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Review Article

What to Know about Neonatal Alloimmune Thrombocytopenia (NAIT)?

Suzan Omar Mousa*

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***Correspondence:** Pediatric Hematology and Oncology unit, Pediatric department, Faculty of Medicine, Minia University, Egypt.
Email: suzanmousa@mu.edu.eg
Full list of author information is available at the end of the article.

Abstract

Neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of severe thrombocytopenia in full-term newborns. In the mother and fetus with incompatible platelet antigens, there is a risk of developing anti-platelet alloimmunization. It corresponds to Rhesus (Rh) alloimmunization in pathophysiology. These platelet alloantibodies pass trans-placentally into fetal circulation and cause fetal platelet destruction. Although its presentation may be isolated thrombocytopenia, some affected infants may suffer major hemorrhages, including intracranial hemorrhage (ICH), which may occur as early as 16 weeks of gestational age, and the first pregnancy may not be spared. Death or neurologic impairment occurs in up to 25% of the affected infants. NAIT is managed both ante- and postnatally. Postnatal management of NAIT depends upon the platelet count and the neonate's clinical condition. At the same time, antenatal management of NAIT aims to ameliorate fetal thrombocytopenia in subsequent pregnancies after diagnosis of NAIT in a previous pregnancy and thus prevent fetal and neonatal ICH.

Key words: Neonatal alloimmune thrombocytopenia, NAIT, alloimmunization, anti-platelet antibodies

Introduction

Neonatal thrombocytopenia is one of the commonest hematological abnormalities occurring in the neonatal period, it represents up to one third of NICU admissions. [1,2] The most common cause of severe thrombocytopenia in healthy term newborns is neonatal alloimmune thrombocytopenia (NAIT). Its pathophysiology is analogous to Rhesus (Rh) alloimmunization. In NAIT, transplacental passage of maternal alloantibodies against fetal platelet antigens inherited from the father, leads to fetal antigen-positive platelet destruction. Its clinical presentation varies from accidentally detected thrombocytopenia in a term newborn to life-threatening hemorrhages in utero or early postnatal. In contrast to Rh, alloimmunization antigenic exposure occurs early in pregnancy, so that it may affect the first pregnancy in 40% to 60% of cases, with progressive increase in severity in subsequent pregnancies. [3] The importance of diagnosing NAIT is determining the risk of thrombocytopenia and hemorrhages in future pregnancies and the need for future antenatal management plans. [4]

Neonatal thrombocytopenia

Neonatal thrombocytopenia is a neonate with a platelet count of < 150,000/μL, which affects 0.5% to 0.9% of neonates. [5] This definition is based on lower than fifth percentile adults' values. Although, studies have found that in preterm infants ≤ 32 weeks, the fifth percentile was 104,000/μL, and in late preterm and term infants, the fifth percentile was 123,000/μL. [4]

Neonatal thrombocytopenia is marked as severe if the platelet count is < 50,000/μL. In clinical experience, below this platelet count, there is an increment in the incidence of neonatal hemorrhages, whether major life-threatening hemorrhages (e.g., pulmonary, intraventricular) or minor hemorrhages (e.g., petechiae, hematuria).

[6] Other clinical factors augmenting the frequency of major hemorrhages in neonates besides severe thrombocytopenia are birth weight and gestational age. [7]

The leading causes of thrombocytopenia in preterm neonates are conditions that cause placental 'insufficiency. Placental insufficiency-related thrombocytopenia is characterized by being early onset (within 72 hours postnatally), always self-limiting, and recovering within 4 weeks. [8] Therefore, if the platelet count remains above 50,000/μL, further investigations of such cases are unnecessary [9, 10] Other common causes of early onset thrombocytopenia in preterm are perinatal hypoxia; perinatally acquired bacterial infection (Group B streptococcus infections); TORCH, or other viral infections, especially cytomegalovirus (CMV). In short, the high prevalence of the other causes of thrombocytopenia in preterm neonates makes NAIT relatively uncommon to cause thrombocytopenia in them [11-13]

On the contrary, NAIT is the most important cause of thrombocytopenia in term newborns who are otherwise well, after excluding maternal idiopathic thrombocytopenic purpura or secondary thrombocytopenia. [14] After excluding spurious thrombocytopenia, NAIT should be excluded by serological and genetic testing as soon as possible. [7]

Incidence of NAIT

The overall incidence of neonatal alloimmune thrombocytopenia (NAIT) is approximately 1 in 500-1000 births if the definition is expanded to identify mild cases with platelet count <100,000/μL. If NAIT is defined as thrombocytopenia with platelet count <50,000/μL, it is frequent as 1:3000-5000 births, and its frequency may be 1 in 5000-10,000 if it is associated with bleeding manifestations leading to clinical identification. [8]

Pathophysiology of NAIT

Alloimmunization is developing an immune response against an alloantigen. Alloantigens are antigens that are present in a portion of the population and are absent in the rest of that population. In NAIT, mother and fetus with incompatible platelet antigens are at risk of developing anti-platelets alloimmunization. In such pregnancies, maternal immunization occurs due to the passage of the antigen-positive fetal platelets into the antigen-negative mother's circulation, leading to the production of antiplatelet IgG alloantibodies in the maternal circulation against the fetal platelet antigen. These IgG alloantibodies pass trans placentally into the fetal circulation and bind to fetal platelets (Fig 1). The antibody-coated fetal platelets are rapidly removed from the circulation by phagocytes of the reticuloendothelial system. The severity of fetal platelet destruction is determined by several variables, including maternal IgG alloantibodies subclass and concentration; fetal-neonatal platelets antigen concentration; reticuloendothelial system phagocyte activity; and on the other hand, fetal-neonatal bone marrow ability to counteract these factors and compensate for the rapid platelets destruction. [4]

In humans, there are 24 identified platelet-specific alloantigens. They are named using the human platelet antigen (HPA) system by number in the order in which they were first described. Six (HPA-1 to -5 and HPA-15) are biallelic in representation. Biallelic platelet alloantigens are further defined into "a," designating the high-frequency alloantigen, and "b," designating the low-frequency alloantigen. [15] Antibodies to platelet antigen HPA-1a are responsible for approximately 80% of the cases of NAIT in the white population, while anti-HPA-4a are responsible for 80% of the cases of NAIT in the Asian population. [15-16] NAIT caused by alloantibodies against HPA-1a tends to have a more

severe clinical course. [5] This may be attributed to the expression of HPA-1 antigens on platelet GPIIIa. So, anti–HPA-1a antibodies affect platelet aggregation and trigger platelet destruction, which may explain the severity of bleeding symptoms. [17]

About 2% of the mothers in the white population are HPA-1a negative. However, it was found that if during pregnancy HPA-1a–negative mothers are exposed to HPA-1a–positive platelets only 10% develop alloimmunization. This was explained by other factors that modulate the development of NAIT and its severity in the offspring, such as HLA type, especially anti–HLA-2 antigens. [18- 20] The presence of HLADRB3*0101 allele in HPA-1a–negative women increase the NAIT risk as much as 25-fold. [8]

Clinical picture of NAIT

NAIT has a wide range of clinical presentations, from accidentally discovered thrombocytopenia in a healthy full-term infant to severe life-threatening hemorrhages. The typical infant with NAIT is full-term with an average birth weight. The firstborn infant is affected 40% to 60% of the time. Unfortunately, in most discovered cases, thrombocytopenia is usually unexpected and often severe with hemorrhagic symptoms. [4]

NAIT should be suspected in a thrombocytopenic neonate with purpura, intracranial or visceral hemorrhage but no evidence of sepsis or other systemic diseases that may cause thrombocytopenia, including maternal immune thrombocytopenia (ITP) or systemic lupus(SLE). [21]

A case series on infants with NAIT resulting from anti–HPA-1a antibodies showed that hemorrhages frequencies of representation in the 88 neonates were as follows: purpura (90%), hematomas (66%), GIT bleeding (30%), ICH (14%) and retinal hemorrhages (7%). [12] Twelve studies reported intracranial

hemorrhage occurring in 8% to 22% of cases.[13] Factors increasing the risk of ICH in NAIT are having a platelet count <20,000/μL and a positive family history of a sibling with ICH. In cases with positive family history, ICH tends to occur earlier than in the sibling. [4]

When ICH occurs in NAIT, it tends to be severe and intracranial. Moreover, it most frequently occurs prenatally, before delivery, and may be detected on ultrasonography during antenatal care visits of apparently uncomplicated pregnancies. Intrauterine death may occur. [8]

If the mother was sensitized in a previous pregnancy, IgG alloantibodies could cross the placenta as early as week 14, and fetal GPs are expressed on platelets starting at 16 weeks intrauterine. So, intraparenchymal bleeds can occur as early as 16 weeks of intrauterine life. [24] On the other hand, it should be noted that bleeding and symptoms may be delayed in some cases because the platelet count usually falls further during the first several days of life. Mortality or neurologic morbidity occurs in up to 25% of infants. [22] Platelet counts recover to normal within 2- 4 weeks. [8]

Diagnosis of NAIT

NAIT is suspected when there is severe thrombocytopenia <50,000/μL in the first 24–48 h of life in a term infant, after exclusion of other common causes of neonatal thrombocytopenia. Usually, there is no family history of previously affected infants, as firstborns can be affected [25] On the other hand, a history of a previously affected neonate or fetus provides solid supportive evidence for the diagnosis of NAIT.

The diagnosis is confirmed by finding platelet antigen incompatibility between mother and baby. Laboratory evaluation should include HPA typing of the mother, father, and (only if needed) the child to establish incompatibilities. After proving antigen incompatibility, maternal serum should be investigated to detect

alloimmunization by identifying platelet-specific antibodies, especially HPA-1, 3, and 5 antibodies (most frequent), as well as HPA-4 antibodies in those of Asian descent. HPA-9b and 15 are the next most common antigen incompatibilities [8], which is usually done serologically using monoclonal antibody–specific immobilization of platelet antigens assays to detect maternal anti-HPA antibodies. [26, 27] The other 80% of cases with a clinical diagnosis of NAIT have no antibodies or maternal-neonatal platelet incompatibility to the previous common HPA antigens. [28, 29] Some of these unexplained cases were found to have antibodies against minor HPA (such as HPA-6w and HPA-9w) [30, 31]

Management of NAIT

- **Postnatal management**

Thrombocytopenia in most NAIT cases resolves within 1 to 2 weeks without long-term sequelae. Therapy depends on the platelet count and the neonate's clinical condition in such cases. The algorithm for the management of NAIT is shown in (Fig 2).

All neonates with suspected NAIT should be screened for ICH by cranial ultrasound. If there is any neurological abnormality and ultrasound is unrevealing, an MRI is mandatory [8] because ICH in NAIT is associated with a very high risk of severe neurodevelopmental disabilities, such as cerebral palsy. [28] For well neonates with documented or suspected NAIT who have no evidence of hemorrhage, we recommend immediate transfusion of platelets where the platelet count is <30,000/μL. Some studies reported that HPA-1a- and HPA-5b negative platelets are preferred as 95% of caucasian mothers of NAIT infants are HPA-1a- or HPA-5b negative. [32] Other studies found that maternal or matched platelets are infrequently necessary for effective therapy since there is often good efficacy with the transfusion of unmatched platelets. [8] However, all agree that

treatment should be initiated based on clinical diagnosis before immunologic confirmation for best outcomes. When maternal platelets are used, they must be plasma depleted by centrifugation or washing to remove alloantibodies. [4]

Where there is evidence of major hemorrhage, platelets should be transfused and maintained at a higher threshold of 50,000/μL until the end of the first postnatal week. [32] Intravenous immunoglobulin (IVIG) 1 g/kg per day for 1-3 days can be considered in combination with platelet transfusions, depending on the response, to maintain the platelet count above 30,000/μL and 50-100,000/μL in the presence of life-threatening hemorrhage. Sometimes corticosteroids have been used in conjunction with platelet transfusions and IVIG, despite limited evidence, using a regimen of methylprednisolone (1 mg IV) every 8 hours on days IVIG is administered. [8] Platelet rise after IVIG or glucocorticoids, if used alone, can take 24-72 hours. [4] So, platelet transfusion provides a more rapid increase in platelet count in this condition. On the contrary, in some cases, thrombocytopenia may persist for up to 8–12 weeks. Here, IVIG provides a better alternative to repeated platelet transfusions. [7] If ultrasound reveals ICH, the target platelet count should be >100,000/μL, and an MRI should be performed to define the extent of hemorrhage, which is usually intraparenchymal. Monitoring ICH should be done through repeated imaging to document stabilization and then monthly for 3 months to identify early hydrocephalus, along with neurological assessments and head circumference measurements. Following- up on all infants with NAIT until the platelet count is within the normal range will avoid missing inherited causes of thrombocytopenia. [8]

- **Antenatal management**

The importance of diagnosing NAIT is that all mothers of affected neonates would be managed in subsequent

pregnancies by fetal medicine units to ameliorate fetal thrombocytopenia and thus prevent fetal and neonatal ICH. [8]

Management of women with known HPA antibodies depends on the severity of previously affected neonates with NAIT, the zygosity of the father, and the HPA antibody titer and specificity. [33-36] If a previously affected sibling had severe NAIT, the likelihood of the subsequent fetus being affected depends on the father's platelet zygosity. If the father is homozygous for the antigen responsible, all of his offspring will be affected. Suppose the father is heterozygous or paternal typing is unavailable or uncertain. In that case, fetal HPA typing should be performed preferentially using noninvasive prenatal testing by cell-free fetal DNA or amniocentesis to determine whether the fetus is at risk and to help guide planning antenatal therapy. [8]

Antenatal therapy for mothers depends upon whether their previous fetus with NAIT was with or without ICH. For mothers with previous NAIT pregnancies without ICH, treatment starts later (20 weeks) and is less intensive than for those in which a previous pregnancy had an ICH (12 weeks). IVIG is started in weekly doses of 1 g/kg. Nevertheless, increased doses of IVIG or steroids may be needed, even without a history of ICH, guided by input from maternal-fetal medicine. [4]

Conflict of interest

The author has no conflict of interests to declare.

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Author's details

Associate Professor of Pediatrics, Pediatric Hematology and Oncology unit, Pediatric department, Faculty of Medicine, Minia University, Egypt.

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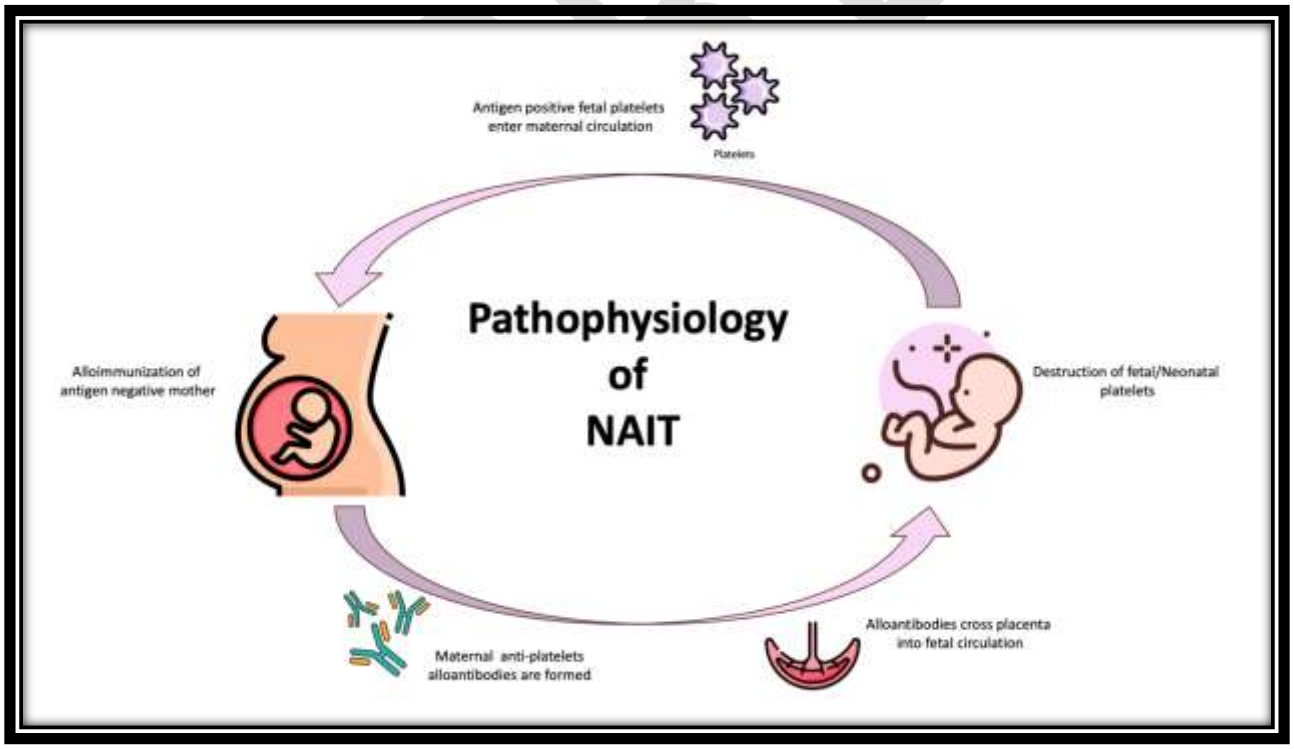

Fig. 1: Pathophysiology of neonatal alloimmune thrombocytopenia (NAIT)

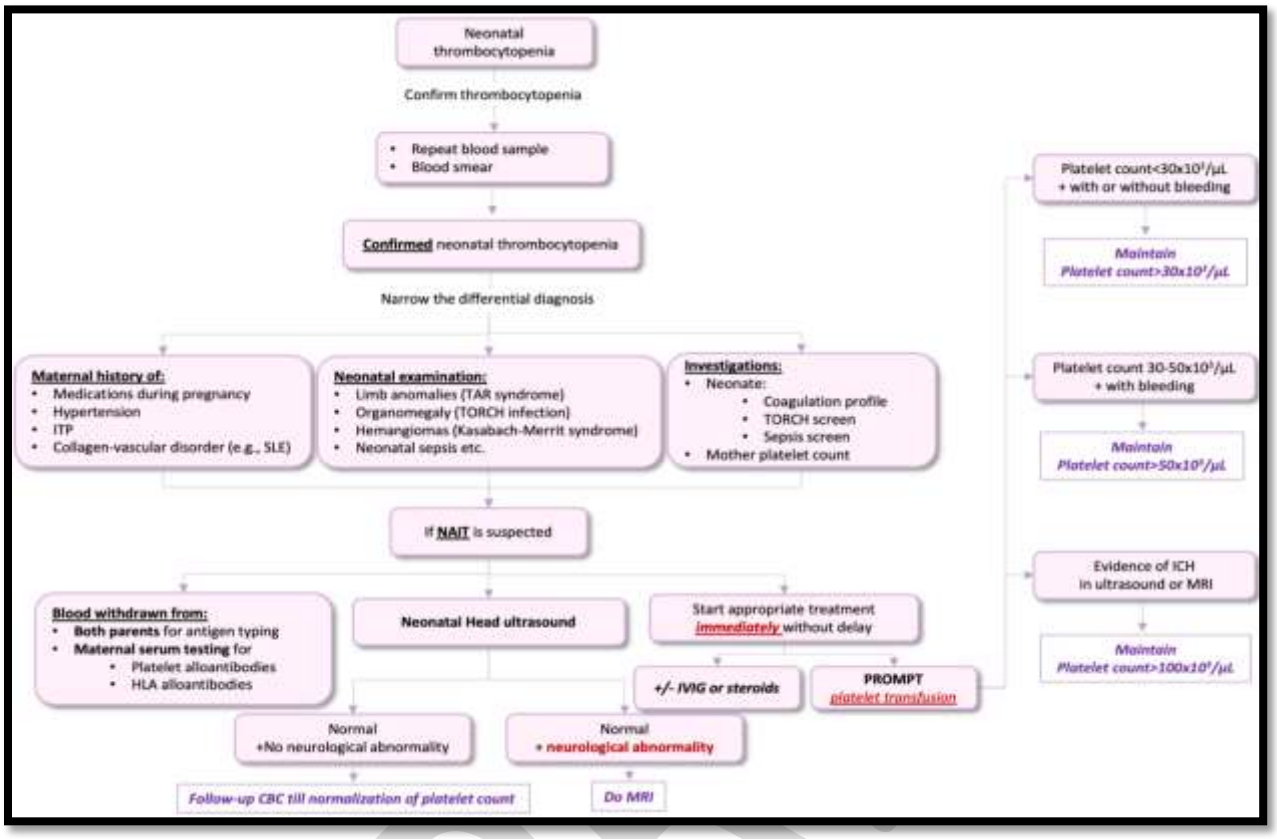

Fig. 2: Algorithm for management of neonatal alloimmune thrombocytopenia (NAIT)

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