Common Etiological Spectrum of indirect Hyperbilirubinemia in Neonates

IhsanulHaq, IsrarulHaq, Sardar Khan, Zahir Sayed

ABSTRACT

BACKGROUND: Jaundice is a clinical sign which indicates hemolysis and hyperbilirubinemia and making pathological hyperbilirubinemia as significant disease burden. Approximately 60% of term and 80% of preterm neonates become jaundiced in 1st week of neonatal life. Among them 5-10% patients need intervention and treatment for hyperbilirubinemia.

OBJECTIVE: To determine the common etiological spectrum of indirect hyperbilirubinemia during neonatal life.

MATERIAL & METHODS: This is a six months descriptive study that was conducted in neonatal unit, Department of Pediatrics, Saidu group of Teaching Hospital, Swat, from 1 July 2016 to 31 December 2016. Total of 201 Newborns upto 28 days of life who presented with jaundice were included in the study. Biodata and clinical profiles of all these newborns were collected on a pre-designed proforma. Special smear with retic count, direct coomb’s test, baby and mother blood group, total and fractionated serum bilirubin levels and G6PD level assessment were carried out in all these patients. Extremely premature neonates (gestational age<32 weeks), and neonatal sepsis were excluded from the study.

RESULTS: Out of 550 newborns admitted to neonatal unit during the six months’ study period (1 July to 31 December 2016), 201(36.54%) patients had jaundice with male 120(59.71%) and female 81(40.29%). Among these 201 jaundiced patients ABO incompatibility was found in 64 (31.84%) patients, 57(28.35%) patients found to be G6PD deficient, Rh incompatibility in 27(13.45%) and in 53(26.36%) patients no definite cause have been found. All jaundiced patient received phototherapy, exchange blood transfusion was done in 37patients (18.40%), double exchange transfusion was done in 3 patients (1.49%) and 4(1.99%) patients developed Kernicterus.

CONCLUSION: ABO incompatibility, G6PD deficiency and Rh incompatibility are the common causes of unconjugated hyperbilirubinemia. A delay in management or seeking medical advice can lead to Kernicterus.

Key Words: Glucose 6 phosphate dehydrogenase deficiency, ABO incompatibility, Rh incompatibility, Neonatal Jaundice, Hyperbilirubinemia, Total serum bilirubin (TSB), kernicterus.

INTRODUCTION

Jaundice is the most common clinical sign in neonatal life. Approximately 60% of term and 80% of preterm neonates become jaundiced in 1st week of neonatal life. Among them 5-10% need intervention and treatment for hyperbilirubinemia. Usually hyperbilirubinemia resolve by 7-10 days of life and the outcome is benign (termed as physiological Jaundice). The incidence of severe neonatal hyperbilirubinemia is higher in Asians than in whites.

Under certain circumstances, bilirubin may be toxic to the central nervous system and may cause neurologic impairment (kernicterus) even in healthy term newborns. Most studies however have failed to substantiate significant association between a specific level of total serum bilirubin (TSB) during hyperbilirubinemia in term newborns and subsequent IQ or serious neurologic abnormalities (including hearing impairment). Other studies have detected subtle differences in outcomes associated with TSB levels, particularly when used in conjunction with albumin binding tests and/or duration of exposure. In almost all published studies, the TSB concentration has been used as a predictor variable for outcome determinations.

ABO and Rh incompatibilities are important causes of hyperbilirubinemia. The reticulocyte count, a positive direct anti-globulin test and the presence of a sibling with neonatal jaundice have been determined to be the good predictors for the development of significant hyperbilirubinemia and severe hemolytic disease of the newborn.

ABO incompatibility found in the offspring of a mother with blood group type O and baby blood groups A or B. ABO incompatibility may exist approximately in 15-20% of all maternal and fetal pairs but hemolytic disease of the newborn is found in approximately 1% of group O mothers who carry high titer of IgG antibodies antenatally.
Common Etiological Spectrum of indirect Hyperbilirubinemia in Neonates

ABO incompatibility is the most common cause of iso-immune hemolytic disease of the newborn although hemolytic disease caused by ABO incompatibility is clinically milder than Rh incompatibility, however severe hemolysis occasionally occurs and in some cases requires exchange transfusion for severe hyperbilirubinemia. It is desirable to assess the accuracy of a group of tests to predict the development of neonatal hyperbilirubinemia in ABO incompatibility. Then, early treatment is available for minimizing the frequency of exchange transfusion.

Rh disease or Rh hemolytic disease is defined by maternal and fetal Rh (D) antigen incompatibilities and the consequences associated with maternal sensitization. This was the most common and severe cause of hemolytic disease of neonates in US and Europe about 60 year ago. It is now rare in developed countries where Rh prophylaxis has been used.11-12

Severe hyperbilirubinemia is defined as total serum bilirubin above the 95th percentile for age in hours, occurs in 8-10% of babies during the 1st week of life. Severe hyperbilirubinemia can lead to brain damage (kernicterus) because indirect bilirubin is fat soluble and can cross blood brain barrier.13-14

G6PD deficiency is most common enzyme deficiency in humans affecting 400 million worldwide,4 inherits as X-linked recessive disorder and polymorphic with more than 300 variants, G6PD is one of the most common causes of neonatal hyperbilirubinemia. It can also present late in life with hemolytic crisis.7,15 One third of patient with G6PD deficiency develop severe hyperbilirubinemia which if untreated could give rise to kernicterus, significant cause of death and neurodevelopmental delay.16

Significant neonatal unconjugated hyperbilirubinemia is also caused by Prematurity. Premature neonates are at increased risk of hyperbilirubinemia because of hepatic and intestinal immaturity. The postnatal maturation, uptake and conjugation may also be slower in premature neonates.17 The delayed initiation of enteral feeding in premature neonates may limit the intestinal flow and bacterial colonization, resulting a further increase in enterohepatic circulation aggravating hyperbilirubinemia.18

Several other risk factors are also responsible for hyperbilirubinemia in neonates including imbalance between production, conjugation and elimination. Severity of Hyperbilirubinemia is also affected by environmental factors and ethnicity.11

The aim of study was to know about the common causes of unconjugated hyperbilirubinemia in neonatal age group and we found three common etiological factors responsible for hyperbilirubinemia i.e. ABO, Rh incompatibilities and G6PD deficiency in our region, however the data is limited.

MATERIAL AND METHODS

This was a descriptive study, conducted in department of pediatrics neonatal unit, Saidu Teaching Hospital Swat. Duration was six months i.e. from 1 July to 31 December 2016. All neonates (Full term and preterm (POG=32 weeks) of age group(1-28 days) presented with jaundice were included in the study. Neonates having congenital anomalies i.e. cleft palate, cleft lip, clinical features of hypothyroidism, neonatal hepatitis, biliary atresia (direct hyperbilirubinemia) and those who were severely ill were excluded from the study.

Inclusion criteria:
1. Age: 1-28 days.
2. Full term and pre-term neonates (Gestational age >32 weeks)

Exclusion criteria:
1. Neonates having congenital anomalies.
2. Severely ill neonates.
3. Extremely premature neonates (Gestational age <32 weeks)
4. Neonates with Direct Hyperbilirubinemia.

The jaundiced neonates were then subjected to following investigations:
1. Blood smear with retic count (following the standard protocol).
2. Total Serum and fractionated bilirubin level (by colorimetric diazo method).
3. G6PD level (performed by screening kit by SPAN diagnostic BARI 96 MB 100-M 10).
4) Comb’s tests (using comb’s sera by Diagast France).
5) Baby and mother blood groups (using Diagast Blood grouping kit France)

**Procedure of the test for G6PD deficiency**
The test was performed using screening Kit by SPAN diagnostic B.A.R.I method (in Pakistan by global marketing services).

Red cell hemolysate was prepared by adding 2.5ml of water to 0.05ml of EDTA mixed blood and was shaken thoroughly and then allowed to stand for five minutes, 0.5 ml of buffer solution was mixed with powder dye and then 1 ml of red cell hemolysate was mixed with it. The mixture was layered with 2 ml of mineral oil and the tube was placed in incubator at 37°C without being exposed to light and was observed for change of color.

**Interpretation of the result**
The de-colorization time 20-60 minutes is normal, if >60 minutes then considered as G6PD deficient.

**RESULTS:**
Total number of admission n-550
The sex distribution and percentages of jaundiced patients are shown in tables 1 and 2 respectively.

The mean age of appearance of jaundice in ABO and Rh incompatibilities, G6PD deficient neonate is 1.5 ± 0.55 days while range 1-2.5 days

Mean age of jaundiced neonates at the time of admission was 4.25 ± 2.75 days. Range 1- 28 days.

All patients received emergency management. They have been rehydrated and received double phototherapy, 37 patients(18.40%) received exchange blood transfusion, double exchange transfusion was done in 3 patients (1.49%). Four patients developed kernicterus.

**DISCUSSION**
Neonatal jaundice constitutes 36.54% admission to the neonatal unit Saidu group of Teaching Hospital during the six months' study period from 1 July to 31 December 2016.

The prevalence and etiology of un-conjugated hyper bilirubinemia in neonates varies in different parts of the world from country to country and even in different areas of the same country'.

<table>
<thead>
<tr>
<th>Table 1: sex distribution of neonatal jaundice</th>
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<tbody>
<tr>
<td>Total</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<th>Table 2: Causes of Neonatal jaundice n = 201</th>
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<tr>
<td><strong>Cause of Jaundice</strong></td>
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<td>------------------------</td>
</tr>
<tr>
<td>ABO incompatibility</td>
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<tr>
<td>G6PD deficiency</td>
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<tr>
<td>Rh Incompatibility</td>
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<tr>
<td>Other Causes</td>
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<td>Total</td>
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</tbody>
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Hemoglobin level with mean standard deviation and range along with other parameters retic count, serum bilirubin level are given in table 3.

<table>
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<th>Table 3: laboratory finding in G6PD with mean and Range</th>
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<tr>
<td><strong>Test (Unit)</strong></td>
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<td>-----------------</td>
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<tr>
<td>Hemoglobin(gm/dl)</td>
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<tr>
<td>Reticulocyte count</td>
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<tr>
<td>Serum Total Bilirubin(mg/dl)</td>
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The present study reviews the common risk factors responsible for neonatal jaundice, however in 53 (26.36%) patients the cause of hyperbilirubinemia was not identified, this is consistent with a number of national and international studies.\textsuperscript{1,12}

Previous research works which have been conducted at national level showing different results. A study conducted in neonatal unit of Lady Reading Hospital Peshawar showed that neonatal jaundice constituted 23\% of total admission\textsuperscript{3} while in our study the percentage of jaundiced patients is a bit high.

In another study which has been conducted in SCBU (Special Care Baby Unit) Khyber Teaching Hospital Peshawar, neonatal jaundice constituted 39.85\% of total admission which is compatible with our results\textsuperscript{8}.

Several international studies also support our results in regards of neonatal jaundice as significant burden of admission to the neonatal unit of Pediatrics Department\textsuperscript{4,19}.

In our study we found three important causes of neonatal jaundice ABO, Rh incompatibilities and G6PD deficiency, these findings are consistent with several national and international studies results\textsuperscript{3,12,19,20}.

G6PD deficiency inherits as X linked recessive disorder and obviously, it would be evident in male sex but females couldn't be excluded. In our study male to female ratio of G6PD deficiency is 3.3:1.

There is variation in results of G6PD deficiency in different ethnic group in the same region as showed in our study that is more common in Pathans\textsuperscript{1,8}.

Studies on G6PD deficiency conducted internationally showed low frequency in the Middle East compared with results from China, Nigeria and Thailand\textsuperscript{10,16}.

Result regarding sex distribution of G6PD deficiency is different. Study conducted at local level Timergara by Rahim F, male to female ration is 7:1 which shows comparatively male predominance\textsuperscript{21}.

Time of presentation in previous research work is quite early as in our study, but in some studies the presentation is delayed.

In our study four patient developed kernicterus. The reason was delay of seeking medical advice even though exchange blood transfusions were carried out more than once in hope of treating hyperbilirubinemia and ultimately reversing bilirubin encephalopathy (Kernicterus). The same has also been reported by Vinod et al in his research article.\textsuperscript{22}

Patient who presents with early sign of kernicterus were subjected to aggressive management in the form of exchange transfusion with poor out come in the form of neurological handicap. The same has also been observed by Khan et al in a national study\textsuperscript{23}.

It is evident from our research that early diagnosis by proper screening at birth and proper management will improve the outcome in the form of morbidity and mortality as also stated by practice guideline regarding management of hyperbilirubinemia by American academy of Pediatrics (AAP)\textsuperscript{6}.

In our study phototherapy and exchange transfusions were very effective in reducing the serum bilirubin level and ultimately preventing severe hyperbilirubinemia and kernicterus.

**CONCLUSION:**

ABO incompatibility, G6PD deficiency and Rh incompatibility are the common causes of unconjugated hyperbilirubinemia. A delay in management or seeking medical advice can lead to Kernicterus.

**REFERENCES**

4. An early (sixth-hour) serum bilirubin measurement is useful in predicting the development of significant hyperbilirubinemia and severe ABO hemolytic disease in a selective high-risk population of newborns with ABO incompatibility. Pediatrics, 109(4), e53-e53.


