Neonatal Alloimmune Thrombocytopenia: A Case Study

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NEONATAL ALLOIMMUNE thrombocytopenia (NAIT) is a life-threatening disorder caused by fetomaternal platelet incompatibility analogous to that seen in rhesus (Rh) disease. In NAIT, maternal immunoglobulin G (IgG) antiplatelet antibodies cross the placenta, resulting in rapid destruction and removal of fetal platelets by the reticuloendothelial system.[1,2] Studies have shown that NAIT has an incidence of 1 of 1,000 live births,[3,4] with a mortality rate of 10–15 percent[1] and the risk of long-term morbidities up to 20–60 percent if intracranial hemorrhage (ICH) occurs.[3,5]

This column will discuss the pathophysiology, differential diagnosis, morbidities, and treatment of NAIT and conclude with a relevant case study.

PATHOPHYSIOLOGY

Platelets are small cell fragments of very large bone marrow cells called *megakaryocytes*.[6] Platelets normally live for 10 days and then are removed by the spleen and liver. Neonatal thrombocytopenia historically is defined as a platelet count of less than 150,000.[7] However, in recent studies, neonatal thrombocytopenia has been defined as a platelet count less than or equal to 123,000,[7] with severe neonatal thrombocytopenia as a platelet count less than 50,000.[7,8]

NAIT subsequently occurs when the mother produces antiplatelet antibodies to the fetal platelets similar to what is seen with hemolytic disease of the newborn (HDN). Unlike HDN, though, NAIT can occur in the first pregnancy; in fact, 50 percent of all NAIT cases are seen in the first pregnancy.[1] This is because immunoglobulin G (IgG) is the only maternal antibody that crosses the normal placenta as early as 14–16 weeks of gestation. At the same time, platelet antigens are seen in the fetus by 18 weeks of gestation, setting the stage for NAIT to develop. On the other hand, Rh sensitization occurs when there is a breech in the uterine wall, which most often occurs after delivery of the placenta. This is why with HDN, the first pregnancy is not affected.[2,9–11]

For NAIT to develop, human platelet antigens (HPA, formally called PLA1, human platelet antigen 1a) must be absent in the mother but present in the father and subsequently present in the fetus.[12] Human platelet antigens (HPA-1a) are found in 98 percent of the Caucasian population and caused 75 percent of all NAIT cases.[13] The HPA-5b is second in frequency and is responsible for 16 percent of NAIT cases,[14] followed by HPA-5a, 15-a, and 15-b.[2] In Asians, HPA-4 is the predominant cause of NAIT.[3] HPAs are numbered from 1 to 24 in the order in which they were discovered. The letters "a" and "b" describe the frequency of occurrence with "a" being high and "b" being low.[9] HPA-1a, HPA-3a, and HPA-4a cause severe thrombocytopenia and HPA-5a and -5b are milder and rarely have intracranial hemorrhage (ICH).[3]

CLINICAL PRESENTATION

A newborn with NAIT will usually appear healthy. The mother will also be healthy and have a normal platelet count. The infant will often present with petechiae, bruising, excessive bleeding, and mucocutaneous purpura within the first few hours of life. When the newborn presents with these signs and symptoms, the platelet count, when checked, is typically less than 20,000.[2] The platelet level may begin to drop early in pregnancy and may or may not self-correct.[3] Generally, though, a rapid postnatal drop in platelet levels is seen and caused in part by the increased exposure of other platelets from reticuloendothelial cells in the blood flow to the lungs.[2] Fourteen to twenty percent of newborns with NAIT will develop an ICH.[2,5] Fifty percent of ICH occur *in utero*. The presentation of ICH is variable ranging from no clinical signs to obvious signs, such as seizures, retinal hemorrhage, lethargy, tense fontanel, stupor, apnea, and bradycardia.[15]

There is currently no routine prenatal screen for NAIT; therefore, the diagnosis is usually not made until after birth.[9] The mother's pregnancy is at high risk for NAIT if there is a history of a previous infant with NAIT or an infant with thrombocytopenia of unknown etiology.

DIFFERENTIAL DIAGNOSIS

The causes of newborn thrombocytopenia in the otherwise healthy newborn differ from thrombocytopenia seen in the sick newborn. The mother's pregnancy history and physical assessment can help determine a diagnosis. With NAIT, the mother usually experiences an uneventful pregnancy with normal platelet levels.[3] Alternately, thrombocytopenia may be seen in the neonate of women with a history of pregnancy-induced hypertension (PIH), drug use, or infection.[16] The most common cause of severe

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thrombocytopenia in the well newborn is NAIT.[11] NAIT accounts for 20 percent of cases of thrombocytopenia in the healthy newborn.[5] The second most common cause, resulting in 10 percent of the cases of neonatal thrombocytopenia, is maternal idiopathic thrombocytopenia purpura (ITP).[17] Although only 10 percent of ITP mothers have infants with thrombocytopenia, it can be severe.[6,18] The differential diagnosis for healthy newborns with thrombocytopenia are presented in Table 1.[19]

LABORATORY TESTING

The infant's complete blood count (CBC) is generally normal other than the low platelet count; although if bleeding is severe, anemia may be present. The parents, not the infant, are screened for antigens.[20] NAIT is confirmed by identifying antiplatelet antibodies in the mother's blood as well as antigen incompatibility between the mother and the father.[12,20] The mother should be screened for HPA-1, HPA-3, and HPA-5, as well as for HPA-4, if the mother is Asian.[20] The father should also be screened. It is important to find the specific antigen to protect future pregnancies.[21] This is best done through a laboratory that has DNA testing and the ability to find rare antigens if needed.[21,22]

In the early stages of neonatal thrombocytopenia, infection and bleeding disorders must be ruled out. However, most healthy newborns with severe thrombocytopenia have NAIT.[21]

TREATMENT

Platelet Transfusions

Treatment of NAIT should begin without delay.[15] A platelet transfusion should be given if the infant's platelet count is less than 20,000–30,000 or less than 50,000 if the infant is bleeding or in critical condition.[9,23] In an emergent situation, the first course of action is to transfuse irradiated random donor platelets. HPA-1a negative donor platelets or washed and irradiated maternal platelets are ideal because the recovery is quicker, the effect is faster, and it lasts longer. These HPA-1a negative transfusions do not have the offending antigen, which is responsible for platelet destruction. However, the negative platelets are not always available when the infant is bleeding and needs immediate assistance.[2,3,9] Therefore, if random donor platelets are used that are HPA-1a positive, the infant will have a temporary improvement, but the platelet destruction will continue until the infant has cleared all antigens from the circulation.

The target platelet level is 100,000 or greater.[22] A platelet infusion of 5–10 mL/kg should raise the platelet count by 50,000–100,000,[24] although most references recommend platelets of 10 mL/kg per transfusion.[25] Platelet transfusions are repeated until the level is greater than 100,000.[22] It is especially important to maintain the platelet levels during the first 3–4 days of life to minimize the risk of ICH.[26] Once the platelet level has reached a normal level, it will remain there.

Intravenous Immune Globulin

Intravenous immune globulin (IVIG) is IgG in concentrated form.[27] IVIG is administered to decrease the production of and neutralize circulating antiplatelet antibodies. IVIG also works by blocking platelet Fc receptors and therefore decreasing destruction of platelets.[9,28] IVIG has been shown to reduce the frequency of ICH.[15] The effect of IVIG takes place in one to three days.[23,28] Typical dosage is 500–750 mg/kg, but for infants with NAIT, dosages range from 400 to 1,000 mg/kg. IVIG is given over 2–6 hours and is compatible with dextrose 5% water (D_5W), $D_{15}W$, and total parenteral nutrition (TPN).[27] IVIG can be given up to two days in a row.[20]

The infant's temperature, blood pressure, and respirations must be monitored closely with all transfusions.[29] When giving IVIG, in addition to monitoring the vital signs and intravenous site, also monitor the infant for the rare side effects of bronchospasm, renal failure, and laryngeal edema.[2,27]

Fresh Frozen Plasma

Generally, fresh frozen plasma (FFP) comes from whole blood and is frozen within 6–8 hours after collection.[25] FFP contains one international unit of clotting factors for every 10–15 mL/kg[24]; FFP also contains albumin and many other plasma proteins. FFP is most often used to prevent bleeding in the infant with severe thrombocytopenia of unknown origin. The recommended dose of FFP is 10–20 mL/kg.[25]

Cryoprecipitate

Cryoprecipitate is thawed FFP, refrozen with plasma. The plasma contains high concentrations of clotting factors, especially Factors VII and VIII and fibrinogen.[29] Cryoprecipitate is used to treat infants with low fibrinogen clotting disorders and is not used once NAIT has been confirmed.

SCREENING FOR INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage is the most devastating complication of NAIT, most of which occur *in utero* and can result in mortality or major morbidity. Consequently, all infants with a confirmed diagnosis or suspected NAIT should be screened by cranial ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI).[22] Cranial ultrasounds are usually the least expensive and fastest screen available for visualizing a hemorrhage. However, CT imaging and MRI can be more sensitive in finding some smaller intraventricular hemorrhages (IVHs) and subarachnoid bleeds.[30]

Intracranial hemorrhage is found in 1 of 1,500 term newborns. Twenty-five percent are caused by NAIT, making it the most common cause of severe ICH. Parenchymal hemorrhage and IVH are the most common ICH seen in NAIT.[31] The connection between thrombocytopenia and ICH is most likely caused by the lack of protection of the vessel walls

TABLE 1 ■ Differential Diagnosis for Well Newborn Presenting with Thrombocytopenia[1,2,6,18,19,20,21,22,26]

Diagnosis	Distinguishing Features (Maternal History Symptoms)	Typical Platelet Count and Other Laboratory Exams	Notes
Maternal idiopathic thrombocytopenia purpura	Maternal platelets low (though may be recovering)	Infant platelets 50,000–100,000 Platelets drop during first days of life	Autoimmune ICH 3%
NAIT	Maternal platelet levels normal	Infant platelets under 20,000	Seen within first several hours of life ICH 14%
Neonatal drug exposure	Positive history		Heparin Quinine Rare
TARS (thrombocytopenia-absent radius syndrome)		Severe thrombocytopenia from decreased production	Absent radius ICH
CAMT (Congenital amegakaryocytic thrombocytopenia)		Severe thrombocytopenia	Few megakaryocytes in bone marrow Rare Mimics NAIT
Maternal drugs	Quinidine Penicillin Dioxin Indomethacin Phenytoin Heparin		
Chromosomal abnormalities: Trisomy 18 Trisomy 13 Trisomy 21 Turner syndrome	Clinical features of syndrome	Less than 100,000	Low-percentage platelets 87% 54% 28% 31%
Placental insufficiency—IUGR and PIH	Maternal history, small infant	Borderline low	Recover by Day 10
Wiskott-Aldrich syndrome		Moderate thrombocytopenia	Eczema and immunodeficiency
Fanconi's anemia			Congenital anomalies (muscular, microcephaly, and GU) Rare
Cardiac anomalies			
Thrombosis			Indwelling catheters or protein C deficiency
Kasabach-Merritt syndrome		Severe thrombocytopenia Prolonged PT and PTT	Lesions on trunk Giant hemangiomas

Key: GU = genitourinary; ICH = intracranial hemorrhage; IUGR = intrauterine growth restriction; NAIT = Neonatal alloimmune thrombocytopenia; PIH = pregnancy-induced hypertension; PT = prothrombin time; PTT = partial thromboplastin time.

Note. Neonatal alloimmune thrombocytopenia; Maternal idiopathic thrombocytopenia purpura; Systemic lupus erythematosus; Giant hemangioma; Thrombosis (large renal vein thrombus); Neonatal drug exposure (heparin and quinine); Congenital thrombocytopenia—bone marrow failure (thrombocytopenia-absent radius syndrome and congenital amegakaryocytic thrombocytopenia); Maternal pregnancy-induced hypertension; IUGR from placental insufficiency; Preeclampsia or chronic hypertension; Maternal drug exposure (heparin, penicillin, dioxin, antiseizure medications, and quinine); Congenital heart disease; Chromosome abnormalities (trisomies 21, 18, and 13 and Turner syndrome); Wiskott-Aldrich syndrome; Fanconi's anemia.

normally provided by platelets. It is unknown whether the antiplatelet antibodies actually cause the platelets to be less effective in protecting the vessel walls.[31]

Maternal antibodies begin to leave the infant's circulation at 48 hours of age.[32] Most courses of NAIT resolve by two weeks of age, with platelet levels usually normalizing completely by four weeks.[20,24]

COMPLICATIONS AND LONG-TERM OUTCOMES

Long-term outcomes are dependent on the severity of NAIT and the swiftness of treatment.[3] If there is no ICH, morbidity is low, although these infants are at a small risk for vision problems.[3,33] One-third of infants with NAIT and ICH will die. The rest are at risk for hydrocephaly, especially if the ICH occurs *in utero*; developmental delays, mental retardation, cerebral palsy, and seizures may also be seen.[2,33]

MATERNAL FOLLOW-UP AND PREVENTION IN FUTURE PREGNANCIES

Women who have had a newborn with NAIT must be taught the importance of early and regular prenatal care;[2] especially because all future pregnancies are at 90–100 percent risk for severe fetal and neonatal thrombocytopenia, as the symptoms worsen with each subsequent pregnancy.[4,12] Close maternal follow-up with high-risk obstetrics is especially crucial if the first infant had an ICH.[34] Antenatal management focuses on minimizing the risk of ICH and currently includes treatment with IVIG and prednisone throughout the pregnancy to block maternal production of antibodies.[4,9,20]

NEONATAL FOLLOW-UP

Although NAIT is resolved by two weeks, the outpatient follow-up should include platelet levels for the rare but potential risk of the platelet levels dropping. Developmental and neurologic follow-up is also warranted if the infant experienced an ICH.

CONCLUSION

NAIT causes ICH and death in the otherwise healthy newborn. It is vital that immediate action is taken when NAIT occurs in the first days of life. With quick and proper treatment, the risks of death and long-term disabilities are diminished.

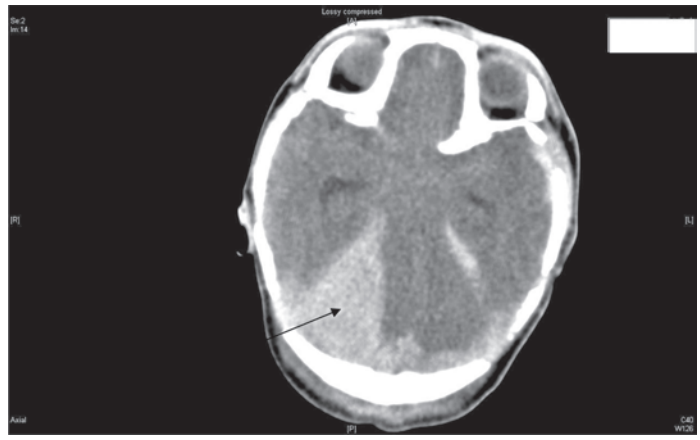
NEONATAL ALLOIMMUNE THROMBOCYTOPENIA: A CASE STUDY

Baby girl A delivered vaginally at 41 weeks gestation, with vacuum assistance, to a 36-year-old, O+, Caucasian, primigravidous mother. The pregnancy was complicated by hypothyroidism, treated with Synthroid. All maternal serologies were negative (rubella immune, Venereal Disease Research Laboratory [VDRL] test negative, human immunodeficiency virus [HIV] negative, hepatitis B virus [HBV] negative, Group B beta Streptococcus [GBBS] negative). Vacuum was used for nonreassuring fetal heart tones. The infant delivered in the vertex position with a loose nuchal cord. At delivery, she cried loudly and became pink quickly. Routine care was given, and the Apgar scores were 8 at one minute and 9 at five minutes. The infant stayed with the mother in the labor and delivery unit for the first hour of life.

The one-hour assessment was normal except for bruising on the scalp. As the mother's blood type was O+, the cord blood was sent and noted to be A+ with a negative Coombs. By six hours of age, the infant was feeding poorly and was hypothermic. On assessment, she was pale pink, with decreased tone, irritability, and hyperresponsiveness to stimulation; her anterior and posterior fontanels were full.

Bruising was noted over the entire scalp, with petechiae covering the entire chest, abdomen, arms, and legs. The infant had clear breath sounds, mild subcostal retractions with periodic breathing, and one episode of apnea; the rest of the exam was normal. The workup included a CBC with differential, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), blood gas, fibrinogen, glucose level, blood culture, and CT scan of the brain. The CBC showed a left shift with a platelet count of 16,000; all other laboratory results were within an acceptable range. The CT scan showed a very large acute subdural hematoma on the right side of the cerebellum. The subdural hematoma extended along the falx (located between the cerebellar hemispheres) and the cerebellum was shifted to the left. The compressed cerebellum caused obstruction of the cisterns and increased the size of the temporal horns of the lateral ventricles, resulting in increased intracranial pressure (ICP) (Figure 1). The platelet count was repeated and dropped from 16,000 to 6,000 in one hour. Platelets were ordered but not available before the transport team arrived.

FIGURE 1 ■ CAT scan shows intracranial hemorrhage. Blood from an acute bleed is seen as white once a clot is formed.



From Manco-Johnson, M., Rodden, D., & Collins, S. (2007). Newborn hematology. In G. Merenstein & S. Gardner (Eds.), *Handbook of neonatal intensive care* (6th ed., pp. 521–547). St. Louis, MO: Mosby.

The infant was then transferred to a Level III NICU. With the results of the CT scan in hand, neurosurgery made an unsuccessful attempt to drain the blood at the bedside to decrease the ICP. The infant was therefore taken to the operating room for emergency surgery to remove the subdural clot. After surgery, the ICP dropped, and the ventricular size was normal on repeat CT scan. In the meantime, the mother was tested for antibodies. Her platelet count was normal, but her screen was positive for anti-HPA-1 antibodies, confirming the diagnosis of NAIT.

During the first 36 hours of life, the infant received four transfusions of random donor platelets, one transfusion of packed red blood cells, one unit of FFP, and one dose of cryoprecipitate. The platelet count was followed every eight hours and showed improvement. By Day 5, the platelet count was 228,000, increasing to 346,000 by discharge on Day 7 of life. The infant was eating well and gaining weight by discharge. The platelet count remained stable at two weeks and one month of age. On the one-year follow-up, the infant is thriving and, most importantly, is developmentally appropriate.

The infant had outpatient laboratory studies to check her platelet levels, which remained normal; she was also followed up in the developmental clinic.

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