Fetal and Neonatal Immune Cytopenias

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One of the articles in this issue of the Portuguese Journal of Pediatrics describes the rare cases of neonatal alloimmune neutropenia (NAIN) diagnosed in a Portuguese laboratory unit, over a 10-year period (2010-2019).[1] This laboratory receives requests from all over the country and has reported on 10 cases, indicating not only the rarity of the disorder but also the need to maintain a high index of suspicion for the diagnosis. The authors highlight the fact that this has been the first study conducted in Portugal on the subject and maintain that the existence of a reference laboratory along with a registry of patients with neonatal alloimmune neutropenia would help to increase knowledge on this rare disorder and improve patient care.

Neonatal alloimmune cytopenias represent a group of hematological disorders in which the placental barrier cannot avoid the effect of the maternal reaction on fetal target cells. Neonatal alloimmune neutropenia, in which maternal antibodies against paternally derived antigens on fetal neutrophils cross the placenta and destruct target neutrophils is, in fact, a disorder that rarely presents to the neonatologist, and is the neutrophil parallel to hemolytic disease of the fetus and newborn (HDFN) and fetal and neonatal alloimmune thrombocytopenia (FNAIT) for red blood cells and platelets, respectively. Multiple different antigens have been identified as potential targets in neonatal alloimmune neutropenia, but the causative antigen remains unknown in approximately 50% of cases.[2] Alloantibodies against the human neutrophil antigen (HNA) 1 antigen are the most frequently identified, and symptoms vary from none to mild skin infections, omphalitis, or more severe infections such as pneumonia, sepsis, and meningitis.[3]

Antibiotics for therapeutic treatment will often be sufficient.[3] Prophylactic antibiotics can be considered in cases with severe neutropenia (< 500 cell/µL), although evidence on effectiveness is lacking. In the reported series, 80% of the patients received prophylactic antibiotics (ampicillin and gentamicin), and 30% developed infections while on antibiotics. Treatment with granulocyte colony stimulating factor (G-CSF) is highly effective and can be considered for neonates suffering from severe infections. Even though benefits from the second-line treatment with intravenous immune globulin (IVIG) are reported in some case reports, more evidence is still required to recommend it as the first-line treatment.[3] In the reported series, the authors have referred to the low frequency of neonatal alloimmune neutropenia directed treatments compared to other series in the literature, namely the use of G-CSF.[1]

Other immune cytopenias (briefly reviewed in the following) occur with relative frequency in the neonatologist day-to-day clinical practice.

Hemolytic disease of the fetus and newborn

Hemolytic disease of the fetus and newborn occurs when maternal immunoglobulin G (IgG) antibodies develop against fetal red blood cells antigens that are paternally inherited and not present on maternal red blood cells.[4] The incidence of HDFN varies significantly with ethnicity, from < 1% in Asians to 35% in some ethnic white groups and is about 15%-16% in the white population.[5]

The ABO blood group system, with incompatibility present in up to 15% of infants, causes hemolytic disease in only 3%-4% of cases.[4,5] Most anti-ABO antibodies are not effectively transported across the placenta since they are predominantly IgM class. Moreover, the A and B antigens are not well developed on fetal red blood cells. Together, this results in a low rate of clinically severe HDFN, although the incidence of milder versions varies from 1:150 to 1:3000.[6] Hemolytic disease of the fetus and newborn is most commonly observed in blood group O mothers with blood group A (European ancestry) or blood group B infants (African ancestry).[6]

The antibodies against fetal red blood cells cross the placenta and enter the fetal blood circulation, causing destruction of fetal red blood cells, anemia, and hyperbilirubinemia.[7] Severe anemia in the fetus can lead to edema, ascites, hydrops, heart failure, and death.[8] In less severe cases, the *in utero* red cell incompatibility can persist postnatally with neonatal anemia due to hemolysis, along with hyperbilirubinemia and erythropoietic suppression.[8] Ongoing anemia can persist for weeks to months after

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birth until the maternal antibodies are no longer present.[8] Bilirubin resulting from red blood cells destruction can rise quickly due to underdeveloped metabolic machinery in the fetal liver, and very high levels of unconjugated bilirubin can lead to bilirubin encephalopathy. Chronic and permanent effects of kernicterus, which is permanent neuronal damage, include cerebral palsy, auditory dysfunction, intellectual, or other handicaps.[9]

The *Rhesus* (Rh) D antigen is the most potent immunogen of all red blood cells antigens.[8] *Rhesus* D incompatibility is the most frequent cause of severe immune hemolytic disease.[8] Before the implementation of Rh(D) immunoprophylaxis at the end of the 1960 decade, 16% of ABO compatible D-negative mothers with D-positive infants developed anti-D antibodies. However, a much lower percentage (< 2%) developed anti-D in mother / fetus pairs that were ABO incompatible as a result of the ABO antibody-mediated clearance of fetal red blood cells from the maternal circulation.[10]

The incompatibility caused by atypical antigens of the Rh system (Cc, Ee), of the Kell (Kk), Duffy (Fya), Kidd (Jka, Jkb), and MNS (M, N, S, and s) systems, although very rarely, can lead to severe disease or intrauterine death.[8] Blood type and Rh factor in the mother and infant, direct Coombs test (direct antiglobulin test), hemoglobin, reticulocyte count, and bilirubin levels (fractionated or total and direct) are necessary for the diagnosis of HDFN in neonates with unconjugated hyperbilirubinemia.[8]

Neonates affected by HDFN may need phototherapy to oxidize unconjugated bilirubin to allow for urinary excretion. For patients with known hemolytic disease of the fetus and newborn, close observation of bilirubin levels and hemoglobin is warranted to determine whether neonatal exchange transfusion is needed to wash out bilirubin and maternal antibody, and/or if blood transfusions will support oxygen-carrying capacity to the tissues.[11] Administration of IVIG to the neonate has been shown to reduce the need for exchange transfusions and phototherapy.[11] Hyporegenerative anemia can last for many weeks after birth, and infants must be carefully monitored for clinical signs.[8]

Fetal and neonatal alloimmune thrombocytopenia

Fetal and neonatal alloimmune thrombocytopenia, in which maternal antibodies traverse the placenta and destroy fetal platelets, may become a serious disease when leading to intracranial hemorrhage or death. Fetal and neonatal alloimmune thrombocytopenia is the most common cause of severe thrombocytopenia (< 30 × 10^9 cells/L) and intracranial hemorrhage in term neonates with an incidence of 1:1000 live births in the United States.[12]

Fetal and neonatal alloimmune thrombocytopenia is caused by maternal sensitization to paternally derived antigens on fetal platelets (human platelet antigen 1a, HPA-1a).[12] Since there is no current routine screening for FNAIT, diagnosis is made following the birth of a severely thrombocytopenic neonate, and antenatal management is only possible in subsequent pregnancies.[12] Intracranial hemorrhage can occur in about 20% of cases, and the only predictor in subsequent pregnancies is the history of an affected sibling.[12] Due to the high risk of recurrence of fetal thrombocytopenia in subsequent pregnancies, protocols for antenatal management, including maternal therapy, have been proposed with IVIG and/or corticosteroids or *in utero* transfusion.[13] After birth, maternal platelet transfusion is the treatment of choice.[13]

Maternal imune thrombocytopenic purpura (ITP)

Imune thrombocytopenic purpura is an autoimmune disease with autoantibodies against the platelet membrane causing platelet destruction in the reticuloendothelial system.[12] Generally, infants of mothers with ITP are not severely affected by thrombocytopenia, compared to infants with fetal and neonatal alloimmune thrombocytopenia.[12] Platelet counts are usually higher in neonates of mothers affected by idiopathic thrombocytopenic purpura. Moreover, in fetal and neonatal alloimmune thrombocytopenia, the thrombocytopenia resolves relatively quickly and rarely lasts longer than 1-2 weeks. In contrast, the infants of mothers with ITP typically have their counts worsen in the 2-4 days after birth and consequently need close neonatal monitoring of their platelet counts. In certain cases, the platelet counts can persist at low levels for months.[12]

The treatment of choice with IVIG, alone or in association with platelet transfusion, has been successful in 80%-90% of cases.[14] However, in the absence of IVIG, an exchange transfusion should be performed in combination with platelet transfusion.[14]

Immune thrombocytopenia may also occur in neonates from mothers with autoimmune thrombocytopenia associated with other maternal conditions, such as systemic lupus erythematosus.[14] It has been reported that mothers with autoimmune thrombocytopenia associated with human immunodeficiency virus have also delivered thrombocytopenic babies.[14]

Final remarks

The exact mechanisms underlying the intricate trafficking of blood cells and antibodies at the fetomaternal interface remain incompletely understood. Immune-

mediated cytopenias illustrate the clinical manifestations of abnormalities in these traffic patterns. Antenatal management of affected fetuses with treatment administered to the mother is now well established, although studies are ongoing.

Due to the lower frequency of neonatal alloimmune neutropenia, compared to other immune cytopenias, further research is needed to develop guidance protocols that will help clinicians provide the best care to the affected infants.

Keywords: Erythroblastosis, Fetal; Hematologic Diseases/immunology; Infant, Newborn; Purpura, Thrombocytopenic, Idiopathic; Thrombocytopenia, Neonatal Alloimmune

Author Contribuitions

The author participated in the conception, drafting and critical revision of the manuscript. The author approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the paper.

Conflicts of Interest

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