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Case Report

Hemolytic Jaundice in Newborn with Risk of Neurotoxicity: Unravelling the Dilemma in Management

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Abstract: Hemolytic disease of the fetus & newborn (HDFN) is a disorder where RBCs are destroyed by maternal erythrocyte alloantibodies and there is increased production of unconjugated bilirubin and anemia and in severe cases, hydrops in the fetus. Rh & ABO incompatibility are the most common causes of severe unconjugated hyperbilirubinemia in newborn babies. Though many treatment options are available for this condition, phototherapy stands first and most important of these all. This article signifies the successful management of OB incompatibility with hemolytic jaundice and clinical sepsis in a term neonate who was successfully managed with phototherapy along with serial BIND (Bilirubin Induced Neurological Dysfunction) scoring rather than going for other treatment options such as intravenous immunoglobulin or exchange transfusion.

Keywords: Hemolytic jaundice, incompatibility, newborn, phototherapy, neurotoxicity.

INTRODUCTION

HDFN was first described by Dr Louis K Diamond in 1932 where he wrote about erythroblastosis fetalis in newborn based on peripheral smears. Iso-immune hemolytic anemia occurs when Rh or ABO incompatibility and occasionally minor blood group incompatibility occurs between the mother and the newborn infant [1, 2].

A, B, AB & O are the four major blood group types. This is the most common form of mismatch. In most cases, ABO incompatibility is not so severe. But in rare occasions ABO incompatibility can lead to hemolytic anemia with neonatal hyperbilirubinemia which needs intensive phototherapy and, in some cases, exchange transfusion. Rh isoimmunization can cause severe anemia and jaundice which can be prevented in most cases by immunization of the mother with anti-D antibodies [3].

When a fetus inherits paternal blood group factors that are absent in the mother, antepartum or intrapartum feto-maternal bleeding can provoke a maternal immune response. This produces maternal antibodies against the antigens in fetal blood. Hence the fetal and neonatal erythroid cells are destroyed by maternal IgG erythrocyte alloantibodies leading to anemia and hydrops in fetus and hyperbilirubinemia & kernicterus in the newborn. Managing HDFN therefore needs both antenatal and postnatal efforts.

Antenatal care includes the monitoring of high-risk cases by laboratory testing and ultrasound to detect fetal anemia. Anti-D immune-prophylaxis plays an important role in prevention of Rh-incompatible hemolytic disease [4]. Postnatal care consists of intensive phototherapy and exchange transfusion to treat severe hyperbilirubinemia. Despite various alternative measures to treat hyperbilirubinemia, phototherapy remains the standard of care [5, 6].

CASE REPORT

A term (39 weeks gestation) female newborn was admitted in NICU in view of respiratory distress at birth, there was no history of perinatal asphyxia. Baby was on nasal oxygen support and total parenteral

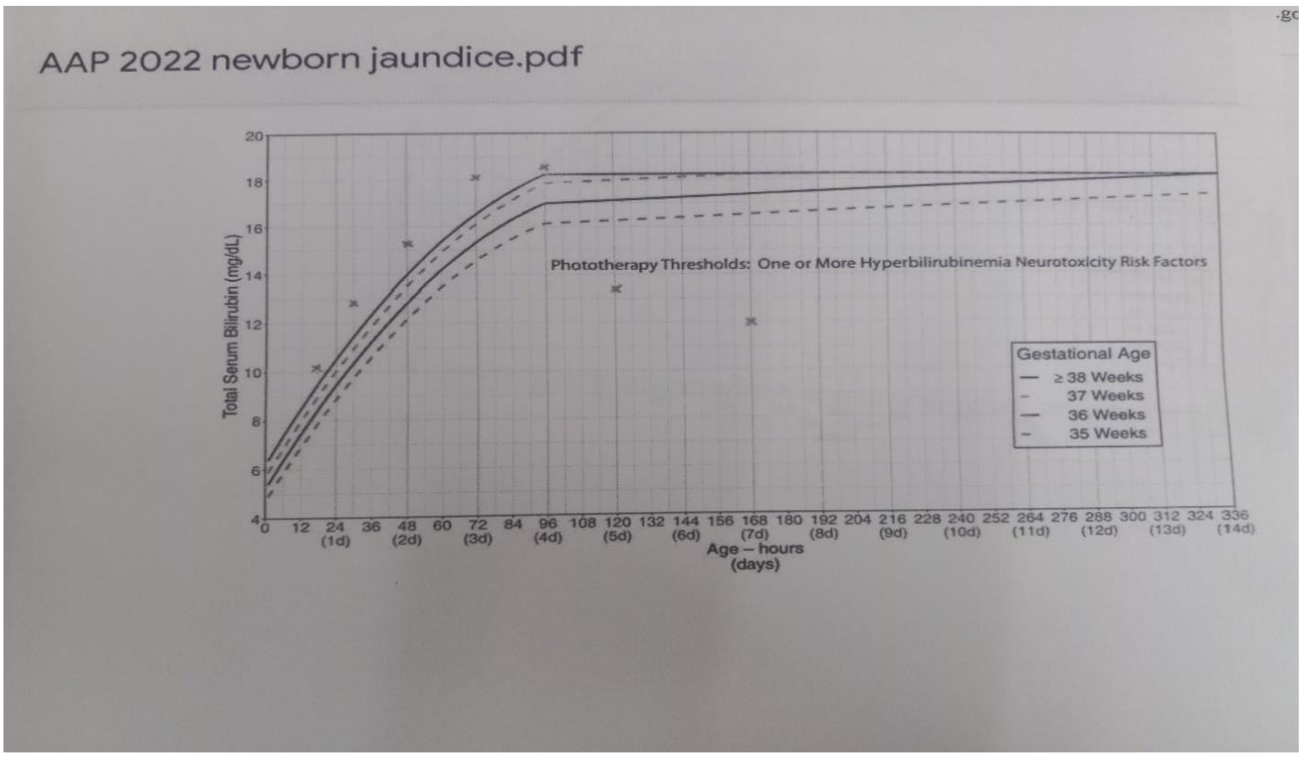
nutrition. Blood counts showed neutrophilic leukocytosis and CRP levels were elevated. Hence baby was started on first line intravenous antibiotics as per the institutional protocol. The baby was jaundiced within 24 hours of life and her serum bilirubin levels were 10.1 mg/dl, with unconjugated bilirubin fraction of 9.1 mg/dl and conjugated bilirubin of 1.01 mg/dl. On clinical examination there was no splenomegaly, her serum TSH levels were within normal range 6.21 µIU/ml. Baby had an albumin level of 4.2 g/dl.

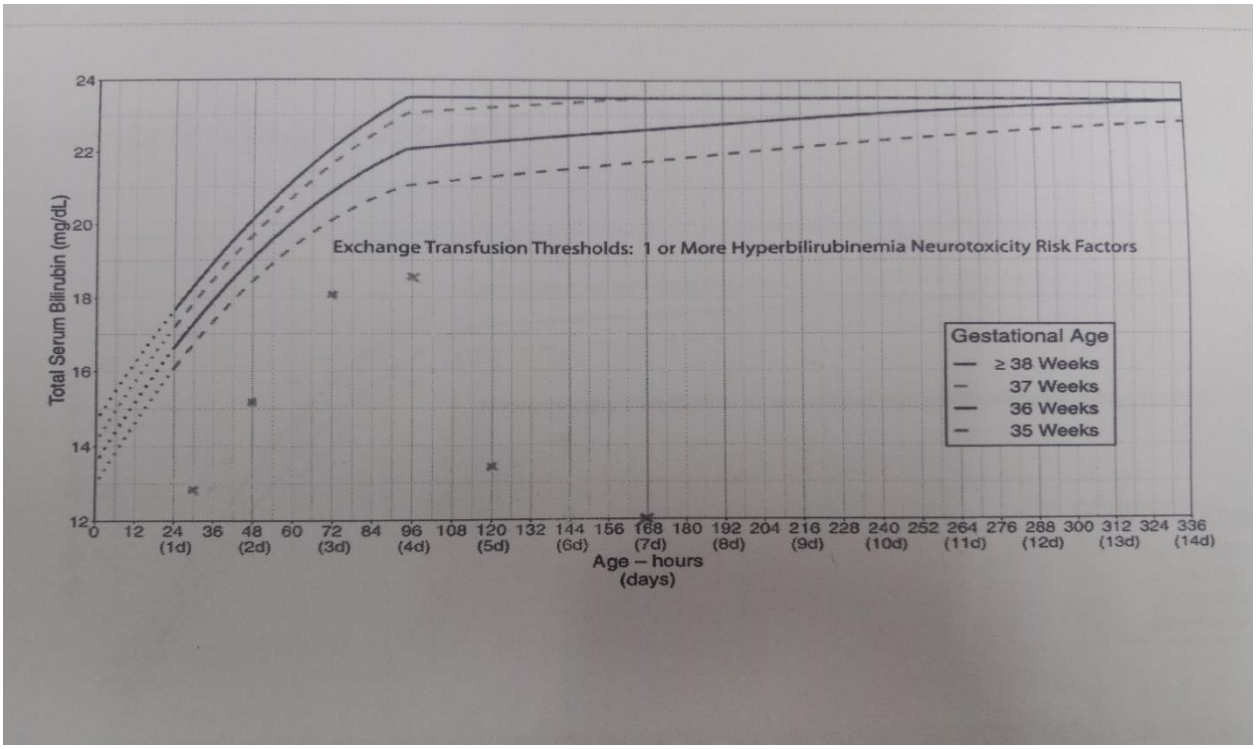
Parameter	D1	D2	D4
Hemoglobin (g/dl)	21.5	19	18.6
HCT (%)	64.0	61.5	56.0
MCV (fl)	102.4	112.6	102.1
MCH (pg)	36.0	36.0	35.7
MCHC (g/dl)	35.1	32.0	34.9
RDW-CV (%)	12	17.5	12

Parameter (mg/dl)	18 HOL	30 HOL	48 HOL	72 HOL (D3)	D4	D5	D7
Total serum bilirubin	10.1	12.9	15.2	18.1	18.6	13.4	12
Unconjugated bilirubin	9.1	11.9	14.0	16.7	17.3	12.4	11.1
Conjugated bilirubin	1.01	1.02	1.22	1.41	1.35	1.02	0.9

The baby's blood group was B-positive and her mother's blood group was O-positive. According to the updated 2022 American Academy of Pediatrics (AAP) nomogram for neonatal hyperbilirubinemia, the baby had more than one neurotoxicity risk factors and her bilirubin levels were in the range for phototherapy. The baby was started on intensive double surface phototherapy. Her bilirubin levels continued to raise even with phototherapy, but not exceeding the range of exchange transfusion. The baby was given continuous intensive phototherapy and she was monitored crucially with BIND scoring periodically which remained zero throughout the treatment period and on follow-up as well.

Direct Coomb's test was positive in this baby (+++) indicating hemolytic jaundice. The reticulocyte count was elevated and the smear showed few schistocytes. Heel prick test was negative for G6PD deficiency. Baby's serum calcium levels were periodically monitored in view of prolonged phototherapy treatment and it was maintained in the normal range. Respiratory distress settled after 48 hours of birth and baby was started on breast feeding. After 3 days of antibiotics, leukocytosis settled down, CRP turned negative. Her blood culture was negative for any micro-organisms. Hence antibiotics were stopped. Intensive phototherapy was continued due to hyperbilirubinemia in range of phototherapy as per AAP norms.





On day 5 of life, the serum bilirubin levels declined to normal range and the baby was shifted to mother-side and observed for rebound hyperbilirubinemia for the next 48 hours. Repeat serum bilirubin levels remained in the normal range and then the baby was discharged on seventh day of life. Postnatally, the baby was followed up periodically and the developmental milestones were attained appropriate for age.

CASE DISCUSSION

According to Fisher-Race nomenclature, the primary RBC antigens involved in blood typing are C, c, D, E & e. Furthermore, many antigen variants have been identified, including Cw & Du antigens, though less frequently encountered. Rh alloimmunization due to the D antigen is the most common cause of HDFN [3]. Other non-Rh antigen variants including Lewis, I, Kell, Duffy & Kidd can also be associated with HDFN. Lewis & I are IgM antibodies and do not cross the placental barrier; therefore, HDFN doesn't result from these antigens. However, the Kell antibody (anti-K), typically produced following a transfusion, can result in severe HDFN with severe anemia, hydrops fetalis & fetal death, though less hyperbilirubinemia than D alloimmunization [4].

During the first few days after birth, there is physiological imbalance between bilirubin production and elimination. Approximately 60% of term and 80% of preterm newborns develop clinically detectable jaundice in the first week after birth. The activity of the bilirubin conjugating enzyme, UGT1A1 – Uridine diphosphate-glucuronyl transferase is diminished in term neonates to about 1% of that of healthy adults. Some newborns may have a high rate of bilirubin production, but in case of relatively mature UGT1A1 activity, they may not develop hyperbilirubinemia [7]. Preterm neonates have even lower UGT1A1 activity and are therefore at higher risk of developing hyperbilirubinemia [8].

Inherent ABO incompatibility, which occurs in 15-25% of pregnancies is one of the causes for HDFN. Only about 1% of those with high IgG titers will develop HDFN due to ABO incompatibility. Compared to Rh-induced HDFN, ABO incompatibility generally causes a less severe HDFN. Studies have poised that this may be due to fetal RBCs expressing fewer ABO blood group antigens than adults or that ABO blood group antigens are expressed by many tissues, reducing the chance that antibodies specifically target the antigen on fetal RBCs [9, 10]. Clinical features include anemia, jaundice, significant lethargy, hepatosplenomegaly, tachycardia, tachypnoea and hypotension. In severe cases, hydrops fetalis may arise, a severe manifestation associated with a significant mortality rate of >50% [11, 12].

The main aim is to provide intensive phototherapy maximum of the infant's surface area as possible. Intensive phototherapy requires a narrow-spectrum LED blue light with an irradiance of at least 30 $\mu W/cm^2/nm$ at a wavelength between 460 to 490 nm. Light outside this range provides unnecessary heat and potentially harmful waves [6, 13]. The advantage of intensive phototherapy is that it can quickly lower the bilirubin levels and shorten the duration of treatment. The primary goal of phototherapy is to decrease the further increases in the bilirubin concentration that would lead to exchange transfusion. The AAP recommended phototherapy thresholds are far below

those at which overt acute bilirubin neurotoxicity or kernicterus occurs. Rebound hyperbilirubinemia is defined as a TSB concentration that reaches the phototherapy threshold within 72 to 96 hours of discontinuing phototherapy. Infants who receive phototherapy at birth are more likely to experience rebound hyperbilirubinemia than those whose treatment with phototherapy starts on readmission. The risk factors for rebound hyperbilirubinemia include younger postnatal age (less than 48 hours), hemolytic jaundice, gestational age <38 weeks, and higher serum bilirubin at the time of phototherapy discontinuation [13, 14].

Although it has been shown that IVIG treatment reduces the duration of phototherapy and hospitalization, the use of IVIG in hemolytic disease due to ABO incompatibility has been controversial in recent years [15, 16]. Studies have concluded that IVIg transfusion didn't decrease either phototherapy duration as well as hospitalization duration or the need for exchange transfusion in newboms with ABO hemolytic disease [17, 18]. An international panel of experts committee in 2022 concluded that IV IG should not be routinely used to treat Rh or ABO antibody-mediated HDN [19].

A multicenter study conducted by Okulu *et al*., in 2021 concluded that the most common indication for exchange transfusion in neonates is hemolytic jaundice (63.6%) and the adverse events were reported in 11.4% cases, the most common being thrombocytopenia [20]. Another retrospective study from Serbia in 2016 had the similar findings with ABO & Rh incompatibility being the most common causes for severe hyperbilirubinemia. It also concluded that exchange transfusion, used as therapy for severe hyperbilirubinemia, trended downwards over the period of 17 years in the retrospective analysis [21] because of the appropriate usage of phototherapy in jaundiced neonates.

Delayed diagnosis or treatment of the pathologic unconjugated hyperbilirubinemia can lead to neurological deficits, defined as bilirubin induced encephalopathy. The incidence of BIE is much more common in underdeveloped countries where diagnosis is delayed owing to inadequate postnatal care. BIE can be acute & transient or chronic & permanent with tetrad of symptoms including visual (upward gaze palsy), auditory (sensory neural hearing loss), dental enamel dysplasia and extrapyramidal disturbances (choreoathetosis cerebral palsy) [22].

CONCLUSION

Diagnosing hemolytic jaundice early and starting phototherapy at the right time is of much importance since bilirubin encephalopathy can lead to permanent neurological dysfunction. Though other treatment options like intravenous immunoglobulins, oral phenobarbitone and metalloporphyrins are available, studies have proven that they all are inferior to phototherapy. Exchange transfusion is advisable when the serum bilirubin levels fall in the range as per 2022 AAP updated nomogram. Though exchange transfusion has its disadvantages, in cases of bilirubin induced neurotoxicity it's the preferred mode of management. Hence early recognition of jaundice, serial BIND scoring and timely intervention by intensive phototherapy can prevent the chances of exchange transfusion and its potential complications as in our case.

Conflicts of Interest: Nil.

Informed Consent: Obtained from parents.

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