

## Neonatal Nursing Education Brief: Neonatal Alloimmune Thrombocytopenia

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Neonatal Alloimmune Thrombocytopenia or NAIT is not common, but can have devastating complications. Healthy infants born to healthy mothers can unexpectedly develop bleeding within the first 72 hours of life. Identification and treatment needs to be immediate to avoid poor outcomes. Thrombocytopenia, neonatal alloimmune thrombocytopenia, NAIT, platelets

# Neonatal Alloimmune Thrombocytopenia

## Purpose and Goal: CNEP # 2116

- Learn about neonatal platelet disorders.
- Learn about neonatal alloimmune thrombocytopenia.

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## Requirements for successful completion:

- Successfully complete the post-test
- Complete the evaluation form

## Date

- November 2019 – November 2021

## Learning Objectives

- Describe the two types of neonatal platelet disorders.
- Describe the pathophysiology of alloimmune thrombocytopenia.
- Describe 2 approaches for treating alloimmune thrombocytopenia.

## Introduction

- Platelet disorders should be considered
  - Whenever a well neonate
  - Presents with low platelet counts
- Most cases of low platelets are the result of:
  - Inappropriate platelet function
  - Abnormal numbers of platelets
    - Too few
    - Too many
- Neonatal alloimmune thrombocytopenia
  - Is also known as NAIT
  - Is the result of maternal antibodies
  - Which are directed against:
    - Fetal platelets
    - Paternal platelets
    - Neonatal platelets
- NAIT can be a life-threatening disorder

## Neonatal Platelet Disorders

- Disc shaped platelets circulate in an inactive state
  - If blood vessels remain intact
  - For a total life span of 10 days
  - Then they are removed by the spleen
- When blood vessels become damaged
  - Platelets become spherical
  - And adhere to vessel walls
  - They also adhere to each other
- Hemostasis is initiated once platelets adhere
  - In conjunction with coagulation factors
  - In conjunction with the formation
    - Of a fibrin plug
    - That stops bleeding
- Platelet abnormalities can be caused
  - By abnormal platelet function
    - Known as qualitative abnormalities
  - By abnormal numbers of platelets
    - Known as quantitative abnormalities

## **Qualitative Platelet Abnormalities**

- Qualitative platelet disorders are characterized by
  - Normal platelet counts
  - Abnormal platelet function
- Infants present with signs of bleeding
  - Purpura
  - Petechiae
  - Mucous membrane bleeding
- Bleeding times are useful in diagnosis
- Because cessation of bleeding involves
  - Platelet adhesion
  - Platelet activation

- Platelet aggregation
- Prolonged bleeding times don't specify
  - Which platelet function is ineffective
  - But is suggestive of platelet dysfunction
- Platelet dysfunction can be acquired or hereditary
- Hereditary forms of platelet dysfunction
  - Genetic forms are a rare cause
  - They generally appear later in life
  - The dysfunction is a failure of aggregation
  - Examples of hereditary forms include:
    - Glanzmann's thrombasthenia
    - Bernard-Soulier syndrome
- Acquired forms of platelet dysfunction
  - Exposure to drugs can cause dysfunction
    - Maternal drugs
      - Aspirin
      - Indomethacin
    - Neonatal drugs
      - Nitric oxide
      - Indomethacin
  - Other causes have been known to include:
    - Uremia
    - Renal failure
  - ECMO is also associated with dysfunction
  - The dysfunction is ineffective aggregation
  - The dysfunction is also ineffective adherence
- Bleeding times are not useful if thrombocytopenia is present

## **Quantitative Platelet Abnormalities**

- Quantitative platelet disorders are characterized by
  - Abnormal platelet counts

- Elevated platelet counts
  - Decreased platelet counts
- An elevated platelet count is uncommon
  - It can be seen in GERD
  - It can be seen in Trisomy 21
  - It can be seen with maternal methadone use
- No adverse effects of elevated counts have been described
- Of note: many preterm infants show elevated counts
  - Around ~4-6 weeks of age
  - Around the nadir of anemia or prematurity
- A decreased platelet count is more commonly seen
  - It is defined as a platelet count <150,000
  - Neonatal thrombocytopenia is <123,000
  - Severe neonatal thrombocytopenia is <50,000
- The incidence varies depending on the infant
  - Just less than 1% of well neonates
  - Between 18-35% of sick neonates
- Infants can present with or without signs of bleeding
  - Generalized signs of bleeding include:
    - Petechiae
    - Melena
    - Hematuria
    - Bloody oral secretions
    - Bleeding from puncture sites
    - Pulmonary hemorrhage
    - Intraventricular hemorrhage
- The platelet dysfunction is related to:
  - Decreased production
  - Increased destruction
  - Platelet sequestration
- Decreased platelet production
  - There are several causes
    - Pregnancy-induced hypertension

- Intrauterine growth restriction
  - Chromosomal abnormalities
- Increased platelet destruction
  - Secondary to an immune response
    - Autoimmune thrombocytopenia
    - Alloimmune thrombocytopenia
  - The immune response results in:
    - Extravascular platelet destruction
    - By maternal antiplatelet antibodies
    - Which are produced by the mother
    - And cross the placenta to the fetus
    - Resulting in a short platelet life span
  - Autoimmune thrombocytopenia
    - Occurs when mothers have immune diseases
      - Systemic lupus erythematosus
      - Idiopathic thrombocytopenia purpura
    - Antiplatelet antibodies do not show specificity
    - Immunoglobulin binds to all platelets
      - Both maternal and fetal
    - Both mothers and infants are thrombocytopenic
    - The immune response lasts weeks to months
      - Low platelet counts are seen in ~10-15%
      - Intracranial hemorrhage is seen in 1%
    - Slow resolution occurs over 1-2 months
  - Alloimmune thrombocytopenia
    - Occurs due to maternal antiplatelet antibodies
    - The mother develops immunity to antigens
      - Inherited from the father
      - And present on fetal platelets
    - If the father is homozygous
      - The antigen is passed to the fetus
    - If the father is heterozygous
      - The antigen isn't passed to the fetus

- Once the antigen is passed to the fetus
  - Maternal antibodies react
  - With antigens on fetal platelets
  - And fetal platelets are destroyed
- This is called neonatal alloimmune thrombocytopenia
  - Also known as NAIT
- The most common antigen is the HPA-1a
  - Which occurs in 1/350 pregnancies
- Transfusion of maternal or matched platelets
  - Is considered optimal treatment

## Differential Diagnosis of Platelet Disorders

- The differential diagnosis in infants
  - Presenting as well
  - With thrombocytopenia
- Is different than thrombocytopenia in sick infants
- The mother's pregnancy history is helpful
  - In pregnancy induced hypertension
  - Neonatal thrombocytopenia is common
  - In NAIT, pregnancy is uneventful
  - The mother's platelet count is normal
- The most common cause of thrombocytopenia
  - Is NAIT
  - Which accounts for 20%
- The second most common cause is
  - Maternal idiopathic thrombocytopenia purpura
  - Also known as ITP
  - Which accounts for 10%
- The differential diagnoses of thrombocytopenia include:
  - NAIT
  - Maternal ITP

- Neonatal drug exposure
  - Heparin
  - Quinine
- Thrombocytopenia-absent radius syndrome
  - Also known as TARS
- Congenital amegakaryocytic thrombocytopenia
  - Also known as CAT
- Maternal drugs
  - Quinidine
  - Penicillin
  - Dioxin
  - Indomethacin
  - Phenytoin
  - Heparin
- Chromosomal abnormalities
  - Trisomy 13
  - Trisomy 18
  - Trisomy 21
  - Turner Syndrome
- Placental insufficiency
  - PIH
  - IUGR
- Thrombosis
- Fanconi's anemia
- Cardiac anomalies
- Wiskott-Aldrich Syndrome
- Kasabach-Merritt Syndrome

## **Neonatal Alloimmune Thrombocytopenia**

- NAIT was first reported in the 1950s
- It is caused by feto-maternal platelet incompatibility

- It occurs when maternal antibodies are directed
  - Against fetal platelets
  - Against paternal platelets
  - But not against maternal platelets
- The range of outcomes include:
  - Asymptomatic infants
  - Mild thrombocytopenia
  - Intracranial hemorrhage
  - Fetal or neonatal death
- The reported incidence is ~2500 infants
  - Severe outcomes occur in 1/1000-2000 infants
  - The risk of IVH and death is as high as 20%
  - The risk of long-term morbidity is 20-60%
    - Especially if IVH occurs
- The diagnosis of NAIT should always be considered
  - When an otherwise well newborn
  - Presents with a low platelet count
    - <50,000
- Most cases of NAIT occur when:
  - Paternal and fetal platelets
    - Express the HPA-1a antigen
  - And the maternal platelets
    - Express the HPA-1b antigens
- NAIT only affects a small number of fetuses
  - But the consequences may be devastating
- There are no routine prenatal screens for NAIT
  - Therefore the diagnosis is made after birth

## **Pathophysiology of NAIT**

- Platelets are small cell fragments
  - Of bone marrow cells

- Called megakaryocytes
- Platelets have a life span of 10 days
  - Then are removed by the spleen
  - Then are also removed by the liver
- NAIT occurs when the parents have different antigens
  - When the fetus inherits antigens from the father
    - That the mother does not have
  - The mother produces antiplatelet antibodies
    - That cross the placenta to the fetus
    - As early as 14-16 weeks gestation
  - Maternal platelets recognize fetal platelets as foreign
    - And they destroy the fetal platelets
    - Leaving the fetus vulnerable to bleeding
- There are several identified human platelet antigens
  - The most common paternal antigen is HPA-1a
- NAIT worsens with increasing gestation age
  - Due to continued exposure
  - Due to continued destruction

## Clinical Presentation of NAIT

- Signs of NAIT in the fetus
  - Brain damage
    - Dilated cerebral ventricles
    - Porencephaly
  - Fetal thrombocytopenia
  - In utero fetal death
  - No spontaneous correction
- Signs of NAIT in the neonate
  - Born to a healthy mother
  - Well appearing infant
    - No malformations
    - No signs of infection
  - Often present in first several hours

- With bruising
- With petechiae
- With excessive bleeding
- With mucocutaneous purpura
- May also see visceral hemorrhages
- May also see unexpected severe IVH
  - In 14-20% of infants
  - 50% of the IVH occurs in utero
  - The signs of IVH include:
    - Apnea
    - Bradycardia
    - Lethargy
    - Tense fontanel
    - Stupor
    - Seizures
- Infants who present with signs of NAIT
  - Have platelet counts <20,000
- Generally the platelet count rapidly drops
- And remains low despite platelet transfusions

## **Diagnosis of Infants with NAIT**

- Routine antenatal testing is uncommon
- Infants with signs of NAIT
  - Should be promptly evaluated
  - With a CBC and platelet count
    - The CBC should be normal
    - Anemia may be present
    - The platelet count will be low
- Other laboratory testing
  - Infection should be ruled out
  - Bleeding disorders should be ruled out

- Both parents should be evaluated
- The parents should be screened for:
  - HPA-1
  - HPA-3
  - HPA-5
  - HPA-4 if the mother is Asian
- NAIT is confirmed by identifying antiplatelet antibodies
  - In the mother's blood
  - Plus incompatibility
    - Between the parents
- Maternal antibodies begin to leave circulation
  - At 48 hours of age
- Most courses of NAIT resolve by 2 weeks of age
  - Platelet counts normalize by 4 weeks

## **Management of Infants with NAIT**

- Treatment of NAIT should begin promptly
- Treatment options include:
  - Platelet transfusions
  - Intravenous immune globulin
  - Fresh frozen plasma
  - Cryoprecipitate
- Platelet transfusions
  - Platelets should be given
  - For platelets <20,000
  - For platelets <50,000
    - If critically ill
    - If actively bleeding
  - Irradiated random donor platelets
    - Are readily available
    - Have temporary effects

- Results don't last until antigens cleared
- HPA-1a negative platelets are ideal
- Maternal platelets are also ideal
  - Washed
  - Irradiated
  - Faster effects
  - Quicker recovery
  - Longer lasting results
- The goal is a platelet count >100,000
  - 5-10 ml/kg platelets
  - Raise the platelet count
    - By 50,000-100,000
- Intravenous immune globulin
  - Also known as IVIG
  - It is IgG in concentrated form
  - It decreases the production
    - Of antiplatelet antibodies
  - It neutralizes circulating antibodies
  - It blocks the destruction of platelets
  - It also decreases the incidence of IVH
  - IVIG can be given up to 2 days in a row
- Fresh frozen plasma
  - Also known as FFP
  - It is derived from fresh blood
  - Then frozen within 6-8 hours
  - It contains one unit of clotting factors
    - For every 10-15 ml/kg
    - FFP also contains albumin
    - And many plasma proteins
- Cryoprecipitate
  - Also known as cryo
  - It is thawed FFP refrozen with plasma
  - The plasma contains high levels

- Of clotting factors
  - Factor VII
  - Factor VIII
  - Fibrinogen
- Screening for intracranial hemorrhage
  - IVH is a devastating complication of NAIT
  - IVH is found in 1/1500 newborns
    - 25% are caused by NAIT
  - All infants should be screened
    - Cranial ultrasound
    - CT scan or MRI
- Infants with NAIT require follow up
  - Serial platelet levels
  - For up to 4 weeks

## **Long-Term Outcomes of NAIT**

- Long-term outcomes are dependent
  - On the severity of NAIT
  - On the prompt initiation of treatment
- If there is no IVH then morbidity is low
  - Although vision problems are common
- One third of infants with NAIT and IVH will die
- The rest are at risk for complications
  - Hydrocephalus
  - Cerebral palsy
  - Seizures
  - Cognitive deficits
  - Developmental delays
- High-risk infant follow up is recommended
  - Neurological follow up
  - Developmental follow up

## Maternal Follow Up and Prevention

- Women who have had an infant with NAIT
  - Should be taught the importance
  - Of early prenatal care
  - Of regular prenatal care
- All future pregnancies are at risk
- The recurrence rate for NAIT is 100%
- There is a 90-100% risk for:
  - Severe fetal thrombocytopenia
  - Severe neonatal thrombocytopenia
- The symptoms of NAIT worsen with each pregnancy
- Antenatal management is controversial
- It focuses on minimizing the risks of in utero IVH
- Current management strategies recommend
  - Weekly IVIG throughout pregnancy
  - Prednisone throughout pregnancy
- The goal of IVIG and prednisone is to:
  - Block maternal production of antibodies
- Maternal platelet transfusions may also help the fetus
  - Serial transfusions with antigen negative platelets

## Summary

- Neonatal thrombocytopenia is commonly seen
- It can be mild and spontaneously resolve
- It can also be moderate to severe
  - Which can be caused by NAIT
  - Which develops within 72 hours of birth
- NAIT involves fetal and neonatal platelets
- It causes IVH in healthy newborn infants

- It also causes death in healthy newborns
- It is critical that prompt action is taken
  - With immediate treatment
  - So that complications are limited
  - And long-term outcomes are improved

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