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Neonatal Thrombocytopenia: Etiology and Diagnosis

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Abstract

Neonatal thrombocytopenia has a broad range of possible etiologies. In this review, an asymptomatic newborn infant was found to have severe thrombocytopenia on laboratory testing for limited sepsis evaluation. The differential diagnosis for thrombocytopenia in the newborn period is discussed, along with recommendations for initial evaluation and follow up of isolated thrombocytopenia in an otherwise well-appearing infant. The clinician should be aware of findings associated with unusual causes of thrombocytopenia that should prompt additional evaluation in the nursery or in the general pediatrician's office. In this illustrative case, a high index of suspicion allowed early diagnosis of Wiskott-Aldrich syndrome and prompt curative therapy by stem cell transplant.

Graphical Abstract

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Evaluation of an infant for thrombocytopenia may result from clinical signs of bleeding or may be found incidentally on laboratory studies drawn for other indications. The severity and etiology of thrombocytopenia have significant bearing on management and potential complications. We present an illustrative case of an infant incidentally found to have severe thrombocytopenia.

ILLUSTRATIVE CASE: PART 1

A hematology consult was requested for a newborn with thrombocytopenia. The patient was a well-appearing male infant who was born at 37 weeks gestation after an uncomplicated pregnancy to a G1P1 mother. The mother had normal serologies but was noted to have group B streptococcus (GBS) colonization without adequate intrapartum antibiotic prophylaxis. Delivery was unremarkable with APGAR (appearance, pulse, grimace, activity, and respiration) scores of 9 at 1 minute and 9 at 5 minutes of life. A complete blood cell count (CBC) with differential was obtained due to the maternal GBS status, and it was normal with the exception of thrombocytopenia at $12 \times 10^3/\text{mcL}$. A repeat platelet count confirmed the abnormal finding. Maternal platelets were within normal range.

Physical examination revealed a vigorous newborn without respiratory distress or abdominal distension. There were no signs of bleeding, such as bruising or petechiae of his skin, or oral mucosa. The infant had normal facies without syndromic features and normal head circumference. He had no hepatosplenomegaly or other notable physical findings. Careful inspection of his upper extremities demonstrated no abnormalities. Head ultrasound was negative for intracranial hemorrhage.

The baby was transferred to the neonatal intensive care unit (NICU) and received a transfusion of random donor platelets, with an initial increase in platelet count to $200 \times 10^3/\text{mcL}$ followed by rapid decline over the following days. He received a second platelet

transfusion on day of life 5 and two doses of intravenous immunoglobulin (IVIG) on days of life 7 and 8. Maternal antiplatelet antibody testing for alloimmunization was negative; cytomegalovirus antigen polymerase chain reaction testing from the infant's urine was negative as well.

On day of life 9, the infant's stools became melanotic with a platelet count of $20 \times 10^3/\text{mcL}$, prompting an additional transfusion of random donor platelets. Platelets initially increased to $170 \times 10^3/\text{mcL}$ and then declined over the next few days. Head ultrasound was repeated and it confirmed the continued absence of intracranial hemorrhage. Ultimately, platelet counts stabilized at 60×10^3 to $70 \times 10^3/\text{mcL}$ without further transfusions or clinical signs of bleeding. The newborn was discharged from the NICU on day of life 17 with close monitoring of his platelet levels as an outpatient.

Discussion

Platelets are highly organized anuclear cellular fragments involved in primary hemostasis. Megakaryocyte progenitor cells develop under the stimulus of thrombopoietin to produce platelets. Mature megakaryocytes then generate and release platelets into the bloodstream, where they have a half-life of 7 to 10 days. Platelets act by attaching to adhesion molecules exposed by breaks in endothelial walls, aggregating together and altering their shape (primary hemostasis). This is followed by activation of the coagulation cascade and fibrin deposition to form a mature clot (secondary hemostasis).¹

The normal range for platelet count in newborns and infants is 150×10^3 to $450 \times 10^3/\text{mcL}$, although some data suggest a slightly lower limit of normal, particularly in preterm infants.² Platelet counts decline over the first few days after birth but then begin to rise by 1 week of life. In the general population, spontaneous bleeding from thrombocytopenia does not occur when platelets are above $100 \times 10^3/\text{mcL}$. Risk of spontaneous bleeding is minimal to mild at counts of 20×10^3 to $100 \times 10^3/\text{mcL}$, moderate between counts of 5×10^3 to $20 \times 10^3/\text{mcL}$, and severe below counts of $5 \times 10^3/\text{mcL}$.³ Newborns in particular may be predisposed to bleeding events as a result of recent trauma associated with the birthing process. The most feared bleeding complication in the newborn population is intracranial hemorrhage (ICH), due to risk of death and adverse neurologic outcomes.

The differential diagnosis for thrombocytopenia is classically divided into disorders of decreased platelet production versus those of increased platelet consumption. However, when assessing the infant with thrombocytopenia, it is more useful to consider the overall clinical picture of the patient, as the common causes of thrombocytopenia in the "sick" infant tend to be distinct from the most likely causes in well-appearing infants (Table 1).³ Thrombocytopenia in the ill or very premature infant is most commonly secondary to sepsis, followed by necrotizing enterocolitis (NEC), birth asphyxia, chronic intra-uterine hypoxia, TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex) infections, or disseminated intravascular coagulation. Additionally, inborn errors of metabolism such as methylmalonic acidemia, use of certain antibiotics and other medications, or thrombosis around an indwelling catheter can lead to thrombocytopenia starting beyond the first few days of life.⁴

In an otherwise healthy-appearing infant, thrombocytopenia is most likely secondary to placental insufficiency or an immune-mediated process, either autoimmune or alloimmune, in which maternal antibodies passed to the newborn in-utero lead to destruction of the baby's platelets. Of these, neonatal alloimmune thrombocytopenia (NAIT) produces the most pronounced thrombocytopenia, with platelets typically below $50 \times 10^3/\text{mcL}$.³ NAIT occurs when the fetus inherits a paternal platelet antigen not carried by the mother; this antigen then becomes a target for maternal antibodies. Maternal platelets are not targeted and are thus within normal range. NAIT affects an estimated 1 in 800 to 1,000 children of live births.⁵ Unlike Rh-incompatibility, NAIT frequently causes disease in a woman's first pregnancy. The severe thrombocytopenia caused by NAIT carries a significant risk of potential morbidity and mortality. Approximately 10% to 30% of newborns with NAIT will develop ICH, with about half occurring in-utero; neurological sequelae and death will occur in 20% and 10% of affected neonates, respectively.⁶

In contrast, placental insufficiency usually produces only mild to moderate thrombocytopenia (50×10^3 to $150 \times 10^3/\text{mcL}$) that resolves spontaneously within 7 to 10 days after birth. Clinical features supportive of this diagnosis include an infant who is small for gestational age, a history of intrauterine growth restriction, or maternal hypertension, diabetes, or preeclampsia.¹ Autoimmune thrombocytopenia typically causes a similarly mild to moderate thrombocytopenia and results from maternal autoantibodies targeting both maternal and fetal platelets. Maternal platelet counts are expected to be low; however, the severity of maternal thrombocytopenia does not correlate well with the degree of thrombocytopenia in the infant.⁶ As a result, a newborn whose mother is known to have idiopathic thrombocytopenic purpura, systemic lupus erythematosus, or other autoimmune disease should be screened for thrombocytopenia at birth, regardless of maternal platelet count at delivery. Platelet levels eventually normalize at age 10 to 60 days as maternal autoantibodies are cleared from the baby's circulation.

In rare instances, an infant may present with thrombocytopenia as part of an inherited or other congenital syndrome. Such cases comprise less than 1% of neonatal thrombocytopenia. Additionally, although such processes are less likely than in a preterm or clinically ill neonate, it is important for the clinician to recognize that thrombocytopenia may occasionally be the initial presenting sign of sepsis, TORCH infection, or other serious condition in an otherwise normal-appearing newborn. Bacterial infection or necrotizing enterocolitis (NEC) is a particular concern when thrombocytopenia develops after the first 72 hours of life.¹ Many clinicians will obtain blood cultures and consider treating with antibiotics to cover for occult infection if the etiology for thrombocytopenia is not apparent.

As there is no systematic screening of well newborns, the true prevalence of thrombocytopenia in asymptomatic newborns is unknown. A study of 5,632 unselected newborns found platelets below $150 \times 10^3/\text{mcL}$ in approximately 1% of all neonates;⁷ about one-third were term infants born after uncomplicated pregnancies and deliveries with no known maternal factors or unusual physical findings.⁷ In practice, a newborn who is otherwise well-appearing may be identified as thrombocytopenic only after noting clinical signs of bleeding or, as in the patient discussed here, as an incidental finding on laboratory studies drawn for another purpose.

Evaluation in Well-Appearing Newborns

An asymptomatic infant found to have a platelet count below $150 \times 10^3/\text{mcL}$ should have the test repeated to rule out a spurious result secondary to platelet aggregation with ethylenediaminetetraacetic acid in laboratory tubes. Platelet counts from heel capillary sticks generally correlate well with venous samples, but occasionally will be falsely low due to clotting within the wound.

Physical examination should pay particular attention to the skin for signs of petechiae or purpura as well as the oral mucosa, which are the most common sites for bleeding to occur. Microcephaly, organomegaly, or “blueberry muffin” rash can be suggestive of TORCH infection. A localized skin lesion, discoloration, or palpated mass may represent a hemangioma of Kasabach-Merritt syndrome, in which platelets are consumed within a congenital vascular malformation. Both thrombocytopenia-absent-radii (TAR) syndrome and Fanconi anemia are associated with abnormalities of the upper extremities. The absent radii of TAR are typically easily noted on examination, but the radial and thumb defects of Fanconi anemia are easily missed. A high index of suspicion in a patient with no other cause of thrombocytopenia should prompt an X-ray of the forearms and hands. Certain chromosomal abnormalities, such as trisomies and Turner syndrome, can be associated with thrombocytopenia. Other genetic disorders, such as congenital amegakaryocytic thrombocytopenia (CAMT), can present with otherwise asymptomatic thrombocytopenia in the newborn period. Some genetic causes will also show abnormal platelet size, such as the small platelets seen in Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenias, or the large platelets found in Jacobsen syndrome.

In the absence of compelling physical findings, management of thrombocytopenia rests on the platelet count and clinical signs of bleeding (Figure 1).⁸ If there is marked thrombocytopenia, CBC results should be reviewed to ensure an isolated deficit of platelets; having decreased counts of multiple hematopoietic cell lines should prompt consideration of an infiltrative disorder of bone marrow. The blood smear should be reviewed for abnormalities in platelet morphology, which may not be detected by automated platelet counting. An infant with platelets below $50 \times 10^3/\text{mcL}$ or a suspected diagnosis of NAIT should have an immediate head ultrasound to assess for ICH; head ultrasound should be repeated if episodes of bleeding or neurologic changes are noted.

The treatment of choice in NAIT is transfusion of processed maternal platelets based on severity of thrombocytopenia and clinical symptoms. Maternal platelets are not targeted for destruction by the maternal alloantibodies, but must be washed to avoid adding more maternal alloantibodies to the newborn’s circulation. Random donor platelets will generally not produce a marked or sustained increase in platelets, but can be used as a temporizing measure in hopes of decreasing risk of ICH. IVIG is indicated when multiple or long-term transfusions are required, although it does not have an immediate effect on platelet counts.

Diagnostic and Follow-Up Considerations in NAIT

Definitive diagnosis of NAIT rests on two factors: first, identifying the human platelet antigen (HPA) carried by the neonate but absent in the mother by genotyping studies; and

second, the identification of corresponding maternal anti-HPA antibodies in the newborn by enzyme-linked immunosorbent assay. If there is clinical suspicion for NAIT, testing for antiplatelet antibodies should be sent on the infant and/or the mother. If positive, both parents as well as the neonate should be genotyped for the five most commonly identified HPA types involved with alloimmune disease. Establishing the involved platelet antigen as well as paternal hetero- or homozygosity has significant implications for reproductive planning for families affected by NAIT, as recurrence in subsequent pregnancies if the fetus carries the incompatible antigen is more than 90%. Unfortunately, more than 80% of neonatal thrombocytopenia believed clinically to be caused by NAIT lacks demonstrable HPA incompatibility, and there are limited data on patterns of HPA incompatibility in non-white populations.²

Thrombocytopenia secondary to NAIT resolves gradually as maternal antibodies are cleared over the first 2 months of life in most patients, although some may take up to 12 weeks or longer.² Infants require close monitoring until platelet counts normalize. Furthermore, pediatricians caring for children with a history of NAIT should carefully monitor developmental milestones for at least the first 2 years of life, as they may manifest signs of previous ICH not apparent on imaging.⁶ Families of children affected by NAIT should be encouraged to receive reproductive counseling and future obstetric care at specialty centers. Efforts to diagnose and treat NAIT in future pregnancies for women with a previously affected infant are of high interest, particularly given the high incidence of ICH in utero, although current therapies have not been consistently shown to be effective.⁶

ILLUSTRATIVE CASE: PART 2

After discharge from the NICU, the patient continued to receive platelet transfusions for bloody stools or epistaxis. A bone marrow biopsy was performed at 5 weeks of age and revealed normally maturing trilineage hematopoiesis, without evidence of neoplasm or infiltrative process. At age 10 weeks, the infant presented to the clinic with a dry, eczematous, scaly rash that was worst at the scalp and spread over his face, trunk, and limbs. Pathologic review of his peripheral blood smear at that time showed a significant subset of the platelets to be small and hypogranular (Figure 2). Wiskott-Aldrich gene sequencing was performed, revealing a nonsense mutation in the coding region that was predicted to result in a truncated protein and clinical disease.

Diagnosis: Wiskott-Aldrich Syndrome

In the absence of family history or significant physical findings to prompt an earlier investigation, consideration of syndromic causes of neonatal thrombocytopenia is warranted when thrombocytopenia persists beyond age 2 months. In the case of this patient, the possibility that his results were related to an etiology other than NAIT was suspected in the NICU given the large boost in his platelet counts after random donor platelet transfusion, which is atypical although not entirely inconsistent with NAIT. His normal bone marrow results ruled out congenital amegakaryocytic thrombocytopenia, which is characterized by severe thrombocytopenia, lack of megakaryocytes in the bone marrow, and potential

development of pancytopenia later in life. The finding of severe eczema, as well as persistent microthrombocytopenia, prompted testing for and subsequent diagnosis of WAS.

WAS is a rare, X-linked primary immunodeficiency disorder with an incidence of 1 to 4 cases for every 1 million live male births.⁹ An affected male inherits a genetic mutation in the *WAS* gene, leading to altered expression or function of WAS protein (WASp), which is involved in a variety of intracellular functions in nonerythroid hematopoietic cells. Female carriers are asymptomatic.

The classic triad of symptoms is severe immunodeficiency, microthrombocytopenia, and eczema, although the presence of all three findings is not required at the time of diagnosis and may not necessarily occur in an individual patient. If clinically suspected, the diagnosis is typically made by flow cytometric assessment of WASp expression, followed by sequencing of the *WAS* gene. In the absence of a known family history, the average age of diagnosis is age 24 months, with most children presenting with bleeding symptoms such as easy bruising and frequent infections, especially otitis media and pneumonia.¹⁰ Other common symptoms of thrombocytopenia include melena, hematemesis, epistaxis, and gingival bleeding. The severity of thrombocytopenia and associated risk of bleeding episodes can wax and wane over time in an individual patient.¹⁰ Platelets in WAS are uniformly small, with a mean platelet volume of <7 fL (Figure 2).¹¹ Although eczema ultimately affects most individuals with WAS, it is exceedingly rare, and possibly nonexistent, as a sole manifestation of the disease.¹⁰

The immunodeficiency of WAS is both a quantitative and qualitative T-cell deficiency, although most patients will not show profound lymphopenia as seen in other primary immunodeficiency disorders.¹⁰ There is also an abnormal humoral immune response with low immunoglobulin (Ig) G, IgA, and IgM, and high IgE.¹⁰ In addition to frequent sinopulmonary infections, patients are at risk of serious bacterial infections such as sepsis, opportunistic infections, severe and disseminated forms of viral infections, as well as invasive fungal infections. Those who have recurrent infections or abnormal immunoglobulin levels should receive scheduled IVIG infusions. IVIG therapy reduces infections but does not affect platelet counts in WAS.⁹ Children with identified WAS should not receive live or attenuated vaccines but should receive all other routine immunizations at the usual schedule. All patients should also receive *Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole or equivalent agent.

Our patient continued to receive platelet transfusions as well as scheduled IVIG prior to undergoing hematopoietic stem cell transplant (HSCT) at age 1 year. HSCT is currently the accepted curative treatment for WAS, and preferably should be performed prior to onset of significant infectious complications.⁹ In fact, patients have been shown to have the best outcomes when the transplant is performed before age 2 years. Long-term survival following allogeneic HSCT is >80%.⁹

CONCLUSION

The differential diagnosis of congenital thrombocytopenia is broad and has implications for the affected child, parents, and potentially future children. WAS has a variable presentation, and a high clinical index of suspicion is necessary to identify it early and refer to a center that can consider treatment with HSCT.

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Figure 1.

Approach to the well-appearing newborn with platelets <150,000/mcL. CBC, complete blood count; CMV, cytomegalovirus; ICH, intracranial hemorrhage; IVIG, intravenous immunoglobulin; NAIT, neonatal alloimmune thrombocytopenia; PCR, polymerase chain reaction.

* There are currently differing opinions on when exactly is the correct time to transfuse without bleeding, but many centers follow these guidelines. If available, washed maternal platelets are preferred due to high suspicion of NAIT in an otherwise well-appearing term infant with severe thrombocytopenia. Random donor platelets can be used if washed maternal platelets are unavailable. If diagnosis of NAIT is not established, some institutions will transfuse random donor platelets initially to look for a subsequent sustained increase in platelet counts, which suggests against NAIT.

Figure 2.

(A) Peripheral blood smear (Wright-Giemsa, 1000x): platelets with normal size, shape, and granularity in an unrelated normal patient provided for comparison. (B) Peripheral blood smear (Wright-Giemsa, 1000x). Some of the patient's platelets showed normal size and granularity (left side). However, a significant subset of the platelets were small and hypogranular (arrows).

TABLE 1

Causes of Neonatal Thrombocytopenia

	III-Appearing, Premature		Well-Appearing, Full Term	
Type	Early Onset (<24 h)	Late Onset (>72 h)	Early Onset (<24 h)	Late Onset (>72 h)
Common	Sepsis TORCH infection Birth asphyxia DIC NEC	Sepsis Thrombosis DIC NEC Drug-induced	Placental insufficiency Autoimmune Alloimmune (NAIT) Occult infection	Occult infection NEC
Rare	Chromosomal disorders • Trisomy 13 • Trisomy 18 • Trisomy 21 • Turner syndrome	Inborn errors of metabolism Fanconi anemia	Inherited syndromes • Bernard-Soulier • Wiskott-Aldrich • Thrombocytopenia absent radii • Others Vascular tumors • Kasabach-Merritt	Inborn errors of metabolism Fanconi anemia

Abbreviations: DIC, diffuse intravascular coagulopathy; NEC, necrotizing enterocolitis; NAIT, neonatal alloimmune thrombocytopenia; TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus, or herpes simplex.