17 – 20 mg/dl</td>
<td>67</td>
<td>&gt; 15 – 19 mg/dl</td>
</tr>
<tr>
<td>&gt; 20 mg/dl</td>
<td>19</td>
<td>&gt; 19 mg/dl</td>
</tr>
</tbody>
</table>

**Table 3.** Causes of Neonatal Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Various Causes</th>
<th>No of Neonates with Percentage</th>
<th>Male babies No with Percentage</th>
<th>Female babies No with Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO incompatibility</td>
<td>68 26.36 %</td>
<td>37 54.41 %</td>
<td>31 45.59 %</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>50 19.38 %</td>
<td>26 52 %</td>
<td>24 48 %</td>
</tr>
<tr>
<td>Prematurity</td>
<td>46 17.83 %</td>
<td>27 58.7 %</td>
<td>19 41.3 %</td>
</tr>
<tr>
<td>Sepsis</td>
<td>26 10.08 %</td>
<td>15 57.7 %</td>
<td>11 42.3 %</td>
</tr>
<tr>
<td>Rh incompatibility</td>
<td>20 7.75 %</td>
<td>12 60 %</td>
<td>8 40 %</td>
</tr>
<tr>
<td>G6PD Deficiency</td>
<td>18 6.98 %</td>
<td>10 55.6 %</td>
<td>8 44.4 %</td>
</tr>
<tr>
<td>Infant of DM mother</td>
<td>11 4.26 %</td>
<td>6 54.5 %</td>
<td>5 45.5 %</td>
</tr>
<tr>
<td>Breast Milk Jaundice</td>
<td>8 3.10 %</td>
<td>5 62.5 %</td>
<td>3 37.5 %</td>
</tr>
<tr>
<td>Cephal hematoma</td>
<td>4 1.55 %</td>
<td>2 50 %</td>
<td>2 50 %</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3 1.16 %</td>
<td>1 33.3 %</td>
<td>2 66.6 %</td>
</tr>
<tr>
<td>Polycythermia</td>
<td>3 1.16 %</td>
<td>2 66.6 %</td>
<td>1 33.3 %</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>1 0.39 %</td>
<td>1 100 %</td>
<td>0 0 %</td>
</tr>
</tbody>
</table>
DISCUSSION

Hyperbilirubinemia is quite common in newborns and multiple factors are responsible for occurrence of neonatal hyperbilirubinemia. A review article published in North America suggested that the etiology of neonatal hyperbilirubinemia is multifactorial \(^{(3)}\), we also got similar results. In our study out of 258 babies, 144 were male and 114 were female. Male preponderance was observed in previous Publications too \(^{(4,5)}\).

ABO incompatibility was the most common cause of pathological hyperbilirubinemia in our study with 26.36% of babies having ABO incompatibility similar to the results of other studies. Study done by Anil Shetty et al: Neonatal hyperbilirubinemia in a tertiary care hospital showed ABO incompatibility as the most common cause of hyperbilirubinemia \(^{(6,7)}\). Similar study done by Mishra at al: Hematological profile in neonatal jaundice showed 20% of neonates develop hyperbilirubinemia due to ABO incompatibility \(^{(4,8)}\).

Idiopathic as an etiology was observed in 15.5% cases in a study by Singh S K et al \(^{(9)}\). In our study, in 19.38% cases, a definite cause could not be ascertained. Similar findings were observed in an Iranian study where 118 neonates were investigated for the cause of neonatal hyperbilirubinemia and the researchers revealed that in 25.4% of neonates the etiology could not be ascertained \(^{(10)}\). A Canadian study also revealed that in the majority of neonatal hyperbilirubinemia cases the underlying cause was not identified \(^{(11)}\). Many authors have unable to establish the etiology of hyperbilirubinemia in more than half of the cases in their series \(^{(12)}\).

Prematurity is an important cause of neonatal hyperbilirubinemia and has been well documented in the literature \(^{(13,14,15)}\). In our study too as many as 18% of the cases were due to prematurity.
Sepsis is a significant cause of neonatal hyperbilirubinemia and the fact is supported by a very large number of literature published worldwide (16, 17).

Another important cause of hyperbilirubinemia is Rh incompatibility. Rh incompatibility has been shown as a risk factor for hyperbilirubinemia in newborns in many studies (4, 9, 18, 19). G6PD deficiency is a fairly common cause of neonatal hyperbilirubinemia but not investigated routinely in developing countries particularly because of the cost involved, as also observed in a study by Anil Shetty et al (5). G6PD deficiency can lead to severe neonatal hyperbilirubinemia, as reported in many studies. In a study conducted by Basoi S et al in a tertiary care hospital in West Bengal showed that 14.68% of the newborn were G6PD deficient and 23.8% of them developed severe neonatal hyperbilirubinemia compared to 12.5% of non G6PD deficient who developed severe neonatal hyperbilirubinemia (20). A cohort study was carried out to access the association between G6PD deficiency and neonatal hyperbilirubinemia. Data suggest that the G6PD deficient neonates are at increased risk of hyperbilirubinemia even in the nursery free from agent that can potentially cause hemolysis to G6PD deficient red cells. (21) Although hemolysis may be observed in neonates who have G6PD deficient and are jaundiced. (22) Other mechanisms appear to play a more important role in the development of hyperbilirubinemia. (23, 24, 25)

Infant born to diabetic mothers are also prone to hyperbilirubinemia. In our study too we had 11 neonates born to diabetic mother who had hyperbilirubinemia. Studies shows that large for gestational age infant of diabetic mother are at increased risk of hyperbilirubinemia then average for gestational age infant of diabetic mother and infant of non diabetic mothers and that increased heme turnover is a significant factor in the pathogenesis (26).

Breast milk jaundice occurs later in the newborn period with the bilirubin level usually peaking in the 6th to 14th day of life (27). This late onset jaundice may develop in up to one third of healthy breast fed infants (28). The underlying cause of breast milk jaundice is not clearly understood. Substance in maternal milk suggests beta glucuronidases and non esterified fatty acids, may inhibit normal bilirubin metabolism (29-32).

Cephalhematoma is a rare but not uncommon cause of hyperbilirubinemia. In our study we had 4 babies with Cephalhematoma leading to hyperbilirubinemia. Hypothyroidism polycythemia and Down's syndrome can also lead to hyperbilirubinemia in many neonates and this is well documented in many studies. In our study too few cases were seem to develop hyperbilirubinemia due to the above three causes.

CONCLUSION

ABO incompatibility is very common cause of neonatal hyperbilirubinemia. Although historically Rh incompatibility has been accorded much importance, ABO incompatibility should alert the attending doctor about the impending risk of significant neonatal jaundice. If discharged early written protocol should be followed where a revisit should be planned within 1 to 3 days for babies with any risk factors so that hyperbilirubinemia if any is detected and treated accordingly to prevent long term neurological morbidity. In this era where India has achieved significant advancement in the field of Medical Science, even a few cases of bilirubin encephalopathy and its associated sequelae is a grim reminder of the state of affairs of our health delivery system and ignorance among the population at large. Much needs to be done to spread awareness particularly in the rural areas where people still approach traditional healers to treat jaundice leading to delay in timely medical interventions.

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