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Approach to Neonatal Thrombocytopenia

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Introduction:

Hello everyone,

Welcome to PedsCases! My name is Justin Park, and I am a fourth-year medical student at the University of British Columbia. In this podcast, we will discuss how we can form an approach to neonatal thrombocytopenia. This podcast was made in collaboration with Dr. Aisha Bruce, associate professor in the Division of Pediatric Hematology & Oncology at the University of Alberta.

Objectives:

After listening to this podcast, the learner should be able to:

1. Define neonatal thrombocytopenia
2. Classify the etiologies of neonatal thrombocytopenia based on onset, history and clinical features
3. Review key points on prenatal and neonatal history that will guide your differential diagnosis and management plan
4. Recognize the clinical manifestations of neonatal thrombocytopenia
5. Discuss the approach to management of neonatal thrombocytopenia

Please note, cell counts mentioned in this podcast are in units of 10E9 counts/L. For simplicity, the exponential term and unit will be omitted when discussing specific values.

Now let's begin with a case.

Clinical Case:

You are working in the NICU when baby-boy John is admitted after a premature delivery at 33 weeks gestation to a G1P0 parent. On Day 4 he appears more lethargic and is feeding less according to his nurse. A CBC with differential is drawn and his platelets are noted to be decreased at 90, the remainder of his cell lines are within normal limits. How would you approach this clinical scenario?

Background:

DEFINITION

We will start off by defining what neonatal thrombocytopenia is.

Neonatal thrombocytopenia (referred to as NT in this podcast) is a state of reduced platelet count of less than 150 in a newborn of any gestational age and can be classified as mild with counts between 100-150, moderate between 50-99, or severe which is less than 50. Familiarizing yourself with NT will be helpful when looking after newborns, as increasing severity of NT is associated with higher risk of bleeding, NICU admission, and morbidity. NT is a common condition found in the NICU, with a reported prevalence of 22-35%; within the general population, it is reported to be around 1-5%.

The risk of early NT is increased with decreased gestational age, meaning that premature babies are more prone to developing the condition. Particularly at risk are also newborns of mothers with a history of thrombocytopenia secondary to autoimmune diseases, those whose previous siblings had NT, those with genetic disorders such as Trisomy 21,18, or 13, or if they acquired congenital infections such as CMV and rubella. The mechanisms of how these risk factors can lead to decreased platelets in newborns will be discussed later in the podcast.

Although in most instances NT is found incidentally with routine blood work, it can also be accompanied by symptoms of bleeding, such as petechiae, ecchymoses, cephalohematoma, or oozing from the umbilical cord or puncture sites. Other symptoms may also be present depending on the etiology of the NT; we will next discuss these various causes of NT, and how we can organize them into different categories to help guide our differential.

Etiology

NT has a variety of etiologies, often with overlapping clinical features, which can lead to challenges when diagnosing the patient. To guide the diagnostic evaluation of NT, the condition can be classified in various ways. These include:

1. The platelet size; that is, do the platelets appear small, normal, or large on a blood smear?
2. Whether it appears to be congenital vs. acquired
3. Gestational age
4. Mechanism, which can be categorized into increased destruction, sequestration and activation of platelets, or decreased production
5. And lastly, the time of onset; NT is considered early if presenting at <72 hours of age, vs. late which is after 72 hours of age

The various causes of NT can present with different combinations of characteristics within these categories, therefore these classifications can help inform the clinician of the possible etiology during the workup. This podcast will present the possible etiologies using a focus on the time of NT onset, as this is a common approach in the clinical setting.

Early thrombocytopenia

Most cases of NT present at birth or within the first 72 hours of life, which is considered early. Generally, the differential for early NT can be classified into immune-mediated, neonatal, feto-maternal, or genetic conditions.

Of these, immune-mediated causes are most often the culprit for NT. Because of this, a term, **otherwise-well** infant with early NT who is symptomatic (with signs of bruising, petechiae, severely low platelet count) without an obvious cause should be assumed to have alloimmune or autoimmune thrombocytopenia until proven otherwise. In immune-mediated processes, platelet destruction can be facilitated by an IgG-mediated immune response, either through autoantibodies, alloantibodies, or drug-dependent antibodies. Specific diagnoses include:

- Neonatal alloimmune thrombocytopenia, which describes the presence of antigens on the fetal platelet inherited from the father which is foreign to the mother. Subsequently, during the pregnancy the mother develops IgG antibodies against these antigens which can cross the placenta into the fetus, leading to destruction of platelets
- Neonatal autoimmune thrombocytopenia, which occurs when autoimmune disorders such as ITP or lupus is present in the mother, leading to both fetal and maternal thrombocytopenia. For this reason, investigating mothers of infants with unexplained thrombocytopenia is good practice.

In addition, issues pertaining to pregnancy or delivery may induce NT. Examples include placental insufficiency - typically, hypertensive disorders during pregnancy lead to decreased utero-placental blood flow secondary to maternal vasospasm. With less blood flow, the fetus receives less nutrients and building blocks for platelet production, increasing the risk of NT. Preeclampsia is a common example of a hypertensive disorder everyone is likely to come across in their training and approximately 1 in 100 live births from mothers with preeclampsia is associated with NT. Other notable conditions associated with placental insufficiency include maternal diabetes and intra-uterine growth restriction. NT due to placental insufficiency typically reach nadir by day 2-4 then resolve spontaneously by day 7-10. Complication during labour, such as perinatal asphyxia is another known risk factor of NT although the exact mechanism is currently unknown.

Neonatal conditions include perinatal infections, notably with GBS, E Coli, haemophilus influenzae, or listeria monocytogenes can lead to disseminated intravascular coagulation (DIC), a disorder secondary to systemic tissue damage inducing overstimulation of the coagulation cascade. This results in excessive thrombosis and therefore massive platelet consumption. Infants will most likely appear unwell and develop severe NT because of DIC. As well, infants with genetic syndromes such as trisomy 21, 18, or 13 are predisposed to developing early NT.

Late thrombocytopenia

With late-onset NT, acquired infectious causes should be at the top of your differential. Infants, especially of those who are preterm, low birth weight, or are admitted to the NICU, are at risk of developing necrotizing enterocolitis (or NEC for short). This is a life-threatening condition in which bacteria invade the bowel walls, leading to inflammation and necrosis of the GI tract. With immense systemic inflammation, there is increased platelet consumption which leads to late-onset NT. For more information on NEC, you can refer to the PedsCases podcast episode on the topic.

Certain drugs can also induce an immune-mediated destruction of platelets. Examples include quinidine (medication for management of malaria) and antiepileptic agents such as valproic acid which the mother takes during pregnancy. As well, heparin, when used to treat thrombosis in newborns, can rarely lead to heparin-induced thrombocytopenia. Antibiotics including vancomycin, metronidazole, or penicillin derivatives have shown association with NT.

Evaluation

Now that we have learned how to organize the various causes of NT into categories, it is time to examine the pertinent patient evaluation points to be able to formulate a differential diagnosis. Of note, NT can be a deadly condition in which immediate life-saving intervention is necessary; in symptomatic patients who show signs of hemodynamic instability, think infectious causes such as sepsis or NEC, or coagulopathies such as DIC. Definitive management strategies with infectious management and transfusion therapy take priority over the diagnostic workup.

The main goals during the evaluation of a baby with NT should be to:

1. Rule out the life-threatening causes of NT
2. Minimize investigations of conditions which are generally self-limiting
3. Recognize conditions which can have health implications for the baby

Once the lab result shows a reduced platelet count and further workup is indicated, it is recommended that the bloodwork is repeated to confirm the result as collection or processing errors is common.

If you are convinced that the patient is stable, then take a comprehensive history including the following pertinent information:

1. The age of onset
    - Early onset at < 72h of age is more likely to be related to the pregnancy and birth, with causes such as immune-mediated processes or congenital/perinatal issues, whereas late onset is likely to be secondary to acquired conditions such as sepsis or NEC.
2. The severity of NT
    - Mild to moderate cases usually resolve spontaneously and further evaluation is generally not required (other than ensuring counts return to normal).
    - However, for severe cases, meaning a platelet count of less than 50 – further evaluation is always warranted.
3. A detailed maternal, neonatal, and birth history
    - The mother's past medical history, particularly any autoimmune disorders, is important to note.
    - Ask if the mother took any medications that could induce NT throughout the pregnancy, such as valproic acid or quinidine. As well, have they had any prenatal infections? Did they receive regular prenatal care, including screening for genetic syndromes and ultrasound biometry for fetal size and amniotic volume measurements?
    - What was the gestational age at birth? Preterm babies typically develop NT due to placental insufficiency, asphyxia, congenital infection, or DIC secondary to sepsis/NEC. On the other hand, NT in term babies is more likely to be secondary to immune mediated platelet destruction.
    - Did the baby require any resuscitation and monitoring following birth? This may suggest history of perinatal asphyxia.
    - What was the birth weight of the baby? Infants of low birth weight are more at risk of developing sepsis.
    - Does the patient have a sibling with a history of NT?

Now we can move on to the physical exam. Start with the general inspection - notable features you can look for are any dysmorphic features that may suggest genetic disorders. As well, measure the head circumference to check for microcephaly, with is seen with CMV infection. In your abdominal exam, be sure to check for evidence of hepatosplenomegaly, which may be related to either a congenital infection, or hypersplenism.

As for laboratory studies, a CBC&D with a peripheral smear should always be included. In addition to the thrombocytopenia, if other cell lines are also reduced in the CBC, it suggests an etiology related to an issue with destruction of the cell lines. As well, on the peripheral smear, take note of the platelet sizes; if large, it suggests a destructive or consumptive etiology whereas small to normal size suggests issues with production. As well, be aware that different congenital and genetic disorders can result in different platelet sizes.

In severe, symptomatic cases or late-onset NT suggestive of infectious causes, obtain coagulation studies and blood cultures as they are associated with the acute and worrisome pathologies including DIC and sepsis.

Hopefully after your thorough history, physical exam, and interpretation of the lab results, you can formulate a working diagnosis and the differential. We will move on now to discuss how NT can generally be managed.

Management:

Please note, treatment of NT often consists of treatment of the underlying etiology. Discussion of the management strategies of the different causes of NT is not within the scope of this podcast. However, we will discuss the general approach to NT management.

Oftentimes, mild to moderate NTs without clinical symptoms will resolve spontaneously typically within 1 week and platelet count monitoring is needed. There are no guidelines to recommend the frequency of monitoring, however the decision should be made based on the gestational age, post natal age, the working diagnosis, the severity of the thrombocytopenia, and whether transfusions were administered. As well, the decision to escalate care with an NICU consultation can be made if the baby appears ill, unstable, bleeding or has severe thrombocytopenia.

Neuroimaging with cranial ultrasounds should be obtained as soon as possible after delivery for infants with suspected neonatal alloimmune thrombocytopenia, as they have an elevated risk for in-utero intracranial hemorrhage. Additionally, preterm infants of less than 32 weeks gestational age should also obtain neuroimaging, given their risk for intra-ventricular bleed from the fragile germinal matrix. In the context of decreased platelets, the sequelae of these conditions can be exacerbated.

The primary intervention generally used prophylactically to reduce the risk of bleeding in NT is transfusion of platelets. Again, no guidelines exist on specific criteria at which platelets should be transfused, and thresholds are typically set based on the institution, clinician, and the latest evidence which is still developing. However, certain clinical scenarios should guide the physician to use a more conservative threshold when debating the indication for a platelet transfusion. These include:

1. Neonates with confirmed bleeding such as ICH, pulmonary hemorrhage, frank rectal bleeds, or any other bleeds

2. Those who will undergo major surgery
3. Ill, unstable infants showing signs of poor perfusion, lethargy, or respiratory distress
4. Severely premature infants, or those who are SGA

Back to Clinical Case:

To apply what we have learned, let's get back to the case.

Baby-boy John is a 33-week GA male presenting at day of life 4 with a platelet count of 90 – moderate NT. Given the late onset of NT and the baby's symptoms such as lethargy and decreased feeding, there is elevated risk of an acquired etiology such as sepsis or NEC. You do a thorough history and physical exam. The history reveals an unremarkable pregnancy apart from preterm birth with routine prenatal care. Prenatal infectious screening was negative. The mother had not taken regular medications apart from prenatal vitamins throughout the pregnancy, and reports the fetal ultrasounds revealed normal biometry. The patient did require resuscitation with blow-by oxygen for a few minutes following delivery but had shown improved vitals and was put on room air shortly after. The physical exam reveals mild intercostal indrawing, distended abdomen, and streaks of frank blood per rectum in the diaper. There are no signs of poor perfusion noted. Apart from the bloody diaper, there are no other signs suggesting active bleeding, such as skin changes, cephalohematoma, or umbilical cord oozing. Through your findings, a clinical diagnosis of NEC is made and you send off the blood cultures and coagulation studies. Appropriate management for NEC stage 1 is initiated.

In regard to John's NT, serial blood work is initially ordered for every 12 hours to monitor the platelet count. You discuss with your preceptor that a conservative transfusion threshold of 80 should be set, as he presents in unstable condition with frank rectal bleeding. Fortunately, the patient begins to stabilize after initiation of treatment, and his platelet level eventually trend towards normal levels. Blood cultures come back negative after 48 hours. By the time baby-boy John is discharged from the NICU, his platelet count remains stable within the normal range.

Key learning points:

In conclusion, the key learning points of this podcast are:

1. NT is a state of reduced platelet count caused by a broad range of etiology's that can be categorized into early versus late onset causes
2. Many cases of mild to moderate NT only require monitoring as they resolve spontaneously
3. Be wary of severe NT, or NT in the context of an unwell baby which should point you toward life-threatening conditions such as sepsis, NEC, or DIC
4. Platelet transfusions are helpful in certain cases to minimize the risk or amount of bleeding in NT

We hope that this podcast was helpful for your learning on how to approach neonatal thrombocytopenia. Thank you for listening!

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