UDK: 616.155.194-053.31

THE NEONATAL HEMOLYTIC ANEMIA - LATE HEMOLYITIC DISEASE OF THE NEWBORN OR PRIMARY AUTOIMMUNE HEMOLYTIC ANEMIA? A CASE REPORT AND LITERATURE REVIEW

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The Hemolytic Disease of the newborn (HDN) and primary autoimmune hemolytic anemia (AHA) in newborn are developed as consequence of hemolysis newborn erythrocytes. In the HDN cause of hemolysis is anti-erythrocyte antibodies by mother immune system which pass through the placenta and bind to newborn erythrocytes and leading to their hemolysis. In AHA hemolysis of erythrocytes is also caused by antibodies but their etiology is unknown. In neonatal period, both disorders are clinically presented very similar. We described a sudden occurrence of severe anemia with hyperbilirubinemia in 15 days old, second-born newborn with positive direct antibody test (DAT). Blood group was O, RhD positive with DAT negative at the birth. After clinical stabilization by erythrocyte transfusions, intensive phototherapy and adequate hydration, DAT was negative. Mother blood group was O, RhD negative. Mother was irregulary controlled the presence of anti-D antibodies in the blood, in the 12th and 36th week of pregnancy and result was negative. Mother was measles affected during pregnancy in the 7th month of gestation. The first child is RhD positive. Immunohematological tests did not confirm anti erythrocyte antibodies in the serum of the mother and newborn. We focused further examinations on the possible autoimmune hemolytic anemia in the newborn. We found high IgG titers of EBV in neonatal serum but within the reference values. Conclusion: Regular antenatal tests in the 12th week of pregnancy and retesting of the 28th and 34th week are necessary and should be performed with each Rh D negative pregnant woman due to prevention of the HDN antenatal application of Rh gama globulin.

Key words: *jaundice, anemia, hemolysis of erythrocytes, Hemolytic Disease of the Newborn, Autoimmune hemolytic anemia*

NEONATALNA HEMOLIZNA ANEMIJA − KASNA HEMOLITIČKA BOLEST NOVOOROĐENČETA ILI AUTOIMUNA HEMOLIZNA ANEMIJA? PRIKAZ SLUČAJA I PREGLED LITERATURE

U hemoliznoj bolesti novorođenčeta (HBN), hemoliza eritrocita je posledica nastanka antieritrocitnih antitela, koja stvara imuni sistem majke. Ova antitela prolaze kroz placentu i vezuju se za eritrocite novorođenčeta i dovode njihove hemolize. U autoimunoj hemoliznoj anemiji kod novorođenčeta hemoliza eritrocita je izazvana antitelima nepoznatie etiologije. Oba poremećaja se klinički prezentuju veoma slično u neonatalnom periodu. Opisali smo iznenadnu pojavu ozbiljne anemije i hiperbilirubinemije kod 15 dana starog, drugorođenog, novorođenčeta koje imalo pozitivan DAT na prijemu. Prvo dete je RhD pozitivno. U 7. mesecu trudnoće majka je obolela od teškog oblika malih boginja. Krvna grupa novorođenčeta je O, Rh D pozitivan, sa negativnim DAT–om na rođenju. Majka je O krvna grupa, Rh D negativna. Ona je iregularno kontrolisala prisustvo anti D antitela antenatalno, u 12. i 36. nedelji trudnoće Imunohematološkim testovima nismo uspeli da potvrdimo anti eritrocitna antitela u serumu majke i novorođenčeta. Dalja ispitivanja usmerili smo na ispitivanje moguće autoimune hemolizne anemije kod novorođenčeta. Našli smo visoke titre IgG na EBV u serumu novorođenčeta u poređenju sa istim titrima u serumu majke, ali u okviru refenetnih vrednosti. Regularna antenatalna testiranja u 12. nedelji trudnoće i retestiranje u 28. i 34. nedelji su neophodna i trebaju biti sprovedena kod svake Rh D negativne trudnice zbog prevencije HBN antenatalnom primenom RhD gama globulina.

Ključne reči: *žutica, anemija, hemoliza eritrocita, hemolizna bolest novorođenčeta, autoimuna hemolizna anemija*

Introduction

Neonatal hyperbilirubinemia occurs in 60-80% of neonates as a consequence of decreased bilirubin conjugation (due to immaturity of the enzyme liver system), reduced bilirubin binding to hepatocytes and increased bilirubin production. In a healthy neonate, the highest values of unconjugated bilirubin are between the first 48 and 72 hours of life. In the end of the second week its values are normalized (1). Neonatal hyperbilirubinemia is always pathologic if it occurs during the first 24 hours of life, if serum bilirubin concentration exceed 205 μmol/L and persist for longer than 7 days, if the increase of bilirubin is greater than 85 μmol/L for 24 hours and if the concentration of direct bilirubin over 34 μmol/L (2). In this case, we described a sudden occurrence of severe anemia with severe hyperbilirubinemia in a 15 day old newborn with Rh D incompatibility, but without proven Rh isoimmunization of mother. Rh isoimmunization is maternal immune response to fetal erythrocyte antigens inherited from his father. It occurs when the red cells of the fetus, on whose surface there are foreign antigens for mother's immune system, found in circulation during various fetomaternal bleeding (labor, artificial or spontaneous abortion, placenta previa, placenta abruption, multiple pregnancy, ectopic pregnancy, prenatal diagnosis). The most immunogenic and clinically most important is the antigen D, which is the most common cause of mother's Rh isoimmunization and severe forms of hemolytic disease in the newborn. Rh isoimmunization was a "disease" with a high rate of perinatal morbidity and mortality, but prophylactic administration to Rh D gamma globulin insensitive Rh D-negative women immediately after the birth of an Rh D-positive child is reduced frequency from 14% to 0.1-0.3% (3-5).

Case report

A male newborn of 15 days old was admitted to the Children's Department because suddenly occur intense jaundice, poor feeding and somnolence. Mild jaundice was developed in the second day of life and resolved to the 6th days without treatment. The newborn was completely healthy, breast feeding regularly and adding to the weight gain. At the 15th day of life, skin was suddenly intensely yellowed, newborn refused breast feeding and was somnolent.

The newborn was the second Rh D positive child from a second, monitored pregnancy during which the mother used Progesteron. Mother's blood group was O, Rh D negative, and she was irregularly controlled the presence of anti D antibodies in the blood, in the 12th and 36th week of pregnancy. Result was both times negative. After both deliveries mother received anti D immunoglobulin. She did not have abortions and did not receive blood transfusions in her life. In the 7th month of pregnancy, the mother was measles affected with severe form of pneumonia. She was treated with Ceftriaxone, Corticosteroids, Aminophylline, oxygen therapy, after there was health improvement and recovery. The pregnancy ended at the 40th week of gestation in vaginal delivery, without complications. At the time of birth, the neonates's weight was 3.100 g, height 51.0 cm, head circumference 33.0 cm. The Apgar score was 10 points at the first and fifth minutes after birth. The newborn's blood type was O, Rh D positive, with a negative direct antiglobulin test (DAT). The complete blood counts showed leukocyte count 24.9 x 10^9/L with normal lymphocyte (37%) and granulocyte count (59.7%). Red blood cells (RBC) count 5.44 x 10^{12}/L, hemoglobin (Hb) 196 g/l and hematocrit (Hct) 55.7% were normal. The newborn was in good condition with a mild jaundice from the second day of life. In the second and third days of life, was applied 1% eye ointment of Chloramphenicol due neonatal conjunctivitis. Immediately after the birth the newborn received vitamin K (Konakion 1 mg), and hepatitis B vaccine. In the fourth day of life was vaccinated with BCG vaccine. Family history was without significant hereditary.

In the 15th day of life, afebrile, somnolent, hypotonic newborn in flexion-extension position and reduced spontaneous motor activity with intensive yellow skin and sclera was admitted to our Children's Department. Body weight was 3.230 g. Primitive reflexes were impaired. The complete blood count showed severe anemia, red blood cells (RBC) count was 2.36 x 10^{12}/L, Hb 79 g/L, Hct 22.7%, with normal erythrocytes indices: mean cell volume (MCV) 96.2 fl, mean cell hemoglobin (MCH) 33.5 pg), mean cell hemoglobin concentration (MCHC) 348 g/L. The total number of white blood cells (WBC) was normal 13.8 x 10^9/L, with increased lymphocyte (lymph) count 66.9%, and low granulocyte (gran) count 26.0. The plateles (Plt) count was also increased 607 x 10^9/L. Biochemical blood analysis showed greatly increased total bilirubin 415 μmol/L, direct bilirubin 30.3 μmol/L and lactate dehydrogenase (LDH) 581 U/L. C-reactive protein (CRP) was 0.1 mg/L. The rest of biochemical analysis showed normal aspartate aminotransferase (AST) 29 U/L, alanin aminotransferase (ALT) 10 U/L, alkaline phosphatase 291, gamma glutamyltranspherase (gama GT) 76 U/L and cholesterol 1.7 mmol/L. Immunohematological studies showed the newborn's blood group to be O Rh D positive with a positive DAT. Serum levels of bilirubin were very high so phototerapy was necessary. After 18 hours of intense phototherapy and adequately hydration, RBC count continued to decline (2.11..

2.09 x 10^{12}/L), as values Hb (67 g/L) and Hct (20.3%). Serum levels of bilirubin were lower (308 285.35 µmol/L) and LDH (523 U/L). Values of glucose, blood urea, creatinine, total proteins, albumin, AST, ALT, CRP, uric acid, acid-base status were in normal range. After 24 hours DAT was negative. Two transfusions of erythrocytes were used due to low hemoglobin levels and continued phototherapy in 42 hours because of hiperbilirubinemia. Repeated blood analysis showed increase in RBC count (3.28 x 10^{12}/L), Hb (107 g/L), and decrese in total bilirubin level (197 µmol/L). Repeated DAT was negative. The newborn was discharged from hospital with diagnosis Neonatal hemolytic jaundice and Anemia sideropenica with the recommendation to start the treatment with vitamin D and antianemic therapy with complex vitamin B 5 g daily and folic acid ¼ tablets of 5 mg. Two days after discharged the newborn was again admitted in our department because of the yellow skin and cough. The presence of jaundice required further examination to detect the cause. Physical examination showed discrete yellow skin color, nasal congestion and laryngitis. Complete blood count was showed normal RBC count (3.24 x 10^{12}/L), Hb (104 g/L), Hct (30.7%), WBC (11.8 x 10^{9}), increased lymphocyte count (61.5%), decreased granulocyte count (32.2%) and normal Plt (424 x 10^{9}). Biochemical blood analysis showed values of total bilirubin 104.7 µmol/L and CRP was 1.6 mg/L. The periphery blood smear showed anulocytosis without other morphological changes. Ultrasound examination of central nervous system and abdomen were normal. During the first hospitalization, due life-threatening hemolysis and rapid disease progression abdominal ultrasound exam and peripheral blood smear not done for technical reasons. Chest X ray was normal. Indirect antiglobulin test (IAT) did not show the presence of anti-erythrocytes antibodies in the serum of the mother and newborn DAT was negative (Table 1).

Table 1. Immunohematological tests

	Blood group	Rh phenotype	DAT	IAT
Newborn	O	CDe/cde	Positive (1+), negative, negative	Negative, negative
Mother	O	Cde/cde	Negative	negative
Father	A	CDe/Cde	/	/
The first child	O	CDe/cde	/	/

DAT- direct antiglobulin test; IAT- indirect antiglobulin test

Viral serology (Epstein-Barr virus- EBV, Cytomegalo-virus- CMV, Herpes simplex virus 1-HSV-1) and serology on Toxopalasmosis showed negative IgM titers to the examined viruses in mother's and newborn's serum. Comparing quantitative titer values, it was founded that IgG for EBV in the newborn (20.83 U/ml) was 10 times higher than the IgG mother titre (1.49 U/ml). Newborn treated with antibiotic therapy and inhalation of cortico-steroid (budesonide of 0.25 mg / ml, 1 ml at 12 h), as recommended by otolaryngologists. In the coming period there was a decreased in RBC (2.62..2.50 x 10^{12}/L), Hg (81..85 g/L) and Hct (22.8..25.2%). White blood cells (11.7..14.5 x 10^{9}/L), lymphocyte count (63.5..76.9%) and granulocyte count (30.1..14.9%) were same. Se-rum levels of total bilirubin (14.3 µmol/L), and direct (3.6) µmol/ were normal, while serum iron level was slightly decreased 10.8 µmol/L (12.5-32.2 umol/L). Recommended antianemic therapy is continued (folic acid, vitamin B complex). We continued to monitor infant during the next 6 months. Early psychomotor development was normal. Body weight (percentiles 53) and body length (percentiles 48) were appropriate for age and gender.

Discussion

Serum bilirubin level more than 340 µmol/L in a newborn represent severe hyperbilirubinemia, while concentration over than 425 µmol/L represent critical hyperbilirubinemia and serious risk of developing kernicterus (6). Hyperbilirubinemia associated with anemia in newborns is commonly caused by hemolytic disease of the newborn (HDN), diseminal intravascular coagulation or the use of some drugs (penicillins) (2). Hemolytic disease of the newborn (HDN) is usually the result of ABO and Rh incompatibility between the newborn and the mother. For the determination of HDN, it is necessary to determine ABO and Rh D blood group, direct and indi-

rect antiglobulin test in newborn, and ABO and Rh blood group and IAT in mother (7). Hemolytic disease of the newborn is consequence formation of antierythrocyte antibodies by mother immune system which pass through the placenta and bind to newborn erythrocytes and leading to their hemolysis. Anemia and jaundice usually manifested at the birth or in the first hours after birth. The most severe form of HDN is the hydrops fetalis that causes the fetal death. Hemolytic disease of the newborn is most commonly caused by anti D antibodies in sensitized Rh D negative mother so that regular antenatal tests in the 12th week of pregnancy and retesting of the 28th and 34th week are necessary and should be performed with each Rh D negative pregnant woman (4). Except anti D, anti c, anti E and anti K antibodies are the most common causes of severe HDN forms (8, 9). A ten year retrospective study in our country confirmed the presence of irregular antibodies in 0.64% of pregnant women. Of this number, 68% were anti-D antibodies in pregnant women as a result of active immunization, and the conclusion of the study was that in Serbia had high percentage of immunized Rh D negative pregnant women (9). In literature was described the case of the Rh D negative pregnant woman who was twice controlled presence of anti D antibodies in the second trimester of pregnancy and the result was negative. But at the birth newborn developed HDN with a positive DAT and anti D antibodies were proven in the blood of the mother after delivery (10). It is very important to regularly and correctly control the presence of anti D antibodies in the 12th, 28th and 34th weeks of pregnancy for the prevention of HDN. In our case, mother did not control regularly presence of anti D antibody. Hemolytic disease of the newborn can be caused by anti-erythrocyte antibodies to antigens with very low incidence, the Kell system antigens have the highest clinical signifycance (11-14). Although it is typical of HDN in the first hours after birth, occurrence of HDN in midneonatal period is described. During early neonatal period neonates were in good condition with mild jaundice, both newborns developed severe anemia, metabolic acidosis and was vital threatening in 12th and 18th day of life. At birth, in both newborns DAT was positive (15). The exact reason for the late hemolysis and anemia is still not evaluated, because the concentration of antierythrocyte antibodies in the circulation of the newborn is the highest at the birth. Hurdle AD. and Davis JA., described the case of a newborn with HDN in second week of life with a positive DAT and IAT, anti D antibodies at the birth. It is assumed that the cause of late HDN persistence of anti D antibodies in the blood of the newborn, even after exchange transfusion with Rh D negative blood, that destroy newly formed Rh D positive red cells (16). Rare HDN cases with negative DAT were described, with subsequently detected anti A and anti B antibodies in the maternal and neonatal serum. Also, in another case which ended with a fatal outcome of newborn, DAT was negative on fetal blood but anti C and anti c antibodies were subsequently confirmed in the mother's blood (17). Hemolytic disease of the newborn can be result from disorders in the structure of the membrane of the erythrocyte which are characterized by rapidly progressive hyperbilirubinaemia after birth, positive family history, negative DAT, and abnormalities in the peripheral blood smear where the most common spherocytes. Defects in the synthesis of erythrocyte enzyme (pyruvate kinase deficiency and glucose-6-phosphate dehydrogenase) cause HDN during the first few hours and days after the birth of a serious jaundice without anemia. Neonatal haemolysis due to hemoglobinopathy, excluding α-thalassemia major, does not manifest clinically in the neonatal period (18).

Hemolysis of red blood cells followed by severe anemia and hyperbilirubinemia is consequence of the presence anti erythrocytes antibodies in the blood which bind to surface membrane of erythrocytes and leads to their destruction. The etiology of the formation of antierythrocyte antibodies, which lead to hemolysis may be different. If the etiology is unknown, it is a primary autoimmune hemolytic anemia, while secondary autoimmune hemolytic anemia is caused by drugs, infectious agents, malignant, lymphoproliferative and autoimmune diseases (19).

In literature, the cases of autoimmune hemolytic anemia in 6 months old infant are described due to infection CMV (20), and in seven years old girl due to EBV infection (21). Autoimmune hemolytic anemia in children was also described after vaccination. A 20-year-old girl had two attacks of hemolysis, the first after oral polio vaccine, the other seven months later after the MMR vaccine. A case of hemolysis was reported in a 21-month-old boy a few days after Di-Te-Per, Haemophilus influenza, Hepatitis B, and polio vaccine (22). Tsuchiya et al. described the case of hemolytic anemia in this 9-year-old boy probably caused by vaccine against influenza virus (23). A case of hemolytic anemia occurred in a 5 year old girl who treated with Ceftriaxone due to urinary tract infection. The presence of antibodies to ceftriaxone in the blood was proven (24). In almost all of these cases, DAT was positive. Motta M et al. described a case of autoimmune hemolytic anemia in 12 hours old neonates that developed a serious anemia with hepatomegaly. Peripheral blood smear showed spherocytosis with anisopoicilocytosis while the puncture bone marrow showed blocked erythro-

poiesis on basophilic erythroblasts. The cause of this hemolysis in newly born child remained unknown (25). Viral infection may be associated with different hematological disorders because caused by modulation of the immune response. The viruses have the ability to redirect the host immune response against the antigen's own tissues by molecular mimicry process. The loss of immunological tolerance is result of dysregulated immune response directed against the virus. In autoimmune hemolytic anemia, macrophage phagocytosis of autoantibodies related to the surface of erythrocytes in the spleen and their hemolysis. Viral infections have the ability to change the expression of the cytokine profile and to accelerate the phagocytosis of autoantibodies associated with the erythrocyte surface. In viral infections, high values of IgG against viruses can cause sensitization of erythrocytes. The change in cytokine expression can lead to the reactivation of latent viral infections in the organism and the redirection of the immune response (22). During the first 6 weeks of life, the ability of the newborn to produce antibodies is limited due to the immaturity of the immune and reticuloendothelial system. Early immune stimulation is synthesized very low titer of immunoglobulin M specific antibodies, with delayed switching from IgM to IgG class. The immature immune response in newborns is variable and the ability to synthesize autoimmune antibodies maybe not be excluded (25).

Conclusion

Data of Rh D incompatibility, the second pregnancy and the birth of both Rh D positive children, typical clinical manifestation, instigated us to think about late HDN. But we did not prove HDN by immunohematological tests. Negative IAT in the mother may be the consequence of the administration of Rh D gamma globulin after delivery. In our case, antenatal testing was started in the 12th week of pregnancy, and was repeated in the 36th week due measles infection of the mother. Further investigations focused on possible autoimmune hemolytic anemia in the newborn. Although we do not have reliable indicators that hemolysis of erythrocytes is caused by EBV, CMV and HSV viruses, changes in the lymphocytes count and laryngitis in newborn may indicate that hemolysis is consequence of some respiratory viral infection.

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