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Neonatal Thrombocytopenia

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Jelena Roganovic*
Division of Hematology and Oncology, Department of Pediatrics, Clinical Hospital Centre Rijeka and School of Medicine University of Rijeka, Istarska 43, Croatia

Neonatal thrombocytopenia is generally defined as a platelet count less than 150,000/μL. Depending on the lowest platelet count recorded, it is subdivided into mild (platelet count 100,000 to 150,000/μL), moderate (platelet count 50,000 to 99,000/μL) and severe (platelet count < 50,000/μL) [1]. Thrombocytopenia is present in 1% to 5% of newborns at birth. It is much more common in preterm and sick newborns, occurring in 22% to 35% of all neonates admitted to neonatal intensive care units (NICUs) [2]. About 75% of NICU cases are considered mild or moderate, and do not warrant intervention. Extremely low birth weight infants have a higher incidence of severe thrombocytopenia, which can cause significant morbidity.

The causes of neonatal thrombocytopenia are very diverse. They can be divided into three groups: increased platelet destruction, decreased platelet production and combined mechanisms. Based on the time of onset, neonatal thrombocytopenia can be classified as early (occurring within the first 72 hours) and late (occurring more than 72 hours after birth) [3].

Increased Platelet Destruction

Neonatal thrombocytopenia secondary to platelet destruction can be divided into immune and nonimmune disorders. Common presentations of immune-mediated thrombocytopenia are neonatal alloimmune thrombocytopenia and neonatal autoimmune thrombocytopenia.

Neonatal alloimmune thrombocytopenia (NAIT), also termed fetomaternal alloimmune thrombocytopenia, is the platelet equivalent of hemolytic disease of the newborn. NAIT results from transplacental passage of maternal alloantibodies directed against paternally inherited antigens present on fetal platelets but absent on maternal platelets. The incidence of clinically apparent NAIT is approximately 1 in 1,500 live pregnancies [2]. The most common alloantigen is human platelet antigen (HPA)-1a, responsible for 80% of serologically confirmed cases. The degree of thrombocytopenia in NAIT can be severe, with platelet count less than 10,000/μL on the first day of life. Clinical findings vary from mild with petechiae and bruising resolving in the first week of life, to severe, with intracranial hemorrhage occurring in 10% to 15% of cases. The maternal platelet count is normal, an important laboratory finding for distinguishing NAIT from neonatal autoimmune thrombocytopenia. The diagnosis is confirmed by demonstrating platelet antigen incompatibility between mother and neonate; maternal and neonatal serum can also be examined for the presence of antiplatelet antibodies. However, serologic evidence is lacking in at least one third of cases, and NAIT is primarily a clinical diagnosis. The treatment of choice for infants with platelet count < 30,000/μL and/or clinically significant bleeding is transfusion of washed irradiated maternal platelets. If maternal platelets are not timely available, random-donor platelets can be used. The threshold for platelet transfusion is higher in preterm infants or sick term infants with risk factors [3]. Intravenous immunoglobulin (IVIG), 1 g/kg daily for 2 consecutive days or 0.5 g/kg daily for 4 days, is effective in prolonging the survival of transfused platelets [4]. The aim should be to maintain a platelet count at > 30,000/μL for the first week of life or as long as there is evidence of hemorrhage. Antenatal treatment for NAIT remains controversial. It includes fetal blood sampling with weekly maternal IVIG treatment or with repeated intrauterine platelet transfusions for thrombocytopenic fetuses [2,3].

Neonatal autoimmune thrombocytopenia occurs in infants of mothers with autoimmune disorders and is caused by placental passage of maternal platelet autoantibodies. In general, this condition is less serious than NAIT. Thrombocytopenia

***Corresponding author:** Jelena Roganovic, Division of Hematology and Oncology, Department of Pediatrics, Clinical Hospital Centre Rijeka, Istarska 43, HR - 51000 Rijeka, Croatia, Tel: +38551659214, Fax: +38551659216, Email: roganovic.kbcri@gmail.com

in the newborn is usually mild to moderate (the incidence of cord platelet count < 50,000/μL is 3%), and resolves gradually over the first few months of life owing to clearance of maternal antibodies. The risk of intracranial hemorrhage is less than 1% [2]. However, all neonates of mothers with a previous history of immune thrombocytopenia should have a cord blood platelet count determined at birth and repeated at 24 hours. In thrombocytopenic neonates, the platelet count should be monitored daily for the next few days, until the spontaneous rise (by day 7 in most cases). The treatment depends on the severity of thrombocytopenia and bleeding manifestations. Platelet transfusions are given only to infants with severe thrombocytopenia or evident clinical bleeding. IVIG (1 g/kg daily for 2 consecutive days) typically produces a rapid response. The degree of maternal thrombocytopenia is a poor predictor of the degree of thrombocytopenia in the neonate, and perinatal management of mothers with immune thrombocytopenia, including the mode of delivery, is controversial [5].

Nonimmune neonatal thrombocytopenia secondary to increased platelet consumption and/or sequestration is present in a number of conditions including bacterial sepsis, necrotizing enterocolitis, respiratory distress syndrome, viral infections (rubella, herpes simplex, cytomegalovirus, human herpesvirus 6, echovirus, human immunodeficiency virus), disseminated intravascular coagulation, thrombosis, polycythemia, exchange transfusion and vascular anomalies [3,5].

Decreased Platelet Production

The major mechanism underlying neonatal thrombocytopenia is impaired platelet production. Causes include genetic disorders and diseases associated with bone marrow infiltration or suppression. Genetic conditions can result in isolated thrombocytopenia or thrombocytopenia combined with dysfunctional platelets and other clinical findings.

Genetic Causes. Congenital and inherited thrombocytopenias accompanied by abnormal platelet function include Wiskott-Aldrich syndrome, Bernard-Soulier syndrome, X-linked thrombocytopenia, Chediak-Higashi syndrome and Quebec platelet disorder. Congenital thrombocytopenias without marked thrombocytopathy include TAR (Thrombocytopenia-absent radius) syndrome, Fanconi anemia, amegakaryocytic thrombocytopenia, May-Hegglin anomaly, Sebastian syndrome and Fechter syndrome [2].

Bone Marrow Suppression and Infiltration. Congenital infections (rubella, toxoplasma, cytomegalovirus, human immunodeficiency virus) and perinatal infections (Escherichia coli, group B streptococcus, Haemophilus influenzae) have been associated with neonatal thrombocytopenia mainly as a result of impaired thrombopoiesis. Transplacental passage of drugs or medication use in neonates can cause thrombocytopenia as a consequence of both bone marrow suppression and the development of drug-dependent antibodies. The most implicated drugs are salicylates, thiazides, quinine, hydralazine and tolbutamide [3,6]. Placental insufficiency and/or chronic fetal hypoxia (e.g. pre-eclampsia, intrauterine growth restriction, pregnancy-induced hypertension and diabetes) and perinatal asphyxia are both associated with decreased platelet production. Neonatal malignant diseases with bone marrow replacement (e.g. congenital leukemia) or infiltration (e.g. metastatic neuroblastoma) are rare causes of thrombocytopenia.

Combined Mechanisms

Many neonates develop thrombocytopenia as a result of a combination of mechanisms. It is likely that adverse fetal environment leads to impaired thrombopoiesis at birth, with a predisposition for thrombocytopenia to worsen when the neonate is exposed to concurrent platelet consumptive condition. The natural history of thrombocytopenia during neonatal sepsis and necrotizing enterocolitis suggests platelet consumption in rapid onset phase followed by reduced platelet production in slow recovery phase [2].

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