Since the first description of the immunologic mechanisms in neonatal and thrombocytopenic purpura and the first report of a maternal antibody directed against a platelet alloantigen inherited from the father, in the 1950s, much has been learned concerning fetal and neonatal alloimmune thrombocytopenia (FNAIT), but questions are still unanswered. FNAIT has been regarded as the platelet counterpart of HDN, but, in contrast to HDN, the first infant is affected in 50 percent of cases. This condition, which has been estimated to have an incidence of 1 in 800 to 1 in 1000 live births, can cause severe bleeding in the fetus and newborn, and all incompatible fetuses will be at risk for subsequent pregnancies. Therefore, it is important to diagnose FNAIT and to manage the subsequent pregnancies to prevent the consequences of severe fetal thrombocytopenia.

1953–2007: the Platelet Alloantigen Story

Over the years, considerable progress has been made in the characterization of platelet-specific alloantigens. Improvements in serologic methods for the detection of maternal alloantibodies—including the use of antigen-capture assays, the monoclonal antibody-specific immobilization of platelet antigens technique, or monoclonal antigen capture ELISA—the development of immunochemical techniques, and the advent of molecular biological techniques have led to the description of 24 platelet-specific alloantigens. A human platelet antigen (HPA) nomenclature was adopted in 1990 to replace the lab-specific nomenclature that was used previously. The antigenic systems are numbered in order of the date of discovery; the high-incidence allele is called “a,” and the low-incidence allele is called “b” in the original population in which the alleles were identified. Under the auspices of the International Society of Blood Transfusion and the International Society of Thrombosis and Haemostasis, a Platelet Nomenclature Committee has published tables that will be updated; these include the list of the HPA antigens, the antigen genetic basis, and the platelet antigen alleles defined by sequencing. The HPA nomenclature will still be used for clinical and scientific purposes. The reader is referred to the table of numbered HPAs, their glycoprotein location, and approximate Caucasian phenotype frequencies in “Scott Murphy’s contributions in the early years of posttransfusion purpura: a remembrance” in this issue of Immunohematology.

HPA antigens are expressed on different integrins playing a role in cellular interactions. \( \alpha_{IIb}\beta_3 \) (GPIIb–IIIa) is the major platelet integrin and is restricted to platelets, whereas the \( \alpha_v\beta_3 \), integrin is expressed more widely. \( \alpha_{IIa}\beta_1 \), also known as GPIa-IIa, is the second most important platelet integrin and is also found on lymphocytes. Antigens located on \( \beta_3 \) (GPIIIa) have been found on other cells, such as endothelial cells, and on activated T lymphocytes when located on \( \alpha_\text{II}^\text{a} \); this may play a pathophysiologic role.

Frequencies of platelet antigens vary among different populations. In Caucasians, HPA-1a is by far the most common antigen implicated in FNAIT, followed at much lower frequency by HPA-5b, then HPA-3. In contrast, in Asians, FNAIT is essentially associated with HPA-4 and HPA-5b. FNAIT has been reported involving rare or private antigens. Recent studies have shown that these low-frequency antigens are not restricted to single families, especially anti-HPA-9bw, which could account for up to 2 percent of confirmed cases; therefore they must not be ignored in the screening for FNAIT with a negative initial laboratory investigation. The humoral maternal response is not uniform in this condition and must be taken into account when undertaking serologic diagnosis. Further study of the characteristics of the maternal alloantibodies and their relevance to the clinical condition would be of interest.
The genetic basis for maternal alloimmunization has been investigated. Alloimmunization to the HPA-1a antigen appears to be associated with HLA class II alleles: DRB3*0101 and DQB1*0201 (odds ratio 24.9 and 39.7, respectively). An anti HPA-1b response was not associated with either DRB3*0101 or any known HLA class II molecules. This finding implies the Leu33/Pro33 substitution on the platelet glycoprotein IIIa plays a role in antigen presentation. Data have shown that the binding of peptides from the Leu33/Pro33 dimorphic region to HLA-DR3*0101 is allele specific with stimulation of specific T cells providing help to B cells for generating alloantibodies; however, the positive predictive value is only 35 percent, and utility for screening is therefore limited.

The immune response to HPA-5b antigen is strongly associated with a particular DRB1 gene sequence encoding residues Glu-Asp at positions 69 and 70 of the DRβ chain. For other antigens, because of the low number of cases, statistical analyses are not significant when compared with the general population, as seen for HPA-6b and DRB1*1501, DQA1*0102, DQB1*0602 haplotypes shared by immunized mothers.

1953–2007: the Fetal and Neonatal Alloimmune Thrombocytopenia Story

Natural history

FNAIT has been known for decades as “neonatal alloimmune thrombocytopenia” (NAIT). The usual presentation is a full-term neonate exhibiting petechiae or widespread purpura at birth, or a few hours after birth, to a healthy primiparous mother. Otherwise, this infant is well with no clinical signs of infection (hepatosplenomegaly) or malformation (hemangioma, absence of radii). Visceral hemorrhages such as gastrointestinal bleeding or hematuria are less common than purpura or hematoma. The thrombocytopenia is isolated. Coexisting anemia is caused by hemorrhage.

Anti-HPA-1a and anti-HPA-3a immunization induce severe neonatal thrombocytopenia with platelet counts less than 50 × 10^9/L in most cases. NAIT linked to HPA-5b incompatibility seems to be less severe than HPA-1a NAIT. The most serious complication is fetal or neonatal intracranial hemorrhage (ICH; 25.5% of cases for HPA-1a, 24% for HPA-3a, 15% for HPA-5b) leading to death in up to 10 percent or neurologic sequelae in up to 20 percent of reported cases.

The risk of life-threatening hemorrhage necessitates prompt diagnosis and effective therapy. Phentoxified platelet transfusion is the best postnatal management. Because of the logistic difficulties in obtaining such platelets in emergency situations, random platelet transfusions with or without IVIG have been proposed. However, compatible platelets give better results. On the other hand, thrombocytopenia may be asymptomatic and pass unnoticed unless there is a routine platelet count performed. Therefore, unexpected or unexplained neonatal thrombocytopenia or severe early onset thrombocytopenia in both preterm and term babies should raise the possibility of NAIT and guide investigations accordingly. The fetal thrombocytopenia tends to worsen in subsequent incompatible pregnancies.

Fetal blood sampling

In 1983, a major advance in the diagnosis of NAIT was the use of ultrasound-guided fetal blood sampling (FBS), which led to a better understanding of the fetal status. The mean platelet count has been evaluated to be more than 150 × 10^9/L by the end of the first trimester of pregnancy in healthy fetuses and similar to the adult platelet count later on. Therefore, thrombocytopenia has been defined in the fetus and the neonate as a platelet count less than 150 × 10^9/L, irrespective of the gestational age.

In 1984, the first fetal alloimmune thrombocytopenia case was documented with FBS at 32 weeks of gestation, and in utero maternal platelet transfusion before delivery was proposed as therapy to avoid perinatal ICH. Severe fetal thrombocytopenia was then documented early during pregnancy when FBS, as part of the antenatal management protocol, was carried out at 21 weeks of gestation for subsequent pregnancies in women with a previously affected infant. A retrospective survey of 5194 fetal blood samplings showed that fetal thrombocytopenia resulting from maternal alloimmunization was the most severe thrombocytopenia observed among the different disorders encountered, including chromosomal malformations, infections, or maternal autoimmune thrombocytopenia.

Development of antenatal management

The rationale for antenatal management is the high rate of recurrence for subsequent incompatible fetuses who usually experience more severe thrombocytopenia. The first attempts to prevent severe
Neonatal alloimmune thrombocytopenia

thrombocytopenia in the preterm period and thus ICH during delivery were in utero platelet transfusions before delivery. However, this management could not prevent in utero ICH, which has been reported primarily before 30 weeks of gestation. Because of the short survival of transfused platelets, weekly fetal platelet transfusions have been proposed and shown to be effective in preventing ICH in a number of cases. The risks of in utero platelet transfusion, bleeding, and fetal loss have been estimated to be 1 to 2 percent per procedure and 8 percent per pregnancy. Fetal cardiac arrhythmia (prolonged bradycardia) has also been reported. Less invasive therapy has also been proposed, involving maternal administration of IVIG, steroids, or both.

The mechanism of action of IVIG is complex, including inhibition of the transplacental passage of maternal alloantibodies and modification of the immune response. Corticosteroids may modulate the maternal immune response. Different IVIG protocols have been developed and differences in results were reported mainly because of the definition of a successful response. Low-dose corticosteroids, as sole therapy, have been given to a limited number of patients, and response to therapy appears highly variable.

The optimal management remains to be determined, and an international forum in 2003 demonstrated the absence of standardization. The decision regarding therapy depends on different factors, among which the fetal status plays a central role. There is no reliable and sensitive parameter for predicting which fetuses will be severely affected and which ones will respond to therapy. The only way to assess the fetal status is to perform FBS, but the risk of serious adverse events from this technique is high, up to 10 percent. Most protocols favor maternal therapy with less invasive strategies with stratification according to the previously affected sibling’s status.

Serial in utero platelet transfusions are considered only as salvage therapy after failure of maternal treatment.

Antenatal screening

No systematic screening for FNAIT exists at the moment, and this condition is still underdiagnosed. Reduction of neonatal death and disability is a public health issue, and recent progress in the prevention of current causes of neonatal disorders has been efficient at reducing the risk of neonatal disorders going undiagnosed and untreated. Prospective studies have shown that although 2 to 3 percent of women are at risk for developing anti-HPA immunization, only 1 in 800 to 1000 newborns will be affected. It has been found that 26 percent of infants born to immunized mothers are nonthrombocytopenic. Until procedures are found that predict which women will have an affected fetus, maternal screening has a low sensitivity. Only identifying thrombocytopenic newborns at birth increases the sensitivity but will miss fetuses severely affected during pregnancy who should have been treated. Cost-effectiveness analysis indicated screening newborns was more cost-effective than screening primiparous women. A consensus on routine investigation and optimal antenatal management has yet to be reached.

Future Directions

Although real progress has been achieved in the more accurate diagnosis and management of FNAIT, further studies must focus on improvements in antenatal management and on mechanisms of maternal sensitization. A recent study has shown that high maternal anti-HPA-1a alloantibody concentrations may provide an indication of severely affected fetuses and this may contribute to a less invasive antenatal therapeutic strategy. However, the follow-up of maternal anti-HPA-1a concentration during pregnancy should not be considered as an indicator of therapeutic effectiveness.

A murine model has also been recently developed, which may contribute to a better understanding of this condition in the future.

References


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