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Neonatal alloimmune thrombocytopenia

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Neonatal alloimmune thrombocytopenia is the commonest cause of early onset isolated thrombocytopenia in an otherwise healthy neonate.[1]

This syndrome is comparable to hemolytic disease of the newborn, although it frequently affects the first infant. The thrombocytopenia results from maternal immunization against specific platelet alloantigens paternally inherited by the fetus. During pregnancy, the maternal alloantibodies can cross the placental barrier as soon as 14 weeks of gestation. The fetal opsonized platelets are then cleared in the reticulo-endothelial system. The resulting thrombocytopenia is not only due to increased platelet destruction but also to impaired platelet production.

The incidence of neonatal alloimmune thrombocytopenia in the unselected Caucasian population has been estimated by prospective studies to be 1/800 to 1/1000 live births.[2,3] The most feared complication is intracranial hemorrhage (ICH) in the case of severe thrombocytopenia. The morbidity has been estimated to be 20% of the reported cases and mortality up to 15%.[4,5] Alloimmune thrombocytopenia can be diagnosed during pregnancy or at birth.

Clinical presentation

The neonate

Since the first description by Harrington in 1953[6] to the breakthrough of fetal medicine in the 1980s the diagnosis has essentially been made in a full-term neonate who exhibits bleeding at birth or a few hours afterwards. Otherwise the infant is well with no signs of infection, malformation or chromosomal abnormalities. The isolated thrombocytopenia is severe, with the platelet count being below 20×10^9/L. In this situation, appropriate therapy must be instituted immediately in order to reduce the risk of significant hemorrhage.

Conversely the infant may be symptomless and thrombocytopenia (a platelet count below 150×10^9/L) is discovered incidentally on a complete blood count performed for a different indication.[7]

Identifying the cause of unexpected or unexplained neonatal thrombocytopenia or severe early onset thrombocytopenia in both preterm and term babies is a matter of concern. The diagnosis of the thrombocytopenia is of importance for both the infant and future pregnancies. The possibility of alloimmune thrombocytopenia in those conditions may be raised and investigations must be conducted accordingly.

The fetus

With the development of fetal medicine, fetal alloimmune thrombocytopenia has been recognized as the most severe form of fetal thrombocytopenia.[8] By the end of the first trimester of pregnancy, the mean fetal platelet count is above 150×10^9/L.[9] A platelet count below this threshold, therefore, defines thrombocytopenia regardless of the gestational age. Severe thrombocytopenia has been observed from 21 weeks of gestation[10] without spontaneous correction as gestation progresses.

Fetal alloimmune thrombocytopenia may be suspected in the case of ICH. Retrospective studies have shown that in feto-maternal alloimmunization 80% of the

reported cases of ICH occur antenatally and 40% of them before 30 weeks of gestation.[5] Laboratory investigations must be performed to confirm the alloimmune origin.

Laboratory diagnosis

The laboratory diagnosis of fetal/ neonatal alloimmune thrombocytopenia is made by identifying the maternal alloantibodies that are directed against specific paternal platelet antigens.

Currently 24 platelet-specific alloantigens have been described.[11] In 1990, a new platelet nomenclature was designed by the Platelet Working Party of the International Society of Blood Transfusion.[12] The human platelet alloantigen (HPA) nomenclature is now in use. The antigens are numbered in order of discovery and the alleles labelled alphabetically in the order of their serologic frequency: *a* is the common one, *b* the rare one. The Platelet Nomenclature Committee is the guardian of the nomenclature.[11]

Alloantibody testing is usually performed by antigen-capture assays such as the monoclonal antibody specific immobilization of platelet antigens (MAIPA),[13] or modified antigen capture enzyme-linked immunosorbent assay (MACE). The maternal serum must be tested versus the paternal platelets and versus a panel of typed O platelets.

Platelet typing is usually done by molecular biology techniques such as polymerase chain reaction (PCR) techniques [PCR-SSP (sequence-specific primer) and PCR-RFLP (restriction fragment length polymorphism)].

In Caucasians, the HPA- 1a alloantigen is the most frequent antigen implicated in fetal/neonatal alloimmune thrombocytopenia, followed by HPA-5b. Alloimmunization against rare platelet antigens is not restricted to a single family; HPA-9bw antigen accounts for up to 2% of the confirmed cases of neonatal alloimmune thrombocytopenia.[14,15]

Thrombocytopenia resulting from anti HPA-1a immunization is usually more severe than that due to anti HPA-5b. However, ICH has been observed whatever the platelet alloantigen implicated.

Given laboratory problems and difficulties in alloimmunization testing (maternal alloantibody not detectable, rare platelet antigens)[14,16,17] investigations must be done in a specialized laboratory. Any difficulty in laboratory diagnosis must not delay the therapy, especially in the case of life-threatening hemorrhage.

In the near future, the development of DNA microarrays and chip technology will probably increase the possibility of large-scale testing.

Therapy

The neonate

Infants with clinical bleeding or a platelet count below 30×10^9/L during the first 24 hours of life should be promptly transfused with platelets. The best choice is to transfuse antigen-negative platelets from phenotyped donors or maternal washed and irradiated platelets. However, in an emergency, transfusion of random donor platelets with addition of intravenous immunoglobulins (IVIG) (1 g/kg body weight) has been proposed.[18] In all cases, the neonate must be monitored closely until a safe platelet count has been reached.

If the infant has no signs of bleeding and a platelet count above the treatment trigger, no therapy is usually required. However, a platelet count is regularly done to ensure that it does not fall afterwards to a level requiring therapy.

Ultrasound examination is recommended to exclude ICH. In the absence of ICH the outcome is usually favorable and the platelet count returns to normal within 8-10 days.

The fetus

Developing antenatal management strategies[19,20] depend on the high rate of 'recurrence' of thrombocytopenia in subsequent fetuses in whom the condition is usually more severe.

The optimal antenatal therapy is still a matter of discussion.[21] However, there is a consensus that women with high-risk pregnancies should be followed in referral centers and that invasive procedures be minimized.[22]

Important considerations for antenatal therapy are the evaluation of the fetal status, the risk of therapeutic procedures and the efficacy of therapy.

Maternal therapy with IVIG, with or without steroids, is now considered the first-line therapy.[23,24] The infant is usually delivered by elective Cesarean section 2-4 weeks before term.

Compatible platelets are transfused to the neonate in the case of severe thrombocytopenia.

Routine antenatal screening

Implementation of routine antenatal screening is a public health question. Without such screening, the first affected infant will be at risk of severe thrombocytopenia. The limitation of antenatal screening is mainly the absence of standard management of the affected fetus. However, recent favorable results of such a program in Norway may lead to this issue being reconsidered.[25]

Future prospects

The main areas of research in fetal/neonatal alloimmune thrombocytopenia are the mechanisms of maternal sensitization, identification of predictive parameters for fetal status,[26] standardization of non-invasive antenatal management and feasibility of antenatal screening.

In this issue of the journal, Killie *et al.* report the results of a prospective study concerning maternal alloantibody titer as a potential predictor for neonatal alloimmune thrombocytopenia.[27]

The outcome of an international forum on the management of alloimmune thrombocytopenia was recently published.[22] The quantification of maternal anti HPA-1a alloantibody as a prognostic parameter for the severity of alloimmune thrombocytopenia was among the questions on the different aspects of alloimmune thrombocytopenia sent to experts in the field. There was no agreement on the value of this parameter. However, in Norway, as in France,[26] evidence was obtained for a correlation between the maternal alloantibody titer and the severity of the thrombocytopenia.

As shown by Killie *et al.* the choice of the serological

method, the statistical calculations and the time that maternal samples are taken, are crucial for establishing such a correlation. These results are of importance for the appropriate management of pregnancies and neonates.

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n-3 fatty acids and cardiovascular disease

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The coronary athero-thrombogenic risk profile and the acute coronary syndrome; the role of n-3 polyunsaturated fatty acids (PUFA)

Cardiovascular risk has been associated with established risk factors such as dyslipidemia, hypertension, smoking, obesity, insulin-resistance / impaired glucose tolerance, physical inactivity, age, gender and genetics.[1] Mild to moderate hyperhomocysteinemia has emerged as an independent cardiovascular risk factor,[4,5,6] probably associated with endothelial dysfunction, and may exert unfavorable effects on the antithrombotic properties of the endothelium.[2] Finally, recent research adds support to the view that atherosclerosis is an inflammatory process.[3]

The acute coronary syndrome usually results from erosion or rupture of a vulnerable atherosclerotic plaque leading to acute coronary occlusion.[3] A thin fibrous cap, surrounding the lipid core with inflammatory cells, is the only structure separating the blood compartment with