CASE REPORT

FIRST REPORTED CASE OF NEONATAL ALLOIMMUNE THROMBOCYTOPENIA CAUSED BY ANTI HPA-1A ALLOANTIBODIES IN MALAYSIA

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Abstract

Neonatal alloimmune thrombocytopenia (NAIT) is a rare cause of thrombocytopenia in newborn; however it is one of the commonest causes of severe thrombocytopenia in newborn. This condition is important, as neonatal outcomes can be significantly impaired i.e. intracranial hemorrhage, permanent neurological disability and death and subsequent pregnancies can be affected. This condition is well described in the Caucasian population. There is to date no data in Malaysia regarding NAIT caused by anti-HPA-1a alloantibody. We would like to present the first reported case of NAIT due to this antibody, which is very rarely reported among Asian women.

Keywords: Neonatal, Alloimmune, Thrombocytopenia, HPA-1a

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Case Report

Neonatal alloimmune thrombocytopenia (NAIT) is a disease that affects fetuses and newborns. Fetomaternal transfusions result in the recognition of these antigens by the mother's immune system as non-self, with the subsequent generation of alloantibodies which cross the placenta. NAIT is caused by transplacental passage of maternal platelet-specific alloantibodies to fetuses and newborns, whose platelets express the corresponding antigens.

We would like to present the first reported case of NAIT due to anti-HPA-1a alloantibodies in Malaysia. This newborn baby girl had an uneventful vaginal delivery with the birth weight of 2.8kg. Her 36-year-old mother, a Para 8, had had 3 previous miscarriages for unknown reasons. The baby presented at 7 hours of life with generalized petechiae and her first platelet count on admission was 7 x 10⁹/L. Full blood picture showed occasional large platelet with markedly reduced peripheral platelet, normal red cells for newborn with some target cells, spherocytes and polychromatic cells. White blood cells appeared normal. Her mother’s platelet count just before delivery was 191 x 10⁹/L. Rubella and cytomegalovirus IgM was also...
negative and coagulation profile was normal. Ultrasonography of the brain did not show any intracranial haemorrhage. She was subsequently given platelet transfusion with non-HPA compatible platelets and the platelet count gradually increased to $125 \times 10^9/L$ before discharge on day 7 of life. No intravenous immunoglobulin was given to the baby because there was no mucosal bleeding or life threatening haemorrhage. She was subsequently discharged well without any serious complications. The cause of thrombocytopenia was not elucidated at that time. With the diagnosis on NAIT in mind, the parents’ and the baby’s blood was sent for alloantibody detection and genotyping was performed. The result showed strong reactive maternal anti-HPA-1a antibody. Below is the HPA genotyping of the patient and her parents.

- **Mother:** 1bb, 2aa, 3bb, 4aa, 5aa, 6aa, 15bb
- **Father:** 1aa, 2aa, 3aa, 4aa, 5ab, 6aa, 15ab
- **Baby:** 1aa, 2aa, 3ab, 4aa, 5ab, 6aa, 15ab

On clinic visits, the infant’s platelet count at 6 weeks old was $186 \times 10^9/L$ and $291 \times 10^9/L$ at 3 months old. Patient’s development remained normal during the last clinic visit at 7 months old.

**Discussion**

Alloimmune thrombocytopenia (AIT) is one of the most important causes of severe fetal and neonatal thrombocytopenia. The other most common aetiologies are congenital infections such as toxoplasmosis, rubella and cytomegalovirus, maternal immune thrombocytopenic purpura, congenital heart disease and disseminated intravascular coagulation. The overall incidence of NAIT has been estimated at 1 in 1000 to 5000 births [1, 2] and the incidence of NAIT due to anti-HPA-1a antibody is about 1 in 1163 livebirths according to Caucasian figures [3]. There is to date no data in Malaysia regarding NAIT and in fact this is the first reported case of NAIT caused by anti-HPA-1a alloantibody in the country.

AIT occurs when fetal platelets contain an antigen inherited from the father that the mother lacks. The mother forms IgG class antiplatelet antibodies against the "foreign" antigen; these cross the placenta and destroy fetal platelets, resulting in fetal and neonatal thrombocytopenia [3].

AIT can result in severe thrombocytopenia in the fetus because platelet antigens form as early as 16 weeks’ gestation [4]. The most serious complication is intracranial hemorrhage (ICH), which occurs in approximately 10 to 20 percent of affected newborns; one-quarter to one-half of these occur in utero [2]. The risk of severe thrombocytopenia and ICH is greater in alloimmune than in autoimmune thrombocytopenia [5].

Platelet antigens are designated as human platelet antigens (HPA). The different forms are designated by the suffix "a" (the more common allele) or "b" (the rarer allele). The parents are incompatible for HPA-1a or -5b up to 95% of cases [3]. Prospective studies in Caucasian populations for AIT due to anti-HPA-1a indicate that about 2% of women are HPA-1a negative [3]. Thus, the HPA-1 antigen is responsible for NAIT in approximately 75 to 90 percent of cases in Caucasians. In Asians, HPA-4 (Yuk/Pen) antigen is the most frequent cause of NAIT [6-8].

The mother of a newborn with NAIT is asymptomatic, although she or a sister may have a history of previously affected pregnancies. Affected newborns typically
are otherwise healthy, with signs consistent with thrombocytopenia. In one case series of 123 livebirths with NAIT, clinical presentations included the following [9]: skin bleeding only 47%, no bleeding 34%, ICH 14%, other major organ bleeding (gastrointestinal tract, lung, retina) 2%. In a large review of the literature, ICH was reported to occur in 26% of cases of AIT due to anti-HPA-1a with a mortality of 7% and in another study of 137 cases of AIT, death due to severe haemorrhage occurred in 7% and there were neurological sequelae in 21% [3].

All other liveborn babies to this couple were well without significant rash or bleeding tendencies during neonatal period and they did not have a platelet count check at birth, therefore we could not conclude that they had subclinical NAIT. The causes of the 3 miscarriages were also not investigated. We suspect, perhaps, these miscarriages were due to the platelet antigen incompatibility as the patient’s father is homozygous for HPA-1a antigen, therefore their offspring all carry the same platelet antigen which is foreign to the mother’s immune system. This could be mere speculation but there has been literature describing recurrent miscarriages as a complication of HPA incompatibility [3].

Initial platelet counts often are less than 10 x 10^9/L in NAIT. The platelet count typically falls in the first few days after birth, then rises over the next one to four weeks as the antibody level declines. In the first affected child, the mother's serum should be tested for antiplatelet alloantibody. If available, genotyping can be performed on the baby’s, maternal and paternal blood to identify the platelet antigen genotypes [3].

Term infants who are not ill and have no other risk factors for hemorrhage (e.g. traumatic delivery) are transfused if the platelet count is <30,000/microL or if there are signs of bleeding [10-13]. The threshold for transfusion is lower (<50,000/microL) in preterm infants or in term infants who are ill or have risk factors (eg, fetal or neonatal distress). The initial evaluation should include a cranial ultrasound examination to detect hemorrhage. If an ICH is present, the lower threshold should be used for platelet transfusion. Adequate platelet counts should be maintained during the first 72 to 96 hours because the risk of intracranial hemorrhage is highest during this period.

Donor platelets that are typed and matched in order to exclude the offending platelet antigen should be used for transfusion to the baby to raise the platelet count to a safe level. Washed maternal platelets can also be used because they will not react with the maternally derived anti-platelet antibodies. However the use of maternal platelets may delay the transfusions process as it may take up to 12 to 24 hours to collect and properly process the cells. In addition, it is highly unlikely that matched platelets will be available in an emergent setting. As a result, in an infant with severe thrombocytopenia or hemorrhage, random donor platelets should be used initially, although survival of incompatible platelets is short. In the meantime, arrangements can be made to acquire maternal platelets. Other possibilities include administration of platelet concentrates that are HPA-1a-negative and HPA-5b-negative [3].

Treatment with intravenous gamma-globulin (IVIG) (400 mg/kg per day for three to four days or 1 gm/kg per day for one to three days) often is effective [9, 14-15]. However, this approach takes longer than platelet transfusion to achieve a safe platelet count and thus should be used as adjunctive therapy.
In families with an affected fetus/infant, the rate of recurrence is more than 75 to 90 percent [16], and thrombocytopenia in the second affected child is always as or more severe than in the previous infant. The recurrence rate of ICH in the subsequent pregnancies of women with a history of AIT with ICH was 72% without the inclusion of fetal deaths, and 79% with their inclusion. The risk of ICH following a previous history of AIT without ICH was estimated to be 7% [3]. As opposed to the thought that NAIT tend to get worse with each subsequent pregnancy, our patient, interestingly and thankfully, did not have severe bleeding or ICH and was neurodevelopmentally normal up until the last clinic visit at 7 months old, despite the fact that her mother had 7 previous pregnancies including 3 miscarriages.

It is very important to provide genetic counseling for the couple if they planned to have another child. As all the HPAs reported to date (with the exception of HPA-14) have been shown to be biallelic with each allele being codominant and the fact that the father is homozygous for HPA-1a genotype, subsequent offspring are at high risk of developing NAIT. If the mother becomes pregnant again in the future, the antenatal management is very important. Prenatal diagnosis and treatment is important because 25-50% of fetal ICH occur while the fetus is in utero [17]. Prenatal management options include fetal blood sampling for platelet count and fetal therapy with in-utero platelet transfusions either weekly or immediately before delivery or maternal therapy with IVIG, corticosteroids, or a combination of the two [3].

There has been a lot of gaps in reporting and collection of data about patients with NAIT as well as prenatal AIT. There may have been a number of neonatal thrombocytopenic cases which had gone unrecognized and undiagnosed. We suggest a registry to be set up to pool all these cases together in order to discover the more prevalent types of anti-HPA alloantibody among mothers in Malaysia so that we can anticipate and manage the condition prenatally as well as postnatally in order to prevent mortality and long term neurological sequelae. There is a large proportion of patients with cerebral palsy in whom the aetiologies could not be identified. By conducting a large scale national reporting and data collection of AIT, it may help to shed some light as to how some of our patients in Malaysia develop cerebral palsy.

References


