

Fetal and Neonatal Alloimmune Thrombocytopenia

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What is alloimmune thrombocytopenia?

Alloimmune thrombocytopenia is the most common cause of severe thrombocytopenia in otherwise normal full-term infants. The pathogenesis is similar to hemolytic disease of the newborn. Thrombocytopenia is caused by the transplacental transfer of alloantibodies to human platelet alloantigens (HPAs). The alloantigen on fetal platelets is inherited from the father and maternal alloimmunization occurs in women who are genetically predisposed to become immunized. Unlike hemolytic disease of the newborn, alloimmune thrombocytopenia often affects the first child.

How often does this occur?

In prospective studies, the incidence of severe thrombocytopenia (less than 50,000/uL) at birth due to alloimmune thrombocytopenia is about 1 in 1,100. The number of asymptomatic cases of alloimmune thrombocytopenia ranges from 10% to 25% of those alloimmunized.

What are the consequences on the fetus or neonate?

The consequences can be devastating in severe cases of thrombocytopenia leading to major physical and mental disability, and blindness. In several retrospective studies, intracranial hemorrhages occurred in up to 10–15% of affected infants, resulting in death. Although there is serious risk of hemorrhage at the time of delivery, nearly 50% of intracerebral hemorrhages occur in utero, between 30 and 35 weeks of gestation.

Could you give some background on what is known about HPAs?

HPAs were initially defined during an investigation of the sera of mothers who became thrombocytopenic after blood transfusion, leading to the disorder of posttransfusion purpura. HPAs actually represent polymorphisms of important platelet surface glycoproteins, mainly glycoprotein IIB-IIIa, IB/IX, and Ia/IIa.

The PLA1 antigen, now indicated as HPA-1A, was the first platelet-specific alloantigen to be described, more than 40 years ago. In subsequent years, numerous other alloantigens

of platelet glycoproteins have been identified, causing maternal alloimmunization during pregnancy, as well as several low-frequency or private alloantigens. To date, we know of approximately 24 platelet-specific alloantigens that have been defined serologically. In fact, we know the molecular basis for the majority of these alloantigens, and they have all been assigned an HPA number.

Glycoprotein IIIa is the most polymorphic molecule of the platelet glycoproteins. The molecular basis of 8 of the antigens on glycoprotein IIIa has been determined. Among white people, anti-HPA-1A is implicated in 80% of cases of alloimmune thrombocytopenia. This is due to the relative immunogenicity of the HPA-1A antigen and to the phenotype frequency of the antigen. Ninety-eight percent of Caucasians are positive for HPA-1A, which means that 2% of pregnant women may produce anti-HPA-1A. However, fewer women make the antibody because the father of the child is heterozygous for the antigen and because of HLA restriction of the alloimmune response.

Antibodies to HPA-5B are responsible for 20% of cases of alloimmune thrombocytopenia in white people. As the density of this antigen is lower, the thrombocytopenia tends to be less severe. Among Asians, anti-HPA-4A and anti-HPA-4B cause thrombocytopenia more often than other platelet antibodies.

What treatment may be administered to the newborn?

In terms of platelet transfusions, it is important to have antigen-negative platelets prepared for the neonate. Previously at our center, we relied upon washed maternal platelets with good success. However, this approach presents logistical problems including the procurement of platelets by pheresis, platelet washing and resultant activation, and the risk of transmitting infection to the neonate. We now rely upon typed platelet donors that are available from our blood center. Since most alloimmune thrombocytopenia is due to sensitization of HPA-1A, many blood centers in the United States now have platelet donors that can be called ahead of time, an important development in the treatment of this disorder.

If antigen-matched platelets are not available and hemorrhage is present, random donor platelets may be administered combined with high-dose intravenous (IV) gamma globulin until compatible platelets are available. IV gamma globulin should not be used alone since the baby will be at risk of significant bleeding.

Why is IV immunoglobulin given and is it effective?

IV immunoglobulin therapy given as an adjunctive therapy to the mother modulates the effect of the alloantibody on platelet destruction. Several reports document therapeutic responses to the maternal administration of IV gamma globulin at a dose of 1 g/kg body weight per week. In our experience, responses occur in 85% of cases. Monitoring the effect of therapy with fetal blood sampling permits the administration of platelet transfusions if the count is low. However, there have been reports of antenatal intracranial hemorrhage. Some studies have found only good responses in the most mildly affected cases. It should be cautioned that fetal sampling is associated with a 1% fetal loss, and the complication rate depends a good deal on the experience of the operator. Because the fetus is thrombocytopenic, the risk of bleeding is higher in pregnancies affected by alloimmune thrombocytopenia.

How are future pregnancies handled if a firstborn child is found to have this disorder?

Patients are referred to high-risk fetal/maternal medicine specialists who are familiar with managing alloimmune thrombocytopenia and are capable of performing in utero blood sampling and fetal genotyping (by amniocentesis or fetal blood sampling) since the recurrence of thrombocytopenia subsequent pregnancies is high, although the risk in part depends upon whether the partner's platelet genotype is homozygous (indicating 100% risk) or heterozygous (indicating 50% risk) for the antigen. Fetal sampling is conducted to determine the fetus genotype and to measure the platelet count of the fetus. If the count is low at that time, a platelet transfusion of antigen-matched platelets will be given.

How are mothers screened for the incompatibility that might lead to this disorder?

At the present time there is no consensus about the utility of screening as there is with hemolytic disease of the newborn. With screening, the primary emphasis is on identifying the HPA-1A incompatibility because this is the most common type. It would be difficult to screen for all 24 known HPAs. Although antenatal hemorrhage may be devastating, some argue that the knowledge of alloimmune thrombocytopenia is as yet insufficient to justify antenatal screening. More research is needed in areas including clinical outcome of affected cases, the identification of factors useful for predicting severe disease, and the preferred option for antenatal intervention with an alloantibody but no previously affected pregnancies.

Where has your research focused over the past several years?

Our group has studied the immunogenetics of platelet alloantigens in different ethnic groups, the mechanisms of

immune destruction of platelets, and the standardization of diagnostic and genotyping tests important in the diagnosis and screening strategies for alloimmune thrombocytopenia. In addition, we have been studying the effect of IV gamma globulin to determine whether or not its administration has an effect upon placental vascular integrity. We have observed that a significant number of our neonates that have alloimmune thrombocytopenia have intrauterine growth restriction. We have related this to abnormalities in placental pathology that appear to be ameliorated with IV gamma globulin administration to mothers. We are investigating the basis of this observation to determine if placental dysfunction contributes to the complications in neonates.

What are some of the major changes in this field over the years?

There have been several: the characterization of the HPAs at the molecular level, the development of sensitive methods to detect platelet alloantibodies, and the improvement in the antenatal and postnatal management of the fetus/neonate. With the growing number of clinical studies, we have a better grasp of the clinical issues and can develop better strategies to diagnose and treat the disorder, and determine how to apply screening strategies in different ethnic populations.

What improvements are needed?

Clinically, more research is needed in developing approaches to screening as mentioned above. In addition, noninvasive methods of studying fetuses at risk are needed. We know that fetal cells can be detected in maternal circulation so that potentially one can genotype these cells for HPA.

The best scenario would be prevention of this disorder, which means identifying women who are already alloimmunized, and then altering their immune system with some type of immunetolerating modality so that they do not produce the antibody.

Immunomodulation of the immune response by manipulation of B or T cells or effector mechanisms may be possible. Identification of the T-cell epitopes would permit the use of peptide sequences to class II molecules bound to the corresponding peptide. These conjugates could be used to induce T-cell tolerance by binding to T cells in the absence of costimulatory signals. Furthermore, it may be possible to make designer molecules that inhibit the binding of pathologic maternal antibodies to fetal platelets or to develop means to target Fc receptors on phagocytic cells.

Suggested Reading

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