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Hemolytic Diseases of Newborns in Al-imamain Al-kadhumain Medical City in Baghdad: A corss-sectional Study

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بِسمِ اللهِ الرَّحمنِ الرَّحيم

الَّذِي خَلَقَنِي فَهُوَ يَهْدِينِ (78) وَالَّذِي هُوَ يُطْعِمُنِي
وَيَسْقِينِ (79) وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ(80)

صدقَ اللهُ العظيم

سورة الشعراء

Dedication

To our wounded and patient country "Iraq".

To our families for their abundant support.

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First of all, I would like to praise Allah the Almighty, for helping me complete this work.

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List of Abbreviations

HDN	Hemolytic disease of Newborn
IUT	Intra-uterine Transfusion
RBCs	Red Blood Cells
G6PD	Glucose 6-Phosphate Dehydrogenase
HcT	Hematocrit
ExTx	Exchange Transfusion
PLT	Platelet
MPV	Mean Platelet Volume
PCT	Plateletcrit
CBC	Complete Blood Count
NICU	Neonatal Intensive Care Unit
WBC	Wight Blood Cells
Hgb	Hemoglubin
Hct	Hematocrit
UAC	Umbilical Arterial Catheter
UVC	Umbilical Venous Catheter

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Abstract

Background: Hemolytic disease of the Newborn is characterized by the presence of IgG antibodies in maternal circulation, which causes hemolysis in the fetus by crossing the placenta and sensitizing red cells for destruction by macrophages in the fetal spleen with consequent hyperbilirubinemia.

Aim: To assess the prevalence of Hemolytic Diseases of Newborns. Also assess the consequences of Hemolytic Diseases of Newborns among the studied groups.

Methods: Infants with indirect hyper-bilirubinemia aged from birth to 7 days old were taken as subjects and were compared with a control group of healthy infants. Inclusion criteria were, age was only neonates from birth to 7 days and confirmed Hemolytic Diseases of Newborns by clinical presentation and laboratory findings. Exclusion criteria were a history of intrauterine growth retardation, known chromosomal abnormalities and other genetic disorders. Questionnaire was given to the parents and had included the name, age, sex, maturity and other demographic data. Phototherapy and exchange transfusion were given to the patients. Laboratory investigations carried out were hemoglobin, hematocrit, and peripheral smear, reticulocyte count in neonates and ABO and Rh D status of father if not done during pregnancy.

Result: The mean age of patients was 2±1.29 (days), also the mean of TSB level, Hb, RBC, WBC, PLT, Retics as 9.97±5.7, 17.8±1.32, 4.36±0.96, 18.74±2.1, 80±7.25 and 3.32±3.6 respectively. ABO incompatibility was the leading cause of hemolysis (48%) followed by Rh incompatibility (22%), septicemia in (26%) and Glucose 6 Phosphate Dehydrogenase deficiency (4%).

Conclusions: In this study, it is concluded that alloimmune hemolytic anemia due to ABO incompatibility is the most common cause of Hemolytic Diseases of Newborns. Gender of the baby and gravidity of the mother does not affect the outcome of disease process.

Introduction

Hemolytic Disease of the Newborn (HDN), also known as erythroblastosis fetalis, isoimmunization, or blood group incompatibility, occurs when fetal red blood cells (RBCs), which possess an antigen that the mother lacks, cross the placenta into the maternal circulation, where they stimulate antibody production[1]. The antibodies return to the fetal circulation and result in RBC destruction[2].

DIFFERENTIAL DIAGNOSIS of hemolytic anemia in a newborn infant[3]:

-Isoimmunization.

-RBC enzyme disorders (e.g., G6PD, pyruvate kinase deficiency).

-Hemoglobin synthesis disorders (e.g., alpha-thalassemias).

-RBC membrane abnormalities (e.g., hereditary spherocytosis, elliptocytosis) -Hemangiomas (Kasabach Merritt syndrome).

-Acquired conditions, such as sepsis, infections with TORCH or Parvovirus B19 (anemia due to RBC aplasia) and hemolysis secondary to drugs.

ISOIMMUNIZATION

A. Rh disease (Rh = Rhesus factor)

(1)Genetics: Rh positive (+) denotes presence of D antigen. The number of antigenic sites on RBCs varies with genotype. Prevalence of genotype varies with the population. Rh negative (d/d) individuals comprise 15% of Caucasians, 5.5% of African Americans, and <1% of Asians[4]. A sensitized Rh negative mother produces anti-Rh IgG antibodies that cross the placenta. Risk factors for antibody production include 2nd (or later) pregnancies, maternal toxemia, paternal zygosity (D/D rather than D/d), feto-maternal compatibility in ABO system and antigen load[5].

(2) Clinical presentation of HDN varies from mild **jaundice** and **anemia** to **hydrops fetalis** (with ascites, pleural and pericardial effusions[2&3]. Because the placenta clears bilirubin, the chief risk to the fetus is anemia. Extramedullary hematopoiesis (due to anemia) results in hepatosplenomegaly. Risks during labor and delivery include asphyxia and splenic rupture. Postnatal problems include: Asphyxia, Pulmonary hypertension, Pallor (due to anemia),Edema (hydrops, due to low serum albumin), Respiratory distress, Coagulopathies (↓ platelets & clotting factors), Jaundice, Kernicterus (from hyperbilirubinemia),Hypoglycemia (due to hyperinsulinemnia from islet cell hyperplasia)[1,4&5].

(3) Laboratory Findings vary with severity of HDN and include: Anemia, Hyperbilirubinemia, Reticulocytosis (6 to 40%),↑ nucleated RBC count (>10/100 WBCs), Thrombocytopenia, Leucopenia,+ Direct Antiglobulin Test, Hypoalbuminemia, Rh negative blood type, Smear: polychromasia, anisocytosis, no spherocytes[6].

(4) Intra-uterine Transfusion (IUT): When iso-immunization is severe, Intra-uterine Transfusion is given to the fetus to prevent hydrops fetalis and fetal death. After multiple IUTs, most of the baby's blood will be Rh negative donor blood. Therefore, the Direct Antiglobulin test will be negative, but the Indirect Antiglobulin Test will be positive. After IUTs, the cord bilirubin is not an accurate indicator of rate of hemolysis or of the likelihood of the need for post-natal exchange transfusion[5&6].

B. Minor Blood Group Incompatibility is uncommon, occurs in ~0.8% of pregnant women and usually with E, c, Kell, Kidd or Duffy. Clinical presentation is similar to Rh disease. Anti-Kell disease may be severe due to hemolysis or erythroid suppression. Lewis antigen stimulates only IgM

production, so maternal antibody screen may be positive, but fetus is not affected[8].

C. ABO Incompatibility

(1) Genetics: With maternal blood types A and B, isoimmunization does not occur because the naturally occurring antibodies (anti-A and -B) are IgM, not IgG. In type O mothers, the antibodies are predominantly IgG, cross the placenta and can cause hemolysis in the fetus. The association of a type A or B fetus with a type O mother occurs in ~15% of pregnancies[5]. However, HDN occurs in only 3%, is severe in only 1%, and <1:1,000 require exchange transfusion. The disease is more common and more severe in African-American infants. Unlike Rh, ABO disease can occur in first pregnancies, because anti-A and anti-B antibodies are found early in life from exposure to A- or B-like antigens present in many foods and bacteria[3].

(2) Clinical presentation: generally less severe than with Rh disease.

(3) Laboratory findings that differ from Rh disease:

Smear: microspherocytosis, MCV <95, microcytic for a newborn (normal for adult), Direct Coombs test is often weakly positive [1&2].

MANAGEMENT:

A. **Preparation prior to delivery should include**:

-Blood: type O Rh negative packed RBCs, cross-matched against the mother. For severe HDN, have blood in the resuscitation room to correct severe anemia immediately after birth by partial exchange transfusion. Anticipate need for later exchange transfusion for hyperbilirubinemia and have additional blood for these [8].

-Surfactant, if infant is preterm.

-Catheters (e.g., angiocaths) for immediate drainage of hydropic fluid.

B.Resuscitation: At birth, the major problems are cardiopulmonary and relate to effects of severe anemia, hydrops and prematurity. Because of the multiple problems with severe HDN, effective resuscitation requires several individuals [9].

-Obtain cord blood for bilirubin (total & direct), albumin, blood type & Rh, Direct Coombs test, CBC, platelets, reticulocyte count and nucleated RBCs.

-If the infant is hydropic, intubate immediately and begin assisted ventilation with oxygen. If ventilation is difficult, drain pleural and ascitic fluid; during paracentesis, take care to avoid puncturing the enlarged liver and spleen.

-Insert umbilical arterial (UAC) and venous catheters (UVC) and immediatelymeasure blood pressures, arterial pH and blood gas tensions, hematocrit (Hct) and blood sugar.

-Correct metabolic acidosis with alkali, but only if giving assisted ventilation [8].

-Correct anemia, which is essential for effective resuscitation.

•If arterial blood pressure is low, give simple transfusion of packed RBCs (e.g., for Hct of 30%, push 10 mL/kg over 5 min; for Hct of 20%, push 10 mL/kg over 5 min, then repeat).

•Do not infuse packed RBCs or blood through UAC because of risk of damage to spinal cord from emboli.

•With normal blood pressure, elevated central venous pressure, metabolic acidosis or hydrops, correct anemia by partial exchange transfusion.

-Measure blood sugar frequently and correct hypoglycemia.

-Follow platelet counts; consider platelet transfusion for counts <50,000 [10].

(C) Hyperbilirubinemia results from continued hemolysis and inability of the neonatal liver to handle a large bilirubin load. Kernicterus (bilirubin encephalopathy) results from high levels of indirect bilirubin (>20 mg/dL in a term infant with HDN). Kernicterus occurs at lower levels of bilirubin in the presence of acidosis, hypoalbuminemia, prematurity and certain drugs (e.g., sulfonamides). -**Measure bilirubin in cord blood and at least q4h for the first 12 to 24h**. Plot bilirubin concentrations over time.

-Begin **phototherapy** shortly after birth. Although phototherapy may not eliminate the need for ExTx, it may delay ExTx and decrease the number required [11].

-Use **ExTx** for hyperbilirubinemia not controlled by phototherapy.

•Indications depend upon absolute serum concentration of bilirubin, the rate of rise of bilirubin, gestational age, albumin concentration and acid-base status. In general, perform ExTx for cord bilirubin >5 mg/dL, for a rate of rise of bilirubin >0.7 mg/h, and to prevent bilirubin >20 mg/dL in a term infant, and lower levels in preterm infants (e.g., maintain serum bilirubin <10X the birthweight in kg) [12].

•Blood should be reconstituted (to Hct ~40-50%) from fresh, O negative packed RBCs cross-matched against the mother and type-specific fresh frozen plasma.

•Technique: About 30 min before ExTx, give albumin 1 g/kg to increase the bilirubin bound to albumin in the circulation and make the ExTx more effective. Exchange 2X the blood volume (estimate blood volume at 85

mL/kg) [13]. Preferred technique is isovolumic ExTx, withdrawing blood from UAC and infusing through UVC (with tip in IVC or low right atrium). Do not infuse blood through UVC if tip is in portal circulation. Alternatively, ExTx can be done through a single catheter (UAC or UVC) using aliquots <5% of the infant's blood volume (e.g., 5 mL/kg). The blood should be warmed and the bag agitated every few minutes (to prevent settling of the RBCs) [14].

•Complications of ExTx [15]:

-Hypocalcemia due to Ca++ binding by citrate. Give Ca-gluconate 100 mg after every 100 mL of blood exchanged.

-Hypoglycemia, particularly after the ExTx, due to dextrose load from anti-coagulant of donor blood and hyperinsulinism in HDN.

-Thrombocytopenia and granulocytopenia due to washout with the ExTx.

-Hyperkalemia, especially with older units of blood.

-Hypothermia, associated with inadequate warming of blood [14&15].

OUTCOME [16]:

(A)**Late anemia**: Antibodies persist for weeks, because continued hemolysis and can cause anemia as late as age 6 months. After discharge, follow Hct weekly. Erythropoietin treatment will help prevent severe anemia and further transfusions.

(B)**Neurological prognosis** is good. Commonest problem is sensorineural hearing loss.

Objectives of the study

1- To assess the prevalence of Hemolytic Diseases of Newborns.

2- To assess the consequences of Hemolytic Diseases of Newborns among the studied groups.

Methods & Materials

2.1 Study setting

In this cross-sectional study, twenty HDN children aged from birth to 7 days old from those who were referred to AL-Imamain AL-Kadhimian Medical City, selected after diagnosis and confirmation of their HDN with clinical presentation and laboratory findings. The study performed during the period of 1, December, 2018 to 1, April, 2019.

2-2. Inclusion and exclusion criteria

Inclusion criteria were, age was only neonates from birth to 7 days and confirmed HDN by clinical presentation and laboratory findings.

2-3. Methods of study

In this study, twenty (20) infants with indirect hyperbilirubinemia were taken as subjects. Phototherapy and exchange transfusion were given to the patients. Questionnaire had included the name, age, sex, maturity. Laboratory investigations carried out were hemoglobin (Hb), hematocrit, and peripheral smear, reticulocyte count in neonates and ABO and RhD status of father if not done during pregnancy.

2-5. Statistical analysis

After collecting the necessary information, data entered in SPSS version 23.0. To describe the data of central tendency and dispersion, mean and standard deviation (SD) were used. The correlation estimated with the Fisher's exact test. The level of significance less than 0.05 considered statistically significant.

Results

This cross-sectional study conducted to evaluate HDN in twenty infants aged from birth to 7 days old with allo-immunization. The mean age of patients was 2±1.29 (days). Table 1 shows the frequency of male patients was 11 (55.0%) and female patients was 9 (45.0%). There was no relation between the HDN and gender of patients with P-value =0.14 which means that statistically insignificant.

Table 1: Gender of Cases.			
Gender	Frequency	Percent	P-value
Males	11	55.0	0.14
Females	9	45.0	
Total	20	100.0	

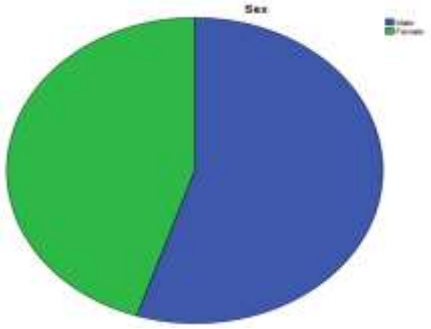

Figure 1: Distribution of gender of patients.

Table 2 shows Onset of jaundice in days was 12 (60.0%) at birth and 8 (40.0%) after the first day of birth.

Table 2: Onset of jaundice in days		
Onset of jaundice	Frequency	percent
At Birth	12	60.0
After one day	8	40.0
total	20	100.0

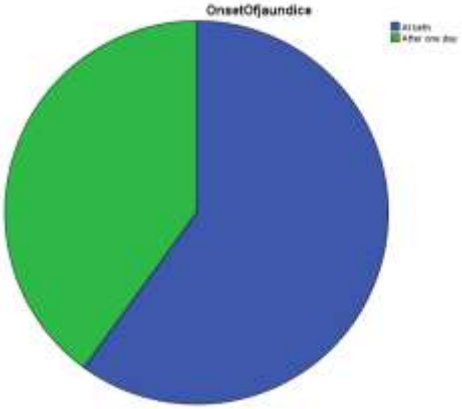

Figure 2: The onset of jaundice in days.

Table 3 shows the mean of TSB level, Hb, RBC, WBC, PLT, Retics as 9.97±5.7, 17.8±1.32, 4.36±0.96, 18.74±2.1, 80±7.25 and 3.32±3.6 respectively.

Table 3: Mean of laboratory findings.			
	Mean	SD	Median
TSB (mg/dl)	9.96	5.72	5.4
Hb (mg/dl)	17.8	1.32	18
RBC (10^{12}/L)	4.36	0.69	4
WBC (10^{9}/L)	18.74	2.10	19
PLT (10^{9}/L)	80	7.25	80
Retics (%)	3.32	0.77	3.6

Table 4 shows ABO incompatibility in the patients and their parents. With P-value =0.0001 that means the relation between ABO of the neonate and their patents was statistically significant.

Table 4: ABO incompatibility in the patients and their parents.							
	Neonate		Mother		father		P-value
	Frequency	percent	Frequency	percent	Frequency	percent	
A	8	40.0	12	60.0	8	40.0	0.0001
B	0	0.0	0	0.0	12	60.0	
AB	12	60.0	0	0.0	0	0.0	
O	0	0.0	8	40.0	0	0.0	

Table 5 shows Rh Incompatibility of neonates and their parents with P-value =0.003 that means the relation between ABO of the neonate and their patents was statistically significant.

Table 5: Rh Incompatibility of neonates and their parents.							
Rh Incompatibility	Neonate		mother		father		P-value
	Frequency	percent	Frequency	percent	Frequency	percent	
+Ve	20	100.0	0	0.0	20	100.0	0.003
-Ve	0	0.0	20	100.0	0	0.0	

Table 6 shows that blood cultures of HDN patients were 4 (20.0%) positive and 16 (80.0%) negative. Blood cultures in case of septicemic patients revealed Klebsiella, Staphylococcus aureus, Streptococcus pneumonia, and Clostridium perfringens.

Table 6: Blood Cultures of cases.		
Blood Cultures	Frequency	percent
+Ve	4	20.0
-Ve	16	80.0

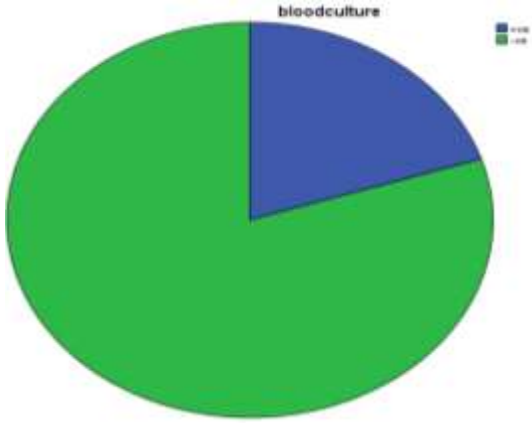

Figure 3: Blood Cultures of cases.

Table 7 shows the treatment applied for HDN patients whether required phototherapy 13 (65.0%), exchange transfusion 3 (15.0%) or both 4 (20.0%).

Table 7: Treatment of HDN cases.		
Treatment	Frequency	percent
Phototherapy	13	65.0
ExTx	3	15.0
Both	4	20.0

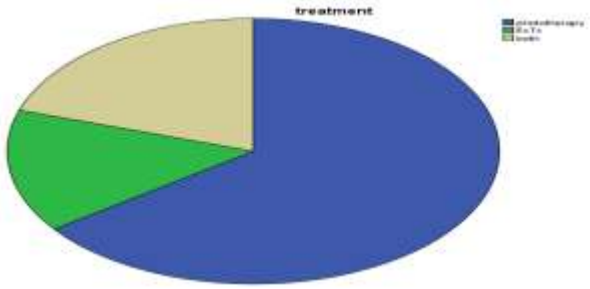

Figure 4: Treatment of HDN cases.

Discussion

In this study, ABO incompatibility was the commonest cause of HDN in contrast to the study conducted by Dharmesh Chandra Sharma et al [17] in whose study Rh incompatibility was the commonest cause of HDN. It is more common in "O" blood group mothers because "O" blood group mothers have been shown to have high titers of IgG than "A" or "B" group mothers. In type A and B individuals, naturally occurring anti-B and anti-A isoantibodies which are largely IgM molecules; that do not cross placenta. In comparison, the alloantibodies present in type O patients are mainly of IgG antibodies. For this reason, ABO incompatibility is largely limited to type O mothers having fetal blood group A or B. The occurrence of IgG anti-A or anti-B antibodies in type O mothers also explains why hemolysis caused by ABO incompatibility frequently occurs during the first pregnancy without prior "sensitization". The pathophysiology of alloimmune hemolysis resulting from Rh incompatibility includes an Rh-negative mother, an Rh-positive fetus, leakage of fetal RBCs into the maternal circulation, and maternal sensitization to D antigen on fetal RBCs.

Regarding the sex, there was no sex predilection and the two sexes are affected equally which was similar to Dharmesh Chandra Sharma et al [17] .

Regarding the modality of treatment, phototherapy was the most commonly applied modality (65.0%) which was similar to a survey by Chung and colleagues in Taiwan[18].

Immunization occurs almost exclusively during pregnancy. Small volumes of fetal RBCs enter the maternal circulation throughout the pregnancy. However, the main feto-maternal transfusion responsible for sensitization occurs during delivery. Rh hemolytic disease rarely ever occurs during the first pregnancy. However, once sensitization occurs, re exposure to Rh (D) RBCs in subsequent pregnancies leads to an anamnestic response and there is a rise in the maternal anti-D titer and an increased incidence of affected infants.

Regarding the risk of sepsis, the positive blood cultures were only (20%) in compare to other studies performed in south of Iran (in Ahvaz) the results were similar [19].

Conclusion
Recommendations
References

CONCLUSION

1- Autoimmune hemolytic anemia due to ABO incompatibility is the most common cause of hemolytic disease of newborn.
2- Gender of the baby does not have significant effect on the outcome of disease.
3- Blood group of patient does not affect the disease outcome.
4- Phototherapy was the most commonly applied treatment and had decreased the need for exchange transfusion.
5- Sepsis was only in 20% of cases.

Recommendations

1-Early diagnosis of HDN can improve the outcome.

2-Frequent monitoring of TSB level is necessary.

3 - Administration of Anti D to RH positive mother will prevent jaundice in subsequent babies.

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