

Clinical Severity of Neonatal Jaundice Especially in ABO and Rh Incompatibility in Northern India

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ABSTRACT

Background: Clinical severity of neonatal jaundice especially in ABO and Rh incompatibility in northern India. The Aims & Objective is to assess role of minor blood group incompatibility as a cause of neonatal jaundice and follow up of late anemia later on. **Methods:** This was a prospective observational study of 180 neonates with unconjugated hyperbilirubinemia requiring phototherapy and/ or exchange transfusion, presented at tertiary care neonatal unit during July 2019 to May 2020. Detailed history, physical examination and laboratory work up were performed. In case, if major blood group incompatibility was found negative, the blood was further processed for G-6PD status and for non-Rh D incompatibility by testing non-Rh D antigens status. **Results:** Among etiology of jaundice commonest cause is ABO incompatibility (63 cases) followed by Rh (D+C+E) incompatibility (54cases) followed by sepsis (36). **Conclusion:** Blood group incompatibilities (ABO & Rh D) and sepsis are important cause of unconjugated hyperbilirubinemia in neonates requiring treatment. Though minor blood group incompatibility (Rh C & Rh E) constitutes not much cases but can be as severe as major blood group incompatibility (Rh D), needs to be investigated.

Keywords: Neonatal jaundice, clinical severity, Rhesus (Rh) D, C, E incompatibility.

INTRODUCTION

Neonatal jaundice is a very well-known condition requiring treatment.^[1-3] It occurs in 70-80% of the neonates, more commonly in preterm.^[4,5] Although only 5-10% of the newborns needs to be treated due to pathological hyperbilirubinemia, the threat of neurologic damage (bilirubin encephalopathy) always remains, especially with very high bilirubin level.^[6,7] Knowing etiology of hyperbilirubinemia is necessary for optimal management of the patients and it may have role for subsequent pregnancies. However, the etiology of neonatal hyperbilirubinemia may remain obscured in more than half of the cases^[8-10]. Hemolytic disease of the newborn (HDN) is one of the common pathologic cause of hyperbilirubinemia during the early neonatal period, mostly due to Rh incompatibility, ABO incompatibility, G6PD deficiency and rarely induced by other alloimmune antibodies.^[9,10] Despite available guideline to perform pre-discharge hour specific serum bilirubin in infants and their follow-up to predict severe hyperbilirubinemia,^[7,11] wide practice of anti-D prophylaxis to prevent Rh D disease and wide availability of effective phototherapy and exchange

transfusion for treatment of hyperbilirubinemia, neonates presenting at tertiary hospital with severe hyperbilirubinemia and bilirubin encephalopathy is not a rarity. There is very little study showing role of minor blood group incompatibility in causation of pathological neonatal jaundice.^[12-15] The present study aimed to delineate the etiology of pathological unconjugated hyperbilirubinemia (requiring treatment) in neonates, its clinical profile and to explore the role of minor blood group (Rh C & Rh E) incompatibility and follow up hemoglobin to detect anemia later on.

MATERIALS AND METHODS

This study was performed at tertiary care hospital after approval by the Institutional ethics committee. Subjects were neonates with unconjugated neonatal jaundice requiring phototherapy. Complete physical examination of the neonate was performed carefully and the data including weight on admission, serum bilirubin and hemoglobin and presence of acute bilirubin encephalopathy (ABE) were recorded. Only moderate to severe grade of ABE was noted, based on mental status, muscle tone and cry¹⁶. Neonates having congenital anomalies, weight <600 g, gestational maturity <26 wks, and perinatal asphyxia with hypoxic ischemic encephalopathy (HIE- stage 3) were excluded.

All neonates fulfilling inclusion criteria were investigated for major blood group status (ABO & Rh D), total serum bilirubin (TSB) as well as direct fraction, complete blood count, reticulocyte

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count and peripheral blood smear & maternal blood group. Sepsis screen and blood culture were performed when indicated. Coomb's test was performed in cases having blood group incompatibility and/ or evidence of hemolysis. A diagnosis of ABO incompatibility was made when the mother had blood group 'O' and the baby's blood group was either 'A' or 'B'. Similarly, diagnosis of Rh D incompatibility was made when mother is Rh D negative but baby is Rh D positive. In case if more than one etiology was identified in a patient, the predominant cause leading to hyperbilirubinemia was ascertained by consensus. When no ABO & or Rh D incompatibility scenario was detected (N=89), we performed quantitative test for G-6-PD deficiency and osmotic fragility test in the infant; and agglutination test in both the infant and their mother to detect Rh C and Rh E antigens on the RBCs. Follow up hemoglobin was done to rule out late anemia after 1 month of discharge.

The decision to initiate phototherapy and to perform exchange transfusion was uniform and in accordance with unit protocol, based on American Academy of Pediatrics, clinical practice guideline – 2004 & National Neonatology Forum India- 2010. Repeat serum bilirubin measurements and complete hemogram were performed as indicated. Other parameters recorded were evidence of hemolysis (Hb<13gm% or PCV <40 along with reticulocyte count > 6%), peak TSB level, age (days) at peak

TSB, duration of phototherapy provided (days) & need of exchange transfusion and its number. For the statistical analysis of results SPSS 22.0 software was used.

RESULTS

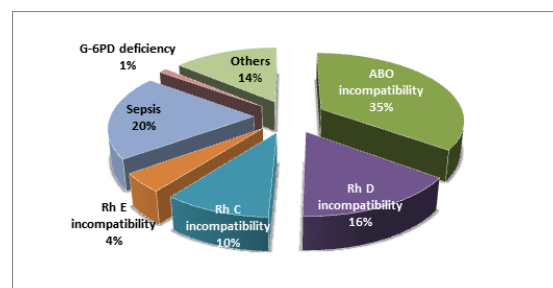


Figure 1: Causes of Neonatal unconjugated hyperbilirubinemia

Table 1: Causes of Neonatal unconjugated hyperbilirubinemia

| Causes | No. Neonates | |
|----------------------|--------------|----------------|
| | N= 180 | Percentage (%) |
| ABO incompatibility | 63 | 35 |
| Rh D incompatibility | 28 | 15.5 |
| Rh C incompatibility | 18 | 10 |
| Rh E incompatibility | 8 | 4.4 |
| Sepsis | 36 | 20 |
| G-6PD deficiency | 2 | 1.1 |
| Others | 25 | 14 |

Table 2: Baseline Maternal and Neonatal parameters in different type of neonatal jaundice

| Parameters | Major incompatibility | | Minor incompatibility | |
|-----------------------------------|-----------------------|---------------------|-----------------------|--------------------|
| | ABO Incom. N=63(%) | Rh D Incom. N=28(%) | Rh C Incom. N=18(%) | Rh E Incom. N=8(%) |
| Parity | | | | |
| Primi | 40 (63.4) | 10(35.7) | 8(44.4) | 4(50) |
| Multi | 23(36.5) | 18(64.3) | 10(55.5) | 4(50) |
| Mode of delivery | | | | |
| Vaginal | 50 (79.4) | 10(35.7) | 14(77.7) | 6(75) |
| Caesarean | 13 (20.6) | 18(64.3) | 4(22.2) | 2(25) |
| Male : Female | 40:23 | 18:10 | 8:10 | 6:2 |
| Term | 40(63.5) | 18(64.3) | 11(61.1) | 4(50) |
| Preterm | 23(36.5) | 10(35.7) | 7(38.8) | 4(50) |
| Predominant mother's milk feeding | 40 (63.5) | 20(71.4) | 13 (72.2) | 5 (62.5) |

Table 3: Severity of neonatal jaundice in ABO and Rh incompatibility (N=117)

| Severity of neonatal jaundice | Major incompatibility | | Minor incompatibility | |
|--------------------------------------|-----------------------|---------------|-----------------------|---------------|
| | ABO | Rh (D) Incom. | Rh(C) Incom. | Rh (E) Incom. |
| Evidence of hemolysis N=22 | 7 | 11 | 3 | 0 |
| Peak TSB ⁺ (mg%) mean ±SD | 17.4±6.2 | 21.7±8.04 | 16.2±4.2 | 16.2±3.4 |
| Acute bilirubin encephalopathy N=7 | 3 | 4 | 0 | 0 |
| Exchange transfusion N=28 | 9 | 17 | 2 | 0 |

During the study period, 1070 patients admitted in the neonatal unit and of these 180 fulfilled the inclusion criteria and were investigated. ABO incompatibility was the commonest cause of pathological hyperbilirubinemia, followed by Rh incompatibility (D+C+E=30%), while the cause could not be found out in 14% of the cases [Figure 1]. Among rhesus minor blood group incompatibility

(Rh C & Rh E) constitutes around 48.1% of cases [Table 1]. Baseline maternal and neonatal parameters of the cases having neonatal jaundice due to ABO & Rh incompatibility are displayed in [Table 2]. There was male preponderance in all the groups of causes except Rh C incompatibility. Rh blood group incompatibilities (Rh D, Rh C & Rh E groups) as a cause of hyperbilirubinemia were more commonly

observed in babies born to multipara mother while in ABO incompatibility most of cases seen in primiparous mother. Most of cases of neonatal jaundice seen in term baby except Rh E where distribution of cases present equal. [Table 3] shows severity of neonatal jaundice with ABO & Rh incompatibility. Evidence of haemolysis was detected in 22 cases with maximum haemolysis in Rh D incompatibility followed by ABO and least in Rh E incompatibility. The number of patients requiring exchange transfusion was maximum in Rh D incompatibility group (17) followed by ABO incompatibility (9), Rh C group (2) while none in the Rh E incompatibility group. It is shown in our

study that between minor blood group incompatibility Rh C is more severe than Rh E. [Table 4] showing basic neonatal characteristics, lab investigation, and management of neonatal jaundice. The duration of phototherapy requirement (days) was longer in the Rh D group and more babies of Rh D group underwent exchange transfusion (57.1%). Out of 7 acute bilirubin encephalopathy 4 were present in Rh D incompatibility while 3 in case of ABO incompatibility. [Table 4] showing that earliest age of admission for jaundice is in Rh D incompatibility. Maximum cases of late anemia develop in Rh D (14.3%) followed by Rh C (5.5%), ABO (3.2%) and none in Rh E incompatibility.

Table 4: Neonatal characteristics, lab investigations and treatment

| Parameters | ABO Incom. N=63(%) | Rh (D) Incom. N=28(%) | Rh (C) Incom. N=18(%) | Rh (E) Incom. N=8(%) |
|--|-----------------------|--------------------------|--------------------------|-------------------------|
| Age at admission (days) mean±SD | 2.5±1.2 | 1.8±1.3 | 2.8±1.4 | 2.8±0.9 |
| TSB†at admission (mg/dl) mean±SD | 15.5±7.0 | 15.7±11.38 | 13.1±7.1 | 13.3±2.8 |
| Age at peak TSB† (days) mean±SD | 3.8±1.3 | 3.4±1.3 | 4.1±1.5 | 4.2±0.4 |
| Coomb's test: +ve | 2(3.2) | 6(21.4) | 3(16.6) | 0(0) |
| -ve | 4(6.3) | 7(25) | 8(44.4) | 5(62.5) |
| Not done | 57(90.4) | 15(53.5) | 7(38.9) | 3(37.5) |
| Duration of phototherapy mean±SD | 7.92±1.42 | 8.45±1.12 | 7.94±1.29 | 6.17±2.04 |
| Follow up hemoglobin for anemia (after 1 month of discharge) | | | | |
| present | 2(3.2) | 4(14.3) | 1(5.5) | 0(0) |
| absent | 40(63.5) | 14(50) | 12(66.6) | 3(37.5) |
| lapse in follow up | 21(33.3) | 10(35.7) | 5(27.8) | 5(62.5) |

DISCUSSION

In our study, the commonest etiology of hyperbilirubinemia requiring treatment was blood group incompatibility, followed by sepsis which is contrary to report by Narang et al,^[8] from India who reported Idiopathic (57.7%) followed by G-6-PD (17.7%), ABO (6.1%) and least in Rh D(2.9%). ABO incompatibility comprise of 35% of cases followed by 30% of Rh incompatibility (RhD-15%, RhC-10% & Rh C-4.4%). 20% of cases occurs due to sepsis and 14% of cases remained idiopathic. ABO incompatibility scenario occur in mother with O blood group with baby blood group either A or B, whereas Rh scenario occur when a Rh negative mother have a baby with a Rh positive blood group. Immune mediated haemolysis and hyperbilirubinemia are usually related to Rh D and ABO incompatibility, rarely due to other minor blood group incompatibilities such as anti-C, anti-E. In the Rhesus (Rh) system, there are five major antigens of clinical importance: D, C, E, c, and e. The most instances of Rh isoimmunisation are due to the Rh D antigen. Since the introduction of anti-D immunoglobulin, the cases of Rh-D haemolytic disease and hyperbilirubinemia has markedly declined, however, it was the case in 15.5% of patients in our study, reflecting inadequate obstetric care. Sporadic cases of haemolysis and

hyperbilirubinemia in neonates have been reported due to minor blood group incompatibility.^[15] In the present study, Rh C and Rh E incompatibility was found in 10% and 4.4% of cases respectively. Isoimmunisation due to non-Rh antigens is similar to Rh D is antigen, but the disease is usually milder especially with Rh C, Rh E however, combination of the antigens can cause severe foetal and neonatal haemolytic disease.^[18] The present study found Rh D incompatibility to be more severe than Rh C and ABO incompatibility.

Sepsis is known to cause of haemolysis and hyperbilirubinemia, probably by increasing oxidative stress damaging red blood cells that are susceptible to cell injury.^[19] Incipient sepsis/ bacteraemia has been reported as a rare cause of hyperbilirubinemia in developed world, however, it accounted for 20% of our cases, reflecting poor perinatal care. The etiology of hyperbilirubinemia could not be found in 25 (14%) of our neonates. The major limitations of the study were that we have not tested for Rh c & Rh e incompatibility including other minor blood group incompatibilities. Also, because of logistic reason, we could not perform antibody titre against various blood group antigens and indirect coomb's test in maternal blood which would have strengthened the diagnosis of blood group incompatibilities.

Late onset anemia is quite common in case of blood group incompatibility due to presence of maternal

antibody which continues to destroy neonatal RBC leading late onset anemia but it may be biased by various facts like physiological anemia of infancy and iron deficiency anemia so more detailed work up of anemia is required in absence of haemolysis.

CONCLUSION

The take home message of our study is that minor blood group incompatibility also constitutes significant proportion (14.4%) of cases and some cases may be as severe as requiring exchanges transfusion. But we have not tested for this in all cases and this may be a limiting factor of our study.

Late onset of neonatal anemia (after 1 month of discharge) is expected in major blood group incompatibility due to presence of maternal antibody but it is not so uncommon in minor blood group incompatibility also. So we have to be aware about developing anemia in case of neonatal jaundice with evidence of hemolysis.

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