

A Newborn with Petechiae and Bruising

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Citation

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Abstract

We report the case of a 29-year-old Caucasian woman (G5P0) who delivered a full-term female infant. Fetal growth and development were normal throughout gestation. The pregnancy was complicated by 3rd trimester preeclampsia, requiring induction of labor at 40 weeks gestation. Diagnosis of neonatal alloimmune thrombocytopenia (NAIT or NATP) or fetomaternal alloimmune thrombocytopenia (FMAIT or FMAITP) was made and is discussed in this article.

CASE REPORT

A 29-year-old Caucasian woman (G5P0) delivered a full-term female infant. Fetal growth and development were normal throughout gestation. The pregnancy was complicated by 3rd trimester preeclampsia, requiring induction of labor at 40 weeks gestation. Urgent cesarean-section was performed due to non-reassuring fetal heart tones and meconium-stained amniotic fluid. Apgars were normal (7¹ and 9⁵) and clinical evaluation revealed a normal healthy newborn with anthropometric measurements at the 95th percentile.

The physician was called to evaluate newly noted bruising approximately 20 hours post-delivery. Physical exam was remarkable for scattered bilateral lower limb ecchymoses and petechial rash in an otherwise well-appearing neonate. The CBC revealed severe thrombocytopenia (platelet count of 20,000/ μ L) with a normal hemoglobin (16.4 g/dL) and white blood cell count (15.4/ mm^3). Work-up for causes of neonatal thrombocytopenia (Table 1) was initiated and empiric antibiotics were started for possible sepsis. Lumbar puncture was deferred due to severe thrombocytopenia. Skeletal survey, head ultrasound, and abdominal ultrasound were performed to rule out congenital anomalies and occult hemorrhage. Because of the isolated thrombocytopenia without clinical evidence of systemic infection, the diagnosis of neonatal allo-immune thrombocytopenia was strongly considered.

Figure 1

Table 1: Differential diagnosis of neonatal thrombocytopenia

Categories	Subtypes	Differential diagnoses
Immune mediated	Alloimmune	Neonatal alloimmune thrombocytopenia
		Maternal ITP, Lupus, other autoimmune disorders
Infectious	Bacterial	GBS, Gram-negative rods, <i>Staphylococcus</i> , etc.
	Viral	CMV, HSV, HIV, enteroviruses
	Fungal	Candida, <i>Malassezia furfur</i>
	Parasite	Toxoplasmosis
Placental insufficiency		Preeclampsia, eclampsia, chronic hypertension
		Intrauterine growth restriction due to placental insufficiency
Disseminated Intravascular Coagulation (DIC)		Asphyxia Sepsis Necrotizing enterocolitis (NEC)
Genetic disorders	Chromosomal abnormalities	Trisomy 13, Trisomy 18, Trisomy 21, Turner's Syndrome, Jacobsen Syndrome
	Inherited thrombocytopenia	Macrothrombocytopenias or MYH9 disorders, Wiskott-Aldrich Syndrome, X-linked thrombocytopenias, Amegakaryocytic thrombocytopenia, Thrombocytopenia absent radii (TAR), Proximal radio-ulnar synostosis with bone marrow failure, Fanconi anemia
	Inborn errors of metabolism	Propionic acidemia, methylmalonic acidemia
Medication induced	Antibiotics	Penicillin and derivatives, vancomycin, metronidazole
	Heparin	
	Anticonvulsants	Phenytoin, Phenobarbital
Miscellaneous	Thrombosis	Renal vein thrombosis, central venous line-related thrombosis, sagittal sinus thrombosis
	Congenital malformations	Kasabach Kasabach-Merritt, hepatic hemangioendothelioma, Cyanotic congenital heart disease
	ECMO	

Abbreviations: ITP: immune thrombocytopenic purpura; HSV: Herpes simplex virus; GBS: Group B Streptococcus; CMV: Cytomegalovirus; HIV: Human Immunodeficiency Virus; ECMO: extracorporeal membranous oxygenation

Figure 2

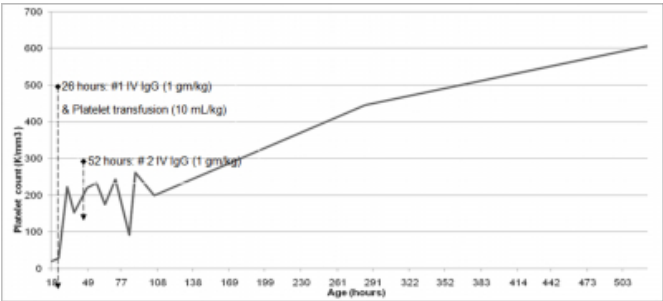
Table 2: Characteristic differences between Rh-incompatibility and Neonatal allo-immune thrombocytopenia

	Rh Incompatibility	Neonatal Allo-immune Thrombocytopenia (NAIT)
Incidence	1:100 (25% severe)	1:1000 (10-30% severe)
Disease pathology	Rhesus blood type incompatibility between fetal and maternal RBC	Human platelet antigen (HPA) incompatibility between fetal and maternal platelets
First pregnancy/ fetus affected	No	Yes
Routine screening for pregnant women in place	Yes	No
Common clinical presentation	Pallor, icterus	Petechiae, purpura, ecchymoses
Clinically severe manifestation	Hydrops fetalis, Kernicterus	Intracranial hemorrhage
Testing for the newborn readily available	Yes	No (done in referral laboratories)
Diagnostic test	Maternal & fetal blood type Coomb's test (direct & indirect) on maternal & fetal/neonatal sample	Maternal HLA and platelet antibody screen Crossmatch maternal plasma with paternal platelets Maternal and paternal Platelet genotyping
Prophylaxis during pregnancy	Yes (RhoGam, antiD antibody)	Yes (IV IgG infusion± steroids)
Antenatal treatment of fetus	Yes (packed red cell transfusions, regular fetal ultrasounds for assessment of hydrops)	Yes (matched donor platelet transfusions, regular fetal ultrasounds for ICH)

Abbreviations: Rh: Rhesus blood type; HLA: Histocompatibility antigen; ICH: Intracranial hemorrhage; IV IgG: Intravenous immunoglobulin G

Figure 3

Figure 1: Clinical course and management of newborn with neonatal allo-immune thrombocytopenia (NAIT)



DISCUSSION

Neonatal alloimmune thrombocytopenia (NAIT or NATP) or feto-maternal alloimmune thrombocytopenia (FMAIT or FMAITP) is the platelet-equivalent of Rh-disease (Table 2),

with an estimated incidence of 1.5 cases per 1000 live births [1,2]. Unlike Rh-disease, NAIT occurs in the first pregnancy in up to 50% of cases and severe fetal thrombocytopenia (<50,000/L) may occur very early in pregnancy. Usually, thrombocytopenia worsens as gestation progresses. Neonates typically present with signs and symptoms of mucocutaneous bleeding, such as petechiae and gastrointestinal bleeding. Occasionally these infants present with symptoms of intracranial hemorrhage (ICH), such as seizures. Thrombocytopenia may also be detected incidentally on blood counts obtained for other reasons, such as a sepsis evaluation.

PATHOPHYSIOLOGY

NAIT occurs when a pregnant woman is exposed to fetal platelets possessing incompatible paternally-derived human platelet antigens (HPAs)[3-5]. These are glycoproteins that act as receptors for the ligands involved in platelet activation [5]. Due to fetomaternal circulation, the mother's immune system is exposed to these antigens on fetal platelets. These antigens are recognized as "non-self" and a B-cell mediated immune response produces IgG antibodies against these antigens. These IgG antibodies cross the placenta, initiating the destruction of fetal platelets leading to immune-mediated thrombocytopenia. Since the mother develops antibodies against a platelet antigen which is absent on her own platelets, this condition is referred as "alloimmune" rather than "autoimmune" thrombocytopenia. In Caucasians, ~80% of cases of NAIT are caused by antibodies against HPA-1a, 15% by anti-HPA-5a, and 5% by other antibodies [2,5].

MORBIDITY AND MORTALITY DUE TO NAIT

The most serious complication of NAIT is ICH, occurring in 10% to 30% of severe cases [2,5]. Mortality due to ICH occurs in 10% of these cases and ~20% of ICH survivors experience neurologic sequelae. There is a 70-80% risk of antenatal ICH in a subsequent pregnancy if the previous pregnancy is complicated by ICH.

DIAGNOSIS OF NAIT

Diagnosis is based on clinical and serologic findings. Typically, a healthy mother with an uneventful pregnancy, no history of bleeding disorder and a normal platelet count delivers a neonate who develops purpura or petechiae minutes to hours after birth [5,6]. Neonatal platelet count of less than 50,000/L is suggestive of NAIT. Detection of maternal HPA or HLA alloantibodies with specificity for paternal antigens confirms the diagnosis. DNA testing

elucidates maternal and paternal platelet antigen genotypes. Head imaging should always be done in infants with suspected NAIT due to the risk of ICH.

DIFFERENTIAL DIAGNOSIS OF NAIT

Thrombocytopenia is a non-specific finding in neonates and can be the result of many different processes: sepsis, thrombosis, congenital TORCH infections, placental insufficiency, bone marrow failure syndrome or other conditions. (Table 1)

TREATMENT OPTIONS OF NAIT

The most important step in the management of severely thrombocytopenic infants, including those with NAIT, is platelet transfusion [6]. Randomly selected apheresis or whole blood derived platelets can be used for immediate transfusion, but antigen-negative platelets are the component of choice [3, 5-7]. Maternal platelets or matched donor platelets can be used. Transfusion to maintain platelet counts above 30,000/ μ L in otherwise healthy term infants and above 100,000/ μ L in infants with ICH is desirable [6]. Clinical judgment should be used in preterm or sick infants. Other treatment strategies include infusions of intravenous immunoglobulin (IVIG; 1g/kg/day) for 1-3 days and/or a course of IV methylprednisolone (1 mg IV q daily) for 1-3 days [3,6].

NATURAL COURSE OF NAIT AND FOLLOW-UP

Platelet counts typically stabilize by 2-4 weeks of age as maternal antibodies are eliminated from the fetal circulation. Platelet counts can be monitored beyond this point to rule out other causes of congenital thrombocytopenia; however, long-term follow-up is unnecessary for infants with NAIT as the thrombocytopenia will not recur.

RECURRENCE RISK AND MANAGEMENT OF SUBSEQUENT PREGNANCIES

It is important to appropriately diagnose NAIT to prevent complications in future pregnancies. The recurrence of NAIT has been estimated to be more than 80% in subsequent pregnancies with HPA-incompatible fetuses[2,5].

Recurrence risk depends on the paternal genotype. If the father is homozygous for the involved antigen, then all future pregnancies should be assumed to be affected; conversely, if the father is heterozygous, approximately half of future pregnancies will be affected. Most studies suggest that the next affected fetus will be at least as severely affected as the previous infant, if not more severely[3-6].

Monitoring and treatment during pregnancy may prevent the

occurrence of ICH.

Treatment options include weekly maternal infusions of IVIG (1g/kg/dose) or prednisone (0.5-mg/kg/day)[8,9]. The fetus may require intrauterine transfusion of matched platelets [9]. Prenatal platelet typing of the fetus is possible but poses a significant risk of bleeding due to the thrombocytopenia and should be avoided. If the mother is able to donate, maternal platelets are the most compatible source of platelets for transfusion [9]. Coordination with a local blood donor center is essential as maternal platelets will have to be irradiated, and washed just prior to transfusion to remove anti-platelet antibodies.

Mothers with an infant affected by NAIT should be referred to high-risk obstetrical specialists for management of all future pregnancies. In addition, mothers should be counseled about their risk of post-transfusion purpura (PTP) should they receive platelet transfusions in the future.

HOSPITAL COURSE AND FINAL DIAGNOSIS

No congenital anomaly and/or occult hemorrhage was identified on skeletal survey and other imaging studies. Septic work-up including blood and urine cultures were negative. She continued to appear clinically-well despite the presence of the petechial rash. HPA-1a antibodies were present in maternal blood. Maternal and paternal platelet genotyping confirmed maternal platelets were HPA-1a antigen negative while paternal platelets expressed HPA-1a antigen. The patient was transfused with HPA-negative platelets (10 mL/kg x 1) and received two doses of IVIG on day 2 and 3 of life, respectively (Figure 1). She responded well, and serial CBCs demonstrated a sustained rise in her platelets. She was discharged on day 5 of life with stable platelet counts, which were rechecked on days 12 and 22 of life and remained stable. The parents were counseled about the risk of NAIT in subsequent pregnancies and the importance of involving the hematologist and high-risk maternal-fetal team early on. The mother was educated about her risk of post-transfusion purpura should she receive platelet transfusions in the future.

An interesting factor in this case was the maternal history of four miscarriages with a previous partner. Because this partner was unavailable for testing, it is unclear if he was also HPA negative and these miscarriages were related to the development of maternal HPA antibodies.

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