Erythroblastosis fetalis or Hemolytic disease of the newborn (HDN)

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SUMMARY

Erythroblastosis fetalis or Hemolytic disease of the newborn (HDN) is now clearly known by the etiologic, pathogenetic and therapeutic point of view. It is caused by specific anti-erythrocytic antibodies of maternal origin entering the fetal circulatory through the placental filter. These antibodies are determined in the newborn hemolysis and variable clinical picture, from uterine death to onset of anemia and hyperbilirubinemia after birth. This work provides a recent take on this pathology.

Due to its frequency and its strong immunization, but also other Rh system antigens or other blood group systems (including ABOs) may induce a clinically significant HDN. Most cases of HDN are due to ABO or other blood type incompatibilities. These cases are generally less severe than RhD incompatibilities (with exceptions) and often occur only in the postpartum period, with a ingravescent hyperbilirubinemia in the first 48 hours after birth.

Elevated levels of bilirubin can be the cause of the most serious clinical complications of HDN: bilirubinemic encephalopathy. Reducing bilirubin levels or at least halting the growth in the first few hours after delivery may therefore be crucial to prevent permanent neurological damage. The standard treatment of severe HDN is based on exanguino-transfusion, which replaces the blood taken with erythrocytes without the antigen involved, while simultaneously removing the excess bilirubin present in the plasma.

DISCUSSION AND CONCLUSIONS

The main cause of HDN is the reaction between the IgG-class maternal antibodies and the antigens present on fetal red blood cells resulting in their destruction, especially in the spleen. HDN rarely occurs during the first pregnancy, unless the mother has previously been sensitized by transfusions. Usually, during the first pregnancy, the primary maternal immunization occurs, characterized by the production of a small amount of IgM antibodies, immunoglobulins that do not cross the placenta. In the following pregnancies, and after further exposure to the antigen, as a result of secondary immunization, IgG antibodies are produced, which can cross the placenta and cause hemolysis. The immune response depends on the EMF, the number of immunizing events and the woman's response capacity.

In addition to the RhD antigen, other antigens belonging to the Rh system and other known blood
group systems with which a subject who has no contact has come into contact with pregnancy or transfusion therapy, are able to trigger the production of IgG antibodies and to cause, consequently, also a HDN. In general, HDN forms not due to RhD incompatibility are clinically benign, so only 10% of them have clinical relevance that requires transfusion.

After the HDN by RhD incompatibility and ABO incompatibility, the most frequent incompatibilities are C antigen incompatibility, Kell antigen incompatibility and incompatibility with the Duffy antigens. Next, in a strict order of magnitude, HDN forms are incompatible with Kidd, MNS and other antigens, all very rare. The anti-Cw, -Fyb, -Jka, -Jkb, -Kk3, -S, -s usually limit the positivity of the direct antigen test (DAT) in the infant and treatment, if necessary, almost always is limited to phototherapy. Anti-M, which can also be of IgG-class, rarely cause HDN. Antibodies such as anti-I,-P1, -Lea and -Leb can be ignored because the corresponding antigens are scarcely present at birth. Several studies have shown that HDN caused by anti-K differs from that of anti-D for a variety of reasons. In women with anti-K, medical history is generally not a predictor of the severity of the disease. There is a low correlation between the antibody titer and the severity of the disease, hemolysis.

The suppression of fetal erythropoiesis, rather than hemolysis, represents the most important pathogenic mechanism in determining fetal anemia. Pregnancy with anti-K maternal fetal alloimmunization, even with a low antibody titre (equal to or greater than 1:8), must therefore be considered at risk for the possible severity of fetal and/or neonatal clinical manifestations.

The increase of migratory flows that has affected Italy in recent years has led to the diagnosis of other forms of HDN, due to non-frequent antigens, at least in the Italian population. The search for irregular antibodies in these forms of HDN is often falsely negative due to the lack of these antigens in the commonly used, for identification, erythrocyte panels, made for Caucasian red cells. In these cases, the alloantibodies involved can be identified using the father's red cells (if ABO compatible with the woman) or, after birth, those of the newborn. Pre-pregnancy, post-natal, and therapy protocols do not differ from those recommended for HDN by RhD incompatibility.

HDFN from ABO incompatibility is, today, the most common neonatal hemolytic disease in the western world. In the 15-20% of pregnancies in the white population, there is in fact incompatibility between parent group O and child A or B. In 10% of them, there is a HDN due to the destruction of fetal erythrocytes caused by IgG-class anti-A and/or anti-B antibodies present in the maternal serum. The mother-child serological situation in which a clinically relevant ABO HDN is most easily developed can be observed when the mother is group O and the infant is group A1. The prevalent modest clinical expression of HDFN by ABO incompatibility is related to several factors:

- Antigens A and B are fewer on fetal and neonatal red blood cells;
- Substances A and B present ubiquitously in endothelial epithelial and placental cells partly adsorb maternal IgGs that cross the placenta;
- Anti-A and anti-B IgGs are predominantly represented by IgG2, an Ig subclass with reduced ability to actively cross the placental barrier.

In the African and Arab populations, the incidence of HDFN from ABO incompatibility is higher; this is due to the high expression of genes A and B in these populations.

The frequency of HDFN from ABO incompatibility is the same in both in the first pregnancy and subsequent pregnancies: therefore, the disease is neither preventable nor predictable. The search for anti-A and/or anti-B IgGs during pregnancy is poorly indicative in predicting the appearance of the ABO HDN in the unborn child. The majority of pregnant women, especially those with group O, have anti-A and/or anti-B (and anti-A, B) IgGs in their serum, while infants with hemolytic disease are relatively few.

When the mother’s group is O and there is evidence of neonatal hematological laboratory evidence (positive DAT) or clinical evidence (jaundice), in the absence of known causes, ABO/RhD group typing is indicated on carotid red cells and the search and titration of anti-A and/or anti-B IgGs in the maternal serum. ABO HDN diagnosis is essentially clinical: even in the presence of ABO and anti-A and/or anti-B IgGs incompatibilities in the maternal serum, the DAT may also be negative or questionable.

Research and titration of IgG-class immunoglobulin anti-A or anti-B antibodies should be performed by IAT after cleavage of anti-A and/or anti-B isoagglutinin present in the maternal serum with reducing substances such as 2-mercaptoethanol (2-ME) or dithiothreitol (DTT), or using other commercially available neutralizing substances. In the case of positive DAT on carotid congestion, the elution of IgGs (anti-A and/or anti-B) is recommended for neonatal red cells. The best anti-A and anti-B IgGs elution technique consists in quickly freezing and thawing. A further method, quick and able to provide useful results, is represented by the heat elution method.
In the presence of laboratory (positive DAT) or clinical evidence (jaundice) of neonatal haemolysis, when the mother’s group is O, it is suggested to perform ABO/RhD-group blood typing on fungi excitation, search and titration of anti-A and/or anti-B IgGs in the maternal serum and, in the case of positive DAT, the elution of IgGs (anti-A and/or anti-B) from neonatal red cells.

Finally, the papers consulted in the study of the Hemolytic disease of the newborn (HDN) are listed in the following bibliography.

**References**


Societa Italiana di Medicina Trasfusionale e Immunematologia, Societá Italiana di Neonatologia e Gruppo di Studio di Ematologia Neonatale. Raccomandazioni per la terapia trasfusionale in Neonatologia. 1ª Edizione, Edizioni SIMITI, Italia; novembre 2006.

