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Scientific Research

Neonatal Alloimmune Thrombocytopenia Due to Maternal Anti HPA1a Antibodies: Case Report and Management of Subsequent Pregnancy

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Abstract

Fetoneonatal alloimmune thrombocytopenia is an infrequent and severe disease that is unexpectedly found after an uncomplicated first pregnancy. Affected infants might show unexplained purpura, intracranial hemorrhage, and/or gastrointestinal or genitourinary hemorrhage. Nevertheless, in asymptomatic newborns the thrombocytopenia may be discovered incidentally. We describe a case report that highlights that the incidental diagnosis of FNAIT allows both properly managing the newborn, and detecting maternal anti-HPA1a antibodies in order to prevent the disease in subsequent pregnancies. A non-invasive treatment based on IVIgG allowed to this patient to prevent FNAIT in her second pregnancy.

Keywords

Fetoneonatal Alloimmune Thrombocytopenia; Anti-HPA1a Antibodies

1. Introduction

Fetoneonatal alloimmune thrombocytopenia (FNAIT) is a rare but severe condition that arises from maternal alloimmunization against a fetal platelet antigen inherited from the father and absent on maternal platelets [1]. The incidence is assessed to be one in 1.000 - 2.000 births in the Caucasian population [1], in which the antigen human platelet antigen 1a (HPA-1a) is responsible for 85% of cases [2]. FNAIT is a main cause of severe throm-

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bocytopenia, as well as intracranial hemorrhage, in both fetuses and term neonates [2]. Classically, neonatal thrombocytopenia is unexpectedly found in first pregnancy [3]. During this first pregnancy, fetal platelets can reach maternal circulation. A large number of fetal platelets in maternal circulation can trigger the maternal production of alloantibodies, firstly immunoglobulin (Ig) M and later IgG, which can cross the placenta. In the same or in following pregnancies with the same partner, these maternal antibodies of IgG class may reach the fetal blood and mediate the immune destruction of the fetal platelets, leading to fetal and neonatal thrombocytopenia [1].

The recovery from FNAIT is usually spontaneous, without any treatment, in the first weeks of life. Nevertheless, 15% of the affected infants have intracranial hemorrhage (ICH), and 25% - 50% of these hemorrhages occur in utero. There is a lack of serological factors that predict the severity of the thrombocytopenia in the newborns [3].

We describe a case in which a woman developed anti HPA 1a antibodies during her first pregnancy, which originated FNAIT. A close follow-up coupled with intravenous immunoglobulin G was essential to prevent alloimmune thrombocytopenia in her second child.

2. Case Report

A 30-year-old woman, gravida 1, para 0, was admitted to La Fe University Hospital (Valencia, Spain) at 39 weeks and 5 days of pregnancy in order to undergo an elective cesarean section due to fetal breech presentation. She had no relevant medical or surgical history. The gestation was uneventful despite the woman suffered gestational hypothyroidism treated with Levothyroxine 50 mg per day.

An uncomplicated cesarean section was carried out. A male weighing 3750 grams was born in breech presentation, whose Apgar scores were 7.10 and 10 after 1, 5 and 10 minutes, respectively. Whereas arterial pH was 7.20 mmHg, venous pH was 7.32 mmHg. The blood group and Rhesus blood group (Rh) of the newborn was A+, the same as his mother. Artificial feeding was given to the newborn male. Both mother and newborn were discharged two days after delivery, when the newborn weighed 3440 grams (he loosed 8.7% of weight).

In his fourth day of life, mother brought the newborn to the emergency department because he presented cutaneous and mucous jaundice during the last 24 hours. Physical examination revealed jaundice, without other skin lesions such as petechiae or hematomas. Blood analysis showed a total bilirubin level of 25.9 mg/dl (normal limits 0.1 - 1.1 mg/dl) and a platelet count of 92.000/µl (normal limits 150.000 - 400.000/µl), without any other abnormal parameter. The mother had her platelet levels within normal limits during the pregnancy. The following day, neonatal bilirubin level was 17.16 mg/dl and the platelet count was 75.000/µl. The newborn only received phototherapy for his jaundice. Three days after the neonatal admission into the Hospital, histotal bilirubin was 13.1 mg/dl and his platelet count was 82.000/µl. While total bilirubin levels were progressively decreasing, platelet count was raising without any further medication. In the study of neonatal thrombocytopenia, it was only found in mother's serum antibodies anti membrane glycoproteins IIb/IIIa HPA1a (PLA 1). A subsequent investigation of the platelet genotype in both parents was done. Whereas the mother genotype was HPA 1b1b, 2a2a, 3a3b, 4a4a, 5a5a, 15a15a, the father genotype was HPA 1a1a, 2a2a, 3a3a, 4a4a, 5a5a, 15a15b. Therefore, FNAIT was diagnosed as the mother had serum alloantibodies against fetal HPA 1ainherited from the father. Twenty days after his admission, the newborn was discharged with a platelet count of 236.000/µl after a spontaneous recovery. Since both mother and father were homozygous for HPA 1, NAITP would be present inlaterpregnancies.

Eighteen months later, the woman underwent her second pregnancy with the same partner. To manage that gestation, percutaneous umbilical blood sampling at 28 weeks of gestation to determine the fetal platelet count, and platelet transfusions through the umbilical cord were considered. Nevertheless, since these options associate significant morbidity and mortality, they were dismissed in an agreement with the Hematology Department in favor to a non-invasive procedure. Thus, maternal serum anti-HPA1a antibodies were quantified at 28 week of pregnancy and pregnant woman received intravenous immunoglobul inG (IVIgG) (70 g weekly) since week 28 until the end of pregnancy. Furthermore, quantification of maternal serum anti-HPA1a antibodies and obstetric ultrasounds were realized every two weeks since the beginning of the treatment. Maternal serum level of alloantibodies remained steady during pregnancy. An elective cesarean section at the 37 week pregnancy was planned in order to avoid the potential risk of fetal or neonatal internal bleeding, such as intracranial bleeding. A female newborn weighing 3050 grams was born in cephalic presentation, whose APGAR scores were 9, 9 and 10 after

1, 5 and 10 minutes. Arterial pH was 7.27 mmHg and venous pH was 7.30 mmHg. Her blood group and Rh was A+, like her mother. Any physical or analytical alterations in the newborn were excluded. Her platelet count was 184.000/µl. Cranial ultrasound confirmed absence of ICH. Both children are health at the moment.

3. Discussion

This case report describes a FNAIT in a newborn who initially only presented jaundice. Since the mother developed anti-HPA1a antibodies during her first pregnancy, she required intravenous immunoglobulin G in her second gestation to avoid a new FNAIT.

Over 100 immunogenic different glycoproteins (Gp) are present in the platelet membrane. The antigens located in a specific part of every Gp are named human platelet antigens (HPA) [1]. It have been described a total of sixteen HPA systems, six major (between HPA 1 and 5, and HPA 15) and other rare [1] [4]. All of them are in two allelic forms named "a" or "b", which are defined by their major or minor frequency [1]. Whereas HPA-1a is the most frequent antigen in Caucasians, responsible for 85% of cases of FNAIT, HPA-5b originates only 15% of cases [4].

Fetal platelets express specific platelet antigens at 16 weeks of pregnancy. Those fetal HPA antigens of paternal origin that are not present on maternal platelets trigger the maternal production of alloantibodies. Thus, FNAIT results from the transplacental cross of maternal IgG antibodies against fetal HPA antigens inherited from the father and absent in the mother [1] [5] [6].

A platelet count less than $<150 \times 10^9$/L at any gestational age defines fetal thrombocytopenia. Term neonates have the same range of normal platelet counts as healthy older children and adults ($150 - 450 \times 10^9$/L) [4]. FNAIT is a potentially devastating condition that may originate intracerebral hemorrhage or a major lung bleed, and even a subsequent intrauterine death [1]. Nevertheless, in the absence of cerebral bleeding FNAIT is a transient disease with a good prognosis. Whereas FNAIT appears in the first pregnancy in approximately 50% ofcases, the recurren cerate in a subsequent pregnancy is 90% [4].

From a clinical point of view, FNAIT is a diagnosis of exclusion. Classically, the disorder is surprisingly identified at birth after an uncomplicated pregnancy. At that moment, the majority of affected infants show unexplained purpura, ICH, and/or gastrointestinal or genitourinary hemorrhage [4]. However, the newborn may be asymptomatic and the thrombocytopenia might be discovered incidentally [4], as occurred in the case report that we have described in which the infant had jaundice. If the disorder remains unnoticed, the risk of a major neurological damage as a consequence of ICH due to severe thrombocytopenia is enhanced [4].

The diagnosis requires the confirmation of the neonatal thrombocytopenia, as well as the detection of parental platelet antigen incompatibility with corresponding maternal alloantibodies [4]. Since FNAIT cannot be prevented, it should be excluded in newborns with petechiae, ICH or abnormal bleeding [4].

The goal of the post-natal therapy is to avoid the potential consequences of severe thrombocytopenia, such as bleeding, ICH and fetal death. Therefore, treatment depends on both the presence of bleeding and the degree of thrombocytopenia, and it requires effectiveness and quickness [1]. Platelet transfusion is the treatment of choice [1]. It is indicated during the first 24 hours of life if the infant has a count less than 30×10^9/L, clinical bleeding, a count less than 100×10^9/L with ICH, or a count of $50 \times 10 \times 10^9$/L with prematurity, birth asphyxia or another predisposition to ICH [4]. It is usually neededa single or a couple transfusions of 10 ml/kg of platelet concentrate. Those transfused platelets will not be destroyed by maternal antibodies in the newborn's circulation, since they are HPA genotyped compatible or cross-matched negative platelets [1]. For severe FNAIT it may be considered a progressive treatment based on 10 - 20 ml/kg of platelet concentrate, IVIgG 1 g/kg/day for 1 - 3 days depending on response, and methylprednisolone 1 mg/8 hours intravenously. A cranial ultrasound, computerized tomography or magnetic resonance is advisable to rule out ICH [4]. Although thrombocytopenia usually resolves within two weeks, it might last six weeks [4]. In our case, fortunately the first newborn recovered spontaneously and the second did not have FNAIT.

In women with previous fetal death or with infants with neurological damage due to ICH, as well as in women with history of identified FNAIT, levels of anti-HPA1a antibodies should be determined in subsequent pregnancies, particularly with the same partner [1] [4]. Actually, maternal anti-HPA1a alloantibody levels during pregnancy are a reliable predictive factor to identify cases at risk for FNAIT [4]. Our patient received a close follow-up during her second pregnancy due to the FNAIT in her prior pregnancy. Quantifications of anti-HPA1a antibodies every two weeks since the week 28 of pregnancy were carried out. In addition to the established fetal

ultrasounds at 12 and 20 weeks of pregnancy to rule out chromosomal and morphologic anomalies, respectively, fetal growth and Doppler parameters of middle cerebral artery and umbilical artery were evaluated by serial ultrasounds every two weeks since week 28 of pregnancy until the end of gestation.

The prenatal management of FNAIT is controversial, as severe hemorrhage may occur early in pregnancy and non-invasive procedures are not able to reliably predict the severity of fetal alloimmune thrombocytopenia [4]. Although serial platelet transfusions are effective, this invasive procedure is associated with significant morbidity and mortality [4]. The first-line treatment is therefore based on maternal administration of IVIgG, with or without steroids [4]. Thus, our patient received IVIgG since 28 week of her second gestation until delivery. Her levels of anti-HPA1a antibody remained steady during pregnancy. In cases with absence of response, the dose of IVIgG must be increased and prednisolone may be added [4]. Percutaneous umbilical blood sampling at 28 weeks of gestation to evaluate the fetal platelet count [1], and serial platelet transfusion may be considered as an alternative invasive treatment, as well as early delivery [4]. Pregnant woman with anti-HPA1a antibodies should undergo a cesarean section 2 - 4 weeks before term [4]. Accordingly, in the presented case report the patient received an elective cesarean section at 37 weeks of pregnancy.

It has been recently proposed a new therapeutic option for women who are alloimmunized against the fetal HPA-1a antigen. A human recombinant high-affinity HPA-1a antibody that competes for binding to the HPA-1a epitope in fetal platelets has been developed. Actually, a first-in-man study has showed that the recombinant antibody prevent destruction of platelets byanti–HPA-1a in the circulation of HPA-1a1b human volunteers. Thus, alloimmunized pregnant women at risk of FNAIT could receiveserialintravenous injections of the recombinant antibody that by crossing the placenta would compete with maternalHPA-1a antibodies in binding to the fetal platelets [5]-[7].

It is known that FNAIT due toHPA-3 and HPA-5 is clinically less severe [1]. Interestingly, it has been shown a strong correlation between the presence of HLA-DR3, HLA-DRw52 and DBQB1*0201 in the mother and the antibody responses to the fetal alloantigen HPA-1a. In fact, the lack of HLA-DRw52 in HPA-1a negative women entails a very low risk of antibody production. Thus, it is associated with a low risk for FNAIT in their infants [1].

4. Conclusion

In conclusion, the incidental diagnosis of FNAIT allows both properly managing the newborn and detecting maternal anti-HPA1a antibodies in order to prevent the disease in subsequent pregnancies. In our case report, a non-invasive treatment based on IVIgG allowed to the patient to prevent FNAIT in her second pregnancy. Serial quantifications of maternal anti-HPA1a antibodies and fetal ultrasounds throughout pregnancy were carried out in order to assess fetal wellbeing.

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