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Neonatal Alloimmune Thrombocytopenia: A Report of Four Cases

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Antibodies against fetal platelet alloantigens in maternal blood cause neonatal alloimmune thrombocytopenia (NAIT). We encountered four newborns with NAIT from three women. A woman carried anti-human platelet antigen (HPA)-1a antibody, and vaginally delivered a newborn who had subarachnoid hemorrhage and platelet transfusions. She delivered the second newborn by a cesarean section who had no symptom. The second woman carried anti-human leukocyte antigen-A2 antibody and vaginally delivered a newborn who had no symptom. The third woman with a history of recurrent pregnancy losses carried anti-HPA-4b antibody, and delivered a newborn by a cesarean section who received platelet transfusions and immunoglobulin infusions. Antiplatelet antibody screening may be helpful in women who have a history of blood transfusion, or previous neonates with thrombocytopenia or intracranial hemorrhage.

INTRODUCTION

Antibodies against fetal platelet alloantigens in maternal blood cause neonatal alloimmune thrombocytopenia (NAIT). Platelet alloantigens of NAIT include human platelet antigens (HPA), human leukocyte antigens (HLA), and ABH alloantigens. Severe NAIT in newborns may cause intracranial hemorrhage (ICH), death and long-term disability. The incidence of NAIT is 1 per 1250 pregnancies, and ICH occurs in 7-26% of newborns with NAIT. [6] Approximately 98% of Caucasians have HPA-1a antigen, and the remaining 2% have HPA-1b antigen. In Caucasians, 75%–80% of NAIT are due to anti-HPA-1a antibody. [1] Because almost all Asians have HPA-1a antigen, NAIT due to anti-HPA-1a antibody is extremely rare in Asian couples. In the Japanese population, the incidence of NAIT is reported to be 1 per 2000 births, and HPA-4b is the most common antigen. [5]

Neonatal alloimmune thrombocytopenia may occur in the first pregnancy, and subsequent pregnancies are usually affected more severely. Perinatal management of women with a history of NAIT is critical. In this study, we report on four newborns with NAIT from three women.

Written informed consent was obtained from the patient for publication of this case report.

CLINICAL CASES

Case 1

A 26-year-old Russian woman married to a Japanese man, delivered vaginally the first male newborn weighing 3636 g at 40 gestational weeks (GW) (Table I, Case 1-1). The newborn had subarachnoid hemorrhage, cephalohematoma, petechiae and thrombocytopenia (15,000/μL); and received platelet transfusions that were regularly prepared. The woman had the anti-HPA-1a antibody (1:128-256), determined by the mixed passive hemagglutination (MPHA) method. The neonate was diagnosed with NAIT attributable to the anti-HPA-1a antibody and was discharged on day 12 without complications. He showed normal development at age of 1 year. The woman divorced and remarried another Japanese man.

The woman visited the Kobe University Hospital 3 years later during her second pregnancy (Case 1-2). HPA types were analyzed with informed consent. She carried HPA-1b/b, -2a/a, -3a/b, -4a/a, -5a/a, -6a/a, and NaK^{a+}, and the partner carried HPA-1a/a, -2a/a, -3a/b, -4a/a, -5a/a, -6a/a, and NaK^{a+}. The titer of anti-HPA-1a antibody in her serum was found to be 1:128-256. HLA cross-matching between his leukocytes and her serum tested

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negative. The infant was assumed to carry HPA-1a/b and was at risk for NAIT. A cesarean section was performed at 37 GW to reduce the risk of ICH. Because platelet concentrates from HPA-1a negative donor are not available in Japan, 400 mL of maternal blood and 0.8 unit of isolated platelets were prepared before the cesarean section. The male newborn weighing 3000 g had thrombocytopenia (67,000/μL) without ICH or petechiae. His HPA-1 type was HPA-1a/b, and the platelet count increased to 286,000/μL five days after birth without medication. The infant showed normal development at age of 1 year.

Case 2

A 30-year-old Japanese woman married to a Japanese man, delivered vaginally the first male newborn weighing 2946 g at 41 GW (Table I, Case 2). The infant had transient tachypnea and thrombocytopenia (47,000/μL), and the platelet count increased to 157,000/μL 7 days after birth without medications. No antiplatelet antibodies in the maternal serum were detected by MPHA method. However, anti-HLA-A2-antibodies were detected by LABScreen PRA (One Lambda, Inc., Canoga Park, CA, USA). The woman carried HLA-A (26, 31), B (61, 51), and Cw (9,10), and the partner carried HLA-A (2,33), B (71, 35), and Cw (9,7). The newborn carried HLA-A (2, 26), B (71, 51), and Cw (9, 7). Although the infant was diagnosed with NAIT attributable to the anti-HLA-A2 antibody, he showed normal development at age of 4 years.

The woman visited the university hospital 2 years later during her second pregnancy. Anti-HLA-A2-antibody was detected in maternal serum. With informed consent, amniocentesis was performed at 32 GW to determine fetal HLA type. The fetus carried HLA-A (31, 33), B (35, 61), and Cw (9,10) and had no risk for NAIT. She delivered vaginally a male newborn weighing 2492 g at 38 GW. His platelet count was 250,000/μL.

During her third pregnancy, anti-HLA-A2 antibody was also detected in her serum. The amniocentesis followed by HLA typing was performed at 31 GW. The fetus carried HLA-A (2, 26), B (51, 71), and Cw (7, 9) and had a risk for NAIT. A cesarean section was performed at 37 GW to reduce a risk of ICH. A female newborn weighing 2528 g had platelet counts of 355,000/μL.

Case 3

A 34-year-old Japanese woman married to a Japanese man had a history of recurrent pregnancy loss (three miscarriages and one stillbirth at 36 GW). Her clinical course during the fifth pregnancy was uneventful. She delivered a male newborn weighing 3116 g at 37 GW by a cesarean section due to breech presentation. Because the newborn had thrombocytopenia (5000/μL) and petechiae, he received therapies of intravenous immunoglobulin and platelet transfusions that were regularly prepared (Table I, Case 3). The platelet count increased to 131,000/μL ten days after. The newborn had anti-HPA-4b antibody determined by MPHA method. With informed consent, HPA types were analyzed. The woman carried HPA-1a/a, -2a/a, -3a/b, -4a/a, -5a/a, -6a/a, and 15a/b, and the partner carried HPA-1a/a, -2a/a, -3a/b, -4a/b, -5a/a, -6a/a, and 15b/b. The newborn carried HPA-1a/a, -2a/a, -3a/b, -4a/b, -5a/a, -6a/a, and 15a/b, and was diagnosed with NAIT attributable to the anti-HPA-4b antibody. He showed normal development at age of 1 year.

DISCUSSION

The present study reported four cases of NAIT caused by anti-HPA-1a, anti-HLA-A2 and anti-HPA-4b antibodies. Case 1-1 and Case 3 received platelet transfusions that were regularly prepared. In Case 1-2, platelet concentrates from maternal blood were prepared before a cesarean section, because platelet concentrates from HPA-1a negative donor are not available in Japan. Transfusion of maternal platelets is recommended as an alternative to antigen-negative donor platelets. However, in cases of unexpected NAIT, the use of random platelet concentrates while waiting for matched platelets is recommended. [4] As a result, none of the four newborns developed any disability.

The prevalence of anti-HPA and anti-HLA antibodies in Japanese pregnant women are 0.91% and 9.4%, respectively. The immunization rate is correlated with the number of pregnancies. [2,5] However, a prospective study of HLA alloimmunization during pregnancy found no correlation. [9] Anti-HLA alloantibodies in maternal blood can be adsorbed by HLA antigens expressed on the placental tissue of a fetus, thus do not reach enough concentration to cause accelerated platelet destruction in fetal circulation. This may be a reason why NAIT did not occur in the third pregnancy of Case 2. The amniocentesis followed by HLA typing of fetuses was performed to determine a delivery mode during the second and the third pregnancies. Because the occurrence of NAIT was not precisely predicted by fetal HLA types as reported in the present study, prenatal testing is not routinely recommended for NAIT attributable to ant-HLA antibody.

ICH occurs in 7–26% of newborns with NAIT, but 80.5% of the ICH occurs antenatally.[7] Van den Akker E et al. reported 32 pregnancies complicated by NAIT, they achieved 72% of vaginal delivery rate with no ICH of

newborns.[10] There is no evidence concerning a delivery mode of for NAIT. A cesarean section can be performed for either maternal obstetric indications or the planned delivery of high-risk pregnancies.[8] However, an elective cesarean section may reduce the risk of ICH and allow for having compatible platelets available at the time of delivery.

Universal screening for anti-HPA-1a antibody in pregnant women is not currently recommended in Caucasians,[3] and antiplatelet antibody screening in Asians has no cost–effectiveness.[5] However, prenatal testing of NAIT caused by anti-HPA-1a is important, because platelet concentrates from HPA-1a negative donor are not available in Japan. This screening may be helpful in women who have a history of blood transfusion, previous neonates with thrombocytopenia or ICH, fetal death or recurrent pregnancy loss as found in Case 3.

Table I. Characteristics of four pregnancies with neonatal alloimmune thrombocytopenia

Case No.	Age (years)	Nationality of women	Nationality of partners	Gravida/ Para	Gestational weeks at delivery	Delivery modality	Birth weight (g)	Platelet counts of newborns (/μL)	Antiplatelet antibody	Symptom	Therapy
1−1	26	Russian	Japanese	1/ 0	40	VD	3636	15000	HPA-1a	Subarachnoid hemorrhage, petechiae	Platelet tansfusion
1−2	29	Russian	Japanese	2/ 1	37	CS	3000	67000	HPA-1a	None	None
2	30	Japanese	Japanese	1/ 0	41	VD	2946	47000	HLA-A2	None	None
3	34	Japanese	Japanese	5/ 1 (stillbirth) SA3	37	CS	3116	5000	HPA-4b	Petechiae	Platelet tansfusion, IVIg

SA, spontaneous abortion; VD, vaginal delivery; CS, cesarean section;

HPA, human platelet antigen; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin.

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