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Hemolytic diseases of newborn caused by Lewis b antibodies-A case report

NALINI A
Department of Neonatology, Madras Medical College

Abstract:
Hemolytic disease of newborn due to minor blood group incompatibility is rare. It is being detected more often nowadays due to 11 cell panel screening of antibodies and antibody elution technique. Rh isoimmunization is decreasing due to Rh antibody administration. There is only one case report so far of alloimmunization due to Lewis b antibody. Here we report a rare case of Lewis b antibody causing hemolytic disease of newborn which presented as prolonged indirect hyperbilirubinemia with anemia. Neonate was treated with phototherapy, exchange transfusion and intravenous immunoglobulin. Mothers serum confirmed Lewis b antibody reacting at 37 C thus clinically significant causing hemolytic disease of newborn.

Introduction:
Hemolytic disease of newborn due to minor blood group incompatibility is rare. It is being detected more often nowadays due to 11 cell panel screening and antibody elution technique. Rh isoimmunization is decreasing due to Rh antibody administration. Lewis system of antigen is a minor blood group component. Here we present a rare case of hemolytic disease of newborn caused by Lewis b antibody from mother.

Case report:
A single live term boy baby, first born to a 21-year-old primi married by non-consanguineous marriage was born at 40+4 weeks of gestation by lower segment cesarean section for postdates. His birth weight was 3.5Kg and he cried at birth with APGAR of 7 and 8 at 1 and 5 minutes of life respectively. He was brought to us at 16 days of life with history of jaundice from 36 hours of life. Jaundice increased to exchange transfusion level at 48 hours of life. He was treated with phototherapy and fluid therapy for 11 days. He was referred to us at 16 days of life for evaluation for prolonged jaundice. Mother's blood group was B positive. There was no history of diabetes, hypothyroidism, abortion or transfusions in mother. There was no clay colored stools or yellow colored urine. There was no history of fever, poor feeding, crying while passing urine, no drug intake and parents are residents of Kanchipuram. There was no family history of jaundice, gall stones, transfusion or abdominal surgery.

On examination, he was pale, icteric up to legs with no bilirubin induced neurological dysfunction(BIND). His vital signs were stable with heart rate of 130 per minute, respiratory rate of 48 per minute and capillary refill time of less than 2 seconds.His hydration and weight gain were adequate. There were no hepatosplenomegaly or abdominal distension. There were no cephalhematoma or subgaleal bleed. Other systems were normal. Mother had no splenomegaly. Investigations showed, serum bilirubin of 22.2mg%, haemoglobin of 10.1 g% on day 3 with normal blood picture. On day 16, Hae moglobin dropped to 5.8g%,reticulocyte count of 3%, blood picture showed hypochromia with anisopoikilocytosis and on day 20 showed macrocytic polychromatic with reactive thrombocytes. Baby's blood group was B positive with direct agglutination test (DAT) negative and indirect agglutination test(IAT) in the mother was positive. LDH was 1413(NORMAL UPTO 430).Serial monitoring of serum bilirubin, haemoglobin and reticulocyte count were done. Serum electrolytes, renal function test, liver enzymes, Hb –electrophoresis, TSHand g6pd levels werenormal. Urine for haemoglobinwas negative.Total and differential count was normal. Red blood cell indices showed MCV of 90, MCH of 32.7 and MCHC of 36.8, all of which were normal. Ultrasound abdomen and cranium was normal. Blood, urine culture sterile and CRP negative.

He was treated with provisional diagnosis of haemolytic anaemia with prolonged indirect hyperbilirubinemia. Differential diagnosis considered for this provisional diagnosis were haemolytic anaemia, increased production of bilirubin, increased enterohepatic circulation, decreased clearance, inborn error of metabolism and metabolic causes. Haemolytic causes suspected were**(a**)Immune mediated like Rh,ABO and minor blood group incompatibility and b) Heritable causes like (i) Membrane defect (Hereditary spherocytosis, elliptocytosis,pyropoikilocytosis and stomatocytosis), (ii)Enzyme defect (g6pd/pyruvate kinase deficiency) and (iii)Hemoglobinopathies (alpha and beta thalassemia)). Causes for increased production such as sepsis, haemorrhage, extravasation, polycythaemia was considered in differentials. Increased enterohepatic circulation such as breast milk jaundice and intestinal obstruction were also considered. Prematurityand g6pd deficiency were considered in differential diagnosis. Inborn error of metabolism such as Crigler-Najjar, Gilbert, galactosemia, tyrosinemia were also suspected. Meta-bolic causes such as Hypothyroidism and hypopituitarism were considered.

Treatment given were intensive phototherapy from day 3 of life, intravenous fluids and direct breast feeds. Packed red blood cell was given on day 26 of life for haemoglobinof 5.9gm%. Double volume exchange transfusion was done on day 32 of life followed

by intravenous immunoglobulin(0.5gm/kg)administrationon day 33 of life. Serial monitoring of serum bilirubin, haemoglobin and reticulocyte count were done showed decreasing trend of bilirubin with no fall in haemoglobin was noted with the above treatment. He was discharged on day 35 of life as he was gaining weight, no pallor or icterus and no rebound hyperbilirubinemia or fall of haemoglobin further. Hearing screening was normal. On follow up at day42 of life, haemoglobin was stable and serum bilirubin was decreasing, no pallor or icterus and he was gaining weight adequately. Mother's serum had anti Le b reacting at 37C, thus clinically significant causinghaemolytic disease of newborndue to alloimmunisation. However, antibody elution could not be done. Hence diagnosis of minor blood group incompatibility with haemolytic disease of newborn due to Lewis b antibody was made. He was followed up at 3months and at 1 year of life with haemoglobin and serum bilirubin which were normal. He was developmentally normal child.

Discussion: Antigens on red blood cell (RBC) react with plasma antibodies which can be naturally occurring or immune antibodies. Antigen may be of protein or carbohydrate type. In 1900, Karl Landsteiner described ABO blood grouping system. There are totally 33 systems of blood grouping. Immunoglobulin has Fab and Fc portion.IgM pentamer constitutes10% and IgG 1& 3 monomer constitutes 75% of total immunoglobulin. Intravascular haemolysis is caused by IgM and IgG anti A or anti B antibodies. Extravascular haemolysis is caused by IgG or RBCs sensitized with complement to C3. Polyspecific Antihuman globulin detects IgG and C3b/C3d.DAT will be positive only if 100-500 IgG attached to RBC and IATwill be positive if 100-200 IgG are present in the serum. Increasing serum to cell ratiowill increase IAT positivity(1).

Procedure of IAT: Incubate RBC with antisera for 30-120min at 37C.Minimum three saline wash to be done. Add Coombs reagent and Centrifuge at 1000 rpm for 20seconds.Examine and grade the agglutination (2).

In an article published under the heading "Role of subgroup incompatibility in newborn jaundice requiring exchange transfusion "comprising82 patients studied from August 2007-2011 in a retrospective study, 17% subgroup had incompatibility,71% of them were DAT positive.Non-invasive prenatal testing(NIPT) measures cell free foetal DNA and MCA doppler in mother (3,4). In another study conducted between January 2008 –January 2009,5347 antenatal women were screened for irregular antibodies using 3-cell and 11 cell antibody screening panel. Among them, 339 (6.34%) were Rh negative. Alloimmunization occurred in 79 women (1.48%; confidence interval 1.17 -1.84). Cause for 37% of 79 alloantibodies positive mothers could not be identified. In another study,54 antibodies in 50 women were identified with clinically significant antibodies causing alloimmunisation in 9.43% (confidence interval 6.55-13.06) in Rh(D) negative and in 0.08 per cent (confidence interval .02-0.2) in Rh(D) positive women. Anti D was the most frequent antibody found in 8.85% of Rh(D) negative women. Anti-C, c, E, Jk(a), Jk(b), M and S being detected in some (5).

Chromosome 19 p and q 13.3 expresses FUT 3 and 2.Lewis and secretor antigens both were present in glandular epithelium. Types of Le a and Le b antigen are Le a+b-, Le a-b+ and Le a-b-. These antigens are secreted by exocrine epithelia and passively adsorbed by RBC.Soluble antigens are produced by tissues and found in plasma are adsorbed onto the RBC. Lewis system depends on Le Se and Hh genes. Genes such as le, h and se do not produce products.If Le gene is inherited, Lea substance is produced. Le Se and H, all should be inherited to convert Le a to Le b.Le– FUT3 adds fucosyl group to oligosaccharide in subterminal portion to form Le a(non-secretor).Se-FUT2 adds fucose to terminal portion. Le b needs 2 enzymes and it is efficient secretor constituted by A,B or H antigen.Le c and Le d antigen are also present in humans. Type 1 precursor oligosaccharide is present in serum and secretion and type 2 in RBC (6).Le a-,Le b- homozygous for le,le, secretor or non-secretor in Africans. FUT2 is responsible for presence of soluble A,B or H antigen (Type 1 chain ABH) linking Lewis with ABO system.

Lewis antigen is distributed among RBC, endothelium, kidney, gastrointestinal and genitourinary tract. Le a+b+ transient is present in infants, secretor increases with age. Japanese have weak Se. H codes FUT on type 2,H antigen h and amorph to type O.Le acts on type 1,leamorph (7,8).Lewis antibodies are naturally occurring type antibodies noted inLe a-b-individuals who have Anti Le a,Le b and Le a+. These antibodies are clinically insignificant in transfusion medicine because Lewis antigenare shed in plasma and acquire recipient Lewis

phenotype. Antigen antibody reaction occur in serum of negative individuals. It is reactive at room temperature, occasionally at 37 C and with antihuman globulin (9).In neonates, Lewis antigen causes no haemolytic diseases of new born, as Lewis antigens are secreted after second birthday sometimes after 6-7 years.

New born has Le a-b-.Pregnancy produces insignificant IgM. Lewis antigen is weakly expressed in pregnancy and present as Le a- b- phenotypedue to increased plasma volume & lipoprotein in pregnancy. However, Ig G antibodies were found only in 13 dyads so far. Reid et al reported one case of haemolytic disease of new born caused by Lewis b antibody (10-12). Diseases associated with Lewis antigens are Le b and H antigens –receptors associated withH. pylori (gastritis, peptic ulcer disease and gastric adenocarcinoma, MALToma), ITP and Norwalk virus induced acute gastroenteritis. Le a-b- individuals are prone for candida and uropathogenic E. coli infections and renal transplant rejection (13-16). Management of alloimmunisation is same as Rh isoimmunisation. Screening in antenatal period with non-invasive monitoring, intravenous immunoglobulin and exchange transfusion.

Conclusion: Minor blood group incompatibility need to be considered in case of prolonged jaundice. Lewis system antigen is not synthesized by RBC and RBC shed their antigen in plasma. Antibodies are usually IgM type, rarely IgG type. Neonate express less antigen. Pregnancy produces antibodies especially IgM type and hence do not cross placenta to cause haemolytic disease of new born.

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