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RH HEMOLYTIC DISEASE OF THE NEWBORN: CASE REPORT[1]

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Abstract: Introduction: Rh hemolytic disease occurs due to the passage of anti-D antibodies present in the plasma of sensitized mothers into the fetal circulation, triggering hemolysis resulting from the destruction of erythrocytes from the Rh-positive fetus. Objective: To highlight the importance of prenatal care, with the aim of identifying pregnant women at risk for Rh isoimmunization and preventing future serious complications for the fetus. Method: This is a descriptive, retrospective study, in the form of a clinical case report. The data contained in the work were obtained by collecting information from the medical records of the patient admitted to the Hospital de Caridade de Ijuí. Results: case report of a newborn with jaundice evident before 24 hours of life with a diagnosis of Rh isoimmunization and its complications. Conclusion: We noted the importance of providing adequate prenatal care to prevent complications resulting from Rh isoimmunization through diagnosis and specific management.
Keywords: Prenatal; Hemolysis; Hyperbilirubinemia.

INTRODUCTION

Hemolytic disease of the fetus and newborn (HDFN) usually results from incompatibility between maternal and fetal blood groups, with the main related etiologies being: maternal-fetal Rh (D) blood incompatibility, ABO incompatibility and incompatibility of other systems of subgroups (antigens irregular) (Castleman et al., 2021). Regarding the first cause, if undiagnosed, the neonatal mortality rate is high, reaching 24% in newborns (SARWAR et al., 2023). Furthermore, epidemiological data demonstrated that the occurrence of Rh negativity is higher among Basque people (36%) and is present in around 15% of the white population and 7% of black people (Aljuhaysh RM et al., 2017).

In Rh hemolytic disease of the newborn, maternal alloimmunization of red blood cells with antibodies of the Immunoglobulin G (IgG) class cross the placenta to destroy fetal erythroid cells that express the antigen involved (Castleman et al., 2021). As a result, the fetus develops a compensatory mechanism for the production of erythropoietin and red blood cells, with an increase in reticulocytes and erythroblasts, due to extramedullary erythropoiesis. Thus, when erythrocyte destruction is very high, anemia and hyperbilirubinemia with jaundice manifest early and in the most severe cases, the fetus can develop hydrops, heart failure, kernicterus and death (Júnior et al., 2021).

Therefore, to prevent the incidence of this situation, the Prenatal and Birth Humanization Program - PHPN (Ministry of Health) recommends requesting blood typing (ABO and Rh) in the first prenatal consultation for all pregnant women. Furthermore, Primary Health Care instituted the administration of anti-Rh(D) IgG preparations in sensitized pregnant women; which practically abolished this phenomenon, when combined with standard postpartum prophylaxis (Pegoraro et al., 2020).

In this context, it is necessary to report a clinical case of Rh hemolytic anemia in a newborn in order to review its etiology and clinical presentation, emphasizing the importance of identifying and managing Rh-negative pregnant women with positive indirect Coombs, in order to prevent these outcomes. adverse neonatal consequences inherent to this pathology.

METHODOLOGY

This is a descriptive, retrospective study, in the form of a clinical case report. The data contained in the work were obtained through the collection of information from medical records electronic. Access to the electronic medical record was authorized by the Research Committee of the Hospital de Caridade de Ijuí. Furthermore, the person responsible for the patient was instructed about the study and signed an Informed Consent Form.

CASE REPORT

Patient WEDSC, newborn (NB) from GFS, 27 years old, fourth pregnancy, with three previous cesarean deliveries, blood type A negative, 17 prenatal consultations, non-reactive serology, positive group B beta-hemolytic streptococcus test, positive indirect Coombs (positive at 19 weeks of gestation), with gestational diabetes mellitus, using insulin, obstetric ultrasounds without changes, there is no record of fetal echocardiogram or morphological ultrasounds. History of a newborn born on 10/15/2011 with positive AB blood typing, without record of anti-D immunoglobulin application after birth.

WEDSC was born by cesarean section, on 03/16/2023 at 10:03 am, intact sac, clear amniotic fluid, cephalic presentation, without cervical cord circumference, delayed clamping of the umbilical cord and no need for resuscitation maneuvers.

RN WEDSC, male, gestational age 37 weeks and 4 days, APGAR 8/9, no malformations, 3275 grams, physical examination without changes, performed skin-to-skin contact, encouraged to breastfeed in the first hour of life and after a period of observation sent for joint accommodation.

Ten hours after birth, the newborn developed significant jaundice (zone 4 according to Kramer's zone) with laboratory results indicating: reticulocytosis (26.7%), direct coombs positive, blood type A Positive, normal blood count, total bilirubin (33.22 mg /dL), indirect bilirubin (32.42 mg/dL) and direct bilirubin (0.80 mg/dL).

Double phototherapy was started (16/03), serum therapy and registered with the State Hospital Admissions Management (Gerint), as the patient presented an indication of exchange transfusion, a procedure not performed in the hospital at the moment. A few hours after the diagnosis, the newborn began experiencing respiratory pauses and a drop-in saturation, maintained a heart rate above 100 bpm, was fitted with an oxygen bell for support and was taken to the Neonatal Intensive Care Unit (ICU).

During the first 6 days of hospitalization in the Neonatal ICU, the patient did not show clinical improvement, with laboratory tests indicating anemia (hemoglobin of 8.3 g/dL) and reticulocytosis (28.0%), with worsening in total bilirubin levels (33. 65 mg/dL) and indirect bilirubin of 31.95 mg/dL, despite the management carried out.

The level of indirect bilirubin decreased slightly (32.37 mg/dL) after four days of intense triple phototherapy in the neonatal ICU. Furthermore, the hemoglobin dropped to 9.6 g/dl and, therefore, there was a need for transfusion of packed red blood cells on the 21st and 30th of March.

After six days of hospitalization in the neonatal ICU, the patient began to show gradual clinical and laboratory improvement, leaving the risk zone for exchange transfusion and later phototherapy, being discharged on 04/04, weighing 3375 g. The child was clinically stable and was discharged with the following laboratory tests: hemoglobin of 10.9 g/dL, total bilirubin of 7.95 mg/dL, direct bilirubin of 0.99 mg/dL and indirect bilirubin of 6.96 mg/dL.

RESULTS

DATE	Total Bilirubin	Indirect Bilirubin	Direct Bilirubin	Hemoglobin	Reticulocytes
03/16/23	33.22 mg/dL	32.42 mg/dL	0.80 mg/dL	11.4 g/dl	26.7%
03/22/23	33.65 mg/dL	31.95 mg/dL	1.7 mg/dL	8.3 g/dl	28%
03/25/23	25.46 mg/dL	24.42 mg/dL	1.04 mg/dL	9.6 g/dl	28.4%
04/03/23	7.95 mg/dL	6.96mg/dL	0.99mg/dL	10.9 g/dl	-

TABLE 1: laboratory tests.

DISCUSSION

Knowledge of blood group systems is essential in clinical practice, especially for hematological disorders and in the clinical evaluation of both pregnant women and newborns. In 1904, Karl Landsteiner discovered human blood groups (ABO and Rhesus systems) and characterized them using Landsteiner's law, which states that corresponding antibodies are present in plasma for each blood group antigen not present on red blood cells. However, this is not the case for rhesus antigen – D antigen (Renske et al., 2022).

Normally, anti-D antibodies are absent in Rh positive (+) and Rh negative (-) individuals, but when Rh- individuals are exposed to the D antigen, they begin to secrete the corresponding antibodies. Therefore, the presence of D antigens and anti-D antibodies in the same person can lead to red blood cell agglutination and hemolysis, which is the basis of Rh incompatibility. (Myle et al., 2021).

Therefore, in Brazil, the occurrence of RhD negative is variable across regions and the prevalence depends, among other factors, on the frequency of the RhD negative phenotype in the population. After stating this, it is estimated that maternal-fetal alloimmunization affects five out of every thousand live births, and without correct immunoprophylaxis, 17% of pregnant women will be alloimmunized after their first pregnancy (MS, 2019).

In this regard, alloimmunization is the process in which an individual without a specific blood group antigen is exposed to the antigen and responds by producing specific antibodies (Renske et al., 2022). Therefore, when a Rh-negative mother is exposed to the Rh D antigen, the D antigen is perceived as an external threat similar to the way bacteria and viruses are perceived. This leads to a series of activations of immunogenic pathways that culminate in the production of maternal anti-D antibodies (COSTUMBRADO et al., 2022).

In this sense, a French midwife first described Rh Incompatibility in 1609, however, it was only in the 1950s that the underlying cause was clarified (Myle et al., 2021). Therefore, there are two main causes responsible for hemolytic disease.

The first is the exposure of a Rh-negative pregnant woman to Rh-positive fetal erythrocytes due to fetomaternal hemorrhage during pregnancy secondary to vaginal delivery, spontaneous or induced abortion, ectopic pregnancy, placenta previa, invasive obstetric procedures (cordocentesis, chorionic villus sampling, amniocentesis), external cephalic version and the second through blood transfusion (Dziegiel et al., 2021).

Generally, no effect is seen in the first pregnancy for Rh-D-mediated disease, as Immunoglobulin M (IgM) is a large pentamer that cannot cross the placental barrier. However, during subsequent pregnancies, subsequent exposure of as little as 0.03 mL of Rh-positive cells can lead to the formation

of anti-D IgG immunoglobulins, which cross the placenta freely and bind to fetal red blood cells containing D surface antigen. (SARWAR et al., 2023).

Consequently, these antibody-coated cells are recognized by the fetal reticuloendothelial system, and destruction of these cells causes the release of large amounts of bilirubin into the fetal circulation. During the prenatal period, maternal conjugating enzymes remove excess bilirubin, but after birth, due to early insufficiency of glucuronyltransferase enzymatic activity, neonates may present with jaundice and severe hemolytic anemia (Renske et al., 2022).

Although the first baby is usually not harmed, antibodies can cause hemolytic disease in subsequent RhD-positive babies (Okwundu et al., 2013). In view of this, the first step in the evaluation is the determination of the Rh blood type in all pregnant women, in accordance with the recommendations of the United States Preventive Services Task Force (USPSTF) (SARWAR et al., 2023).

If a woman is Rh positive, there is no need for further testing. However, if the woman is Rh negative, the second step is to determine the presence of anti-D antibodies in the maternal serum, initially using a qualitative rosette test and subsequently using a quantitative Kleihauer-Betke test. This is a confirmatory test to quantify antibody titers, especially in large hemorrhages (>30ml of blood) recommended by the American College of Obstetricians and Gynecologists (ACOG) (SARWAR et al., 2023).

Indirect Coombs test is used to confirm that antibody titers are positive. This titer must be less than 1:16, a higher level requires serial amniocentesis starting at 16-20 weeks to determine fetal Rh status (CASTLEMAN et al., 2020).

Additionally, negative maternal antibody testing requires paternal Rh testing. If the father is Rh negative, no further testing is necessary. On the contrary, if the father is heterozygous Rh positive, there is a 50% chance that the fetus will be Rh negative or positive. Therefore, in these cases or when paternal Rh grouping is not possible, fetal RhD genotyping is necessary by non-invasive methods or by invasive techniques (SARWAR et al., 2023).

Therefore, non-invasive genotyping of fetal RHD can be performed in the first 12 weeks of pregnancy by collecting a maternal blood sample, with specificity and sensitivity of 93% and 100%, respectively. However, amniocentesis, which takes a sample of amniotic fluid, is the gold standard invasive procedure for analyzing fetal DNA and thus developing a future treatment plan (SARWAR et al., 2023).

After the initial assessment, pregnancy monitoring is necessary for obstetric and pediatric clinical intervention. As for the newborn, blood typing (ABO and D) and the direct antiglobulin test - direct Coombs, must be carried out soon after birth (Júnior et al., 2021). Although laboratory monitoring is an important tool for predicting potential risk, it cannot with certainty predict the clinical severity of the fetus (Renske et al., 2022).

In view of the above, immunoprophylaxis with 300mcg of anti-D immunoglobulin is recommended for RhD-negative mothers of their first pregnancy at 28 or 30 weeks of pregnancy. Immunoglobulin must also be indicated, within 72 hours, after abortion, ectopic pregnancy, molar pregnancy, vaginal bleeding or after invasive procedures, when the father is Rh+ and the mother is Rh- (PRIMARY ATTENTION IN HEALTH, 2017). This reduced the alloimmunization rate from 17% to less than 1% (COSTUMBRADO et al., 2022).

Will determine the intensity of hemolysis caused in the fetus and invasive procedures

may be indicated more quickly (SARWAR et al., 2023). Furthermore, without an appropriate prenatal detection and treatment program, up to 50% of untreated alloimmunization cases will result in neonatal death or harm (Illanes SE, 2023).

It is now known that since the discovery of anti-D-mediated HDFN in the 1950s, management has progressed greatly, making it a rare disease, while drastically reducing perinatal mortality through timely and correct intervention. Despite all these improvements, HDFN has not yet been eradicated and alloimmunization in RhD-negative women still has an estimated incidence of 0.3 to 1.3% (Renske et al., 2022).

In the reported case, the mother had been screened for irregular antibodies at the beginning of the pregnancy, presenting a negative result, however, the indirect Coombs test was positive at 19 weeks' gestational age and the pregnant woman's health record does not contain any referral for further evaluation or guidance on risks to the newborn.

In general, anti-D-induced hemolytic disease of the newborn is rare, however, some cases may be critical enough to require exchange transfusion (Júnior et al., 2021). The newborn in the report presented neonatal jaundice in the first 24 hours of life, being classified as a high-risk zone according to the Bhutani Nomogram, with an indication for exchange transfusion.

In this context, HDFN is a hemolytic disorder that mainly affects Rhesus positive (Rh+) fetuses and newborns of Rhesus negative (Rh-) mothers, as previously seen (Myle et al., 2021). Therefore, the fetal response to the antigen passed by the mother may be sufficient to destroy fetal red blood cells and lead to hemolysis, resulting in the blood's ability to transport oxygen to the baby's organs and tissues. As red blood cells break down, a substance called indirect bilirubin is formed and, consequently, neonatal jaundice and resulting complications are formed (Nassar GN et al., 2022). Our patient presented with severe anemia due to hemolysis with indication at two stages transfusion of packed red blood cells due to clinical and laboratory severity during hospitalization in the Neonatal Intensive Care Unit.

The severity of the disease in the fetus depends on several factors, including the amount and strength of the antibody produced by the mother and the gestational age of the fetus (DE WINTER et al., 2023). In fact, severe hemolytic anemia can lead to high-output heart failure/myocardial ischemia. As the cardiac system unsuccessfully tries to keep up with oxygen supply demands, the myocardium becomes dysfunctional, which can result in strokes, edema, and ascites due to increased hydrostatic pressure. Thus, the combination of fluid accumulation in at least two extravascular compartments is called hydrops fetalis and is an extremely serious condition that can occur (Nassar GN et al., 2022).

In newborns, it may also happen that unconjugated bilirubin (indirect and fat-soluble bilirubin) has the ability to cross the blood-brain barrier and cause kernicterus. The risk of kernicterus is greater with indirect bilirubin levels greater than 20 or rising levels despite phototherapy. Therefore, the newborn may present with lethargy, followed by difficulty breathing and decreased deep tendon reflexes. Aiming at prevention, correct management and prompt treatment are important in high-risk patients with elevated indirect bilirubin (Nassar GN et al., 2022).

Among therapeutic measures, the most used is phototherapy. Thus, it is a treatment based on the interaction of electromagnetic light irradiation with biological tissues, in order to act on the conversion of indirect bilirubin into a soluble substance that is more

easily excreted. Therefore, phototherapy is an effective and safe intervention to treat and prevent severe hyperbilirubinemia (Renske et al., 2022).

Exchange transfusion, a more invasive procedure, was the first successful treatment for severe neonatal jaundice in situations where there is a greater risk of neurotoxicity, contributing to the reduction of morbidity and mortality in newborns with perinatal hemolytic disease (Darlene et al., 2023). In this treatment, the newborn's blood is removed in small volumes, approximately 5 to 10 ml at a time, and replaced with blood.

Furthermore, simple red blood cell transfusion may be necessary in patients with moderate to severe anemia (hematocrit between 25 and 35% and/or symptoms attributable to anemia) in whom exchange transfusion is not available. Furthermore, immunoglobulin therapy may be used in infants with more severe anemia and/or hyperbilirubinemia if exchange transfusion is not readily available (Darlene et al., 2023).

Therefore, the possible consequences and complications of HDFN can be prevented through adequate prenatal care, neonatal clinical assessment in the first 24 hours of life, through history taking, physical examination and laboratory tests, and correct management with timely treatment (Júnior et al., 2021).

Finally, the patient in the reported case, after the management carried out during hospitalization, was discharged from hospital at 19 days old, with no clinical evidence of neurological deficits, but there are still gaps regarding his evolution and normal growth, which will require specialized systematic monitoring.

CONCLUSIONS

Reducing the occurrence of RhD hemolytic disease has become possible since the advent of RhD immunoglobulin and effective and adequate pre- and postnatal care. However, HDFN using anti-D is still a problem due to deficits in the monitoring of pregnant women, the inadequate detection of fetomaternal hemorrhage in susceptible pregnant women and the failure to administer anti-RH immunoglobulin when indicated, as was the hypothesis described in this case.

To prevent the development of this pathology, an obstetric and pediatric investigation is necessary through anamnesis, physical examination, and complementary examinations of the mother and the fetus or newborn.

Therefore, it is clear that universal parental Rh screening and treatment prophylactic treatment with Rh immunoglobulin significantly reduces neonatal morbidity and mortality rates.

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