International Journal of Pediatric Health Care & Advancements (IJPA)
ISSN 2572-7354

Neonatal Cytopenia - What To Think Of, How To Act?

Research Article

Kranjcec Izabela[1], Matijasic Nusa[1*], Pavlovic Maja[1], Jakovljevic Gordana[1,2], MilasVesna[2,3]

[1] Children's Hospital Zagreb, Department of Hematology and Oncology, Zagreb, Croatia.
[2] Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia.
[3] University Hospital Centre Osijek, Department of Pediatrics, Osijek, Croatia.

Abstract

Cytopenia is a relatively common laboratory finding in the neonatal period. Although it is often a benign and transient condition, it may as well be associated with numerous severe, life threatening deseases, and therefore presents a diagnostic and therapeutic challenge. Clinical appearance of the child, time of onset of cytopenia, accompanying comorbidities, and basic laboratory findings are usually sufficient for diagnosis, but the condition sometimes requires additional diagnostic evaluation and prompt therapy. We herein presented 3 different cases of neonatal cytopenia (isolated neonatal neutropenia, anemia and thrombocytopenia), along with a short discussion of each with differential diagnosis and diagnostic pathway.

Keywords: Neonatal; Cytopenia; Neutropenia; Anemia; Thrombocytopenia.

Introduction

Cytopenia - weather isolated neutropenia, thrombocytopenia, anemia, or combined cell deficiencies - is a relatively common laboratory finding in the neonatal period. It is often benign and transient but may as well be associated with numerous severe, life threatening conditions, and therefore presents a diagnostic and therapeutic challenge. Clinical appearance of the child, time of onset of cytopenia, accompanying comorbidities, and basic laboratory findings are usually sufficient for diagnosis, although the condition sometimes requires additional diagnostic evaluation and prompt, life-saving therapy (e.g. transfusions, immunoglobulins). We here in presented 3 different cases of neonatal cytopenia, along with a short discussion of each with differential diagnosis and diagnostic pathway.

Presentation Of Case 1

The 1st patient was a late-preterm female newborn with a gestational age of 36 5/7 weeks, weighing 2900 grams upon delivery. She was born from an in-vitro fertilization (IVF) pregnancy, ending in cesarean section due to mother's uterine myoma. During the patient's 2nd day of life, routine laboratory work-up revealed an isolated, profound neutropenia with an absolute neutrophil count (ANC) of 190/mm^3. Although the newborn appeared healthy, without laboratory signs of sepsis, a dual empiric antibiotic therapy was immediately initiated, along with hematological evaluation. Anti-granulocyte antibodies were negative, as well as TORCH serology screen and polymerase chain reaction (PCR) for cytomegalovirus (CMV) in urine. From 4th to 6th day of life she received intravenous gamma-globulin therapy. The lowest ANC count was 90/mm^3 at the end of the 1st week, but after that showed a significant rise, so the patient was eventually discharged from the hospital on day 14, with an ANC of 545/mm^3. Further diagnostic evaluation continued through outpatient care. Three days post discharge, peripheral blood smear showed normal morphology of scarce granulocytes, while genetic evaluation excluded severe congenital neutropenia (SCN) associated with ELANE or HAX1 mutations. Abdominal and cardiac ultrasound were without pathological findings.

The final diagnosis of this patient was a benign, idiopathic, transitory neonatal neutropenia. As the infant appeared healthy and showed an increase of ANC from the 2nd week of life onward, without coexisting anemia or thrombocytopenia, we decided to

***Corresponding Author**:
Matijasic Nusa,
Children's Hospital Zagreb, Department of Hematology and Oncology, Zagreb, Croatia.
E-mail: nusa.matijasic@gmail.com

Received: February 08, 2020
Accepted: February 22, 2020
Published: March 11, 2021

Citation: Kranjcec Izabela, Matijasic Nusa, Pavlovic Maja, Jakovljevic Gordana, MilasVesna. Neonatal Cytopenia - What To Think Of, How To Act. *Int J Pediat Health Care Adv.*. 2021;07(01):101-105. **doi:** http://dx.doi.org/10.19070/2572-7354-2100029

halt detailed analysis and to continue with weekly ambulatory monitoring, including physical exams and complete blood counts. At week 6, ANC reached 1000/mm^3, so we switched to monthly check-ups. As we write this paper, our patients is a normally developing 5-month-old infant, with an ANC on the lower level of the reference range.

Presentation Of Case 2

The 2nd patient was a 23-day-old male newborn that was admitted to Intensive Care Unit (ICU) due to persistent, severe thrombocytopenia. Pregnancy was complicated by mother's gestational diabetes and hypothyreosis. Term delivery by caesarean section for dystocia was, however, unremarkable. The healthy appearing, euthrophic neonate was discharged in the 4th day of life after short course of phototherapy. By the end of the 2nd week the newborn was hospitalized in Nephrology Unit because of cystopyelonephritis caused by Enterobacter species. Combined parenteral antibiotic therapy (gentamicin, ampicillin) was administered during a 10-day period. Thrombocytopenia detected at the time of admission (platelet count (Plt) 60x10^9/L) gradually progressed (Plt15x10^9/L) without any skin or mucosal signs of bleeding. Intravenous immunoglobulins (2 g/kg) with platelet transfusions (PT) resulted in platelet count recovery (thrombocyte count 106 x 10^9/L). The patient was discharged after 5 days in good clinical condition for outpatient follow-up.

The final diagnosis was transitory neonatal thrombocytopenia (NT) of possible immune etiology. Diagnostic work-up excluded alloimmune etiology of thrombocytopenia. Abdominal ultrasound was normal and brain sonography showed no intracranial haemorrhage (ICH). Excellent response to administered therapy suggested immune etiology. In the follow-up, platelet counts were continuously in the reference range but by the end of the 2nd month of life slightly lower granulocyte counts were noted. Diagnostics of the mild to moderate, yet persistent neutropenia (ANC of 740 to 1200/mm^3) in otherwise healthy and satisfactory developing 8-month infant, is ongoing.

In conclusion, our case was of an acquired, late onset severe thrombocytopenia in well-appearing term newborn without haemorrhagic diathesis, who was treated prophylactically with transfusion and immunoglobulins. The diagnosis that guided the therapy was one of exclusion. Given the good response to applied therapy and neutropenia that developed a few months later, child's predisposition to immune disorders might be presumed.

Presentation Of Case 3

The 3rd patient was a female term newborn with suspected bowel obstruction in the 1st day of life. She was admitted to ICU due to persisting vomiting and absence of stool. Pediatric surgeon's examination, abdominal ultrasound and X-ray excluded mechanical intestinal obstruction. Nasogastric and rectal tubes were placed and the symptoms resolved with in few days. Already, in the 1st day of life, normocytic anemia (erythrocyte count (E) 3.02x10^{12}/L, hemoglobin (Hb) 11.6 g/dL, MCV 114.2 fL) with unconjugated hyperbilirubinemia (188 μmol/L) and elevated lactate dehydrogenase (437 U/L) was detected. Further evaluation revealed ABO incompatibility. Cardiac ultrasound was normal, the neonate was in good general condition and did not require transfusion or phototherapy. Therefore, she was discharged 2 weeks after spontaneous red cell recovery.

Our patient's final diagnosis was extrinsic hemolytic anemia caused by ABO incompatibility. The child's blood group was A Rh D positive (A+) and both direct (DAT) and indirect antiglobulin tests (IAT) were positive. Mother's blood group was 0 RhD positive (0+) and IAT was negative. Physical examination was normal except for jaundice. No hepatosplenomegaly or signs of tissue suffering were present. She was monitored closely. Lowest hemoglobin value was 9.9 g/dL on the 7th day of life and highest bilirubin value was 214 μmol/L. Reticulocytes were within the normal range (57x10^9/L) in the 3rd week of life. Erythrocyte count and hemoglobin raised spontaneously so she was discharged 2 weeks later (Hb 10.5 g/dL). In the 2nd month of life, physiologic anemia occurred (E 2.91x10^{12}/L, Hb 9.4 g/dL, MCV 93.8 fL). The child was followed up through outpatient care for 12 months and her physical examination and laboratory findings were normal.

Discussion

Neonatal neutropenia has been varyingly defined as an ANC <1000/mm^3 [1], <1100/mm^3 [2] or <1800/mm^3 [3]. Statistically, an ANC less than 2 standard deviations below the mean value or below the 5th percentile for the postnatal age, is considered neutropenia. The finding is frequently encountered in preterm neonates, with up to 38% of them having a low ANC (<1000/mm^3) during the first days of life [1]. The three main mechanisms leading to neutropenia are decreased neutrophil production, increased utilization or destruction and excessive margination in the microvascular endothelium (table 1). Most neutropenic episodes are, however, benign, transient and only 10-20% persist beyond a week [4].

Early-onset neutropenia is commonly correlated to maternal hypertension, sepsis, twin-twin transfusion, hemolytic disease and alloimmunization [4, 5]. Neutropenia affects almost half of the newborns born to hypertensive mothers as a result of a granulocytopoiesis inhibitor of placental origin. Although it is observed at birth, ANC generally rises spontaneously within the first days and the predisposition to a bacterial infection is unlikely [4-6]. Persistent neutropenia in a well-appearing new born should be suspicious of an immune-mediated etiology. It can occur due to maternal sensitization to a paternal antigen on fetus' neutrophils (alloimmune neutropenia), transplacental transmission of mother's anti-neutrophil antibodies (neonatal autoimmune neutropenia) or the child's own immune system produces anti-neutrophil antibodies (autoimmune neutropenia of infancy) [5]. SCNs are a cluster of rare disorders characterized by impaired neutrophil maturation. They are mainly inherited by autosomal dominant pattern (mutations in the gene for neutrophil elastase - ELANE), but may also be recessive, e.g. Kostmann syndrome. These patients, in addition to severe, recurrent infections, have a higher risk for developing myelodysplastic syndrome or acute myeloid leukemia [7].

Late-onset neonatal neutropenia is observed in anemic premature infants with marked reticulocytosis, probably due to stem-cell competition between granulocytopoiesis and enhanced erythropoiesis [8]. Another type of neutropenia occurring late in the hospital course is the one associated with inborn errors of me-

tabolism [4].

Additional evaluation is indicated in severe (ANC<500mm^3) and persistent (>5-7 days) neutropenia. It should include a peripheral blood smear, a complete blood count on the mother, maternal neutrophil antigen typing, anti-neutrophil antibody screen, and, if the condition is prolonged (>2 weeks), unusual or refractory, a bone marrow biopsy. According to guidelines proposed by Calhoun and colleagues, all patients identified with severe, chronic neutropenia should be given G-CSF, 10 μg/kg subcutaneously, once per day for three consecutive days, and then as needed to titrate ANC around 1000/mm^3. If the type of neutropenia is yet unknown, and while being evaluated, G-CSF can be considered if ANC is <500 mm^3 for two or more days or <1000/mm^3 for five or more days [9].

Low platelet counts (Plt<150x10^9/L) are verified in up to 5% of children at birth and in more than one third of neonates admitted to ICU, as a result of either impaired production or increased platelet consumption [10, 11]. However, severe thrombocytopenia (Plt<50x10^9/L), associated with high risk of bleeding, is substantially less common. Etiology of NT is diverse, including immune and non-immune mechanisms, and can further be classified as early- (<24h) or late-onset (>72h) in either well- or ill-appearing newborns [12]. It is well known that megakaryocytes, megakaryocyte progenitors and their maturation process biologically differ considerably in early life compared to adulthood, thus making neonates highly susceptible to thrombocytopenia [10]. Prematurity and low birth weight are recognized as additional risk factors [11, 13].

Sepsis and necrotizing enterocolitis (NEC) are among most common causes of early- and late-onset NT in severely ill neonates [10, 12]. Infections, such as HIV or TORCH, present another possible etiology of early NT in a sick newborn, as well as perinatal asphyxia. On the contrary, early onset NT in a healthy, term neonate is mainly a result of increased platelet immunology-based destruction, in form of neonatal alloimmune or autoimmune thrombocytopenia. While autoimmune thrombocytopenia is in most cases mild and self-limiting, alloimune NT, although rare, is usually severe, associated with higher incidence of fetal or neonatal ICH, which requires typed and matched PT with intravenous immunoglobulins, and supplementary transfusion testing, as well as proper management of subsequent pregnancies [14]. Congenital platelet disorders (e.g. Bernard-Soulier), chromosome abnormalities (e.g. trisomy 13) and inborn errors of metabolism are, on the other hand, rare yet permanent causes of NT due to impaired production and therefore not in focus of our interest.

The etiology of NT can usually be identified based on detailed medical history (maternal, neonatal and labour), onset of presentation, physical findings (general condition, bleeding signs, congenital anomalies, hepatosplenomegaly…), basic laboratory testing such as complete blood count, while additional exams (blood culture, coagulation…) are less often required. Although most cases of NT resolve by itself and require only careful monitoring, it is generally recommended that infants with active bleeding (and Plt<50x10^9/L) or those with extremely low counts (Plt<20x10^9/L) are treated with PT. Bleeding episodes are observed in up to 30% of NT cases but firm causative link between NT and ICH, the most devastating haemorrhagic event, has not been established. As PT cannot prevent ICH and higher incidence of adverse events of transfusions is reported in neonates then in other age groups, clear and universally accepted guidelines are still necessary. However, every tenth infant succumbs to NT, whereby mortality rates do not correlate with the severity of the disease, but the number of PTs [15].

Anemia is defined as a decreased erythrocyte and/or hemoglobin count, ≤2.5th percentile for age, race and sex. In neonatal period

Figure 1.

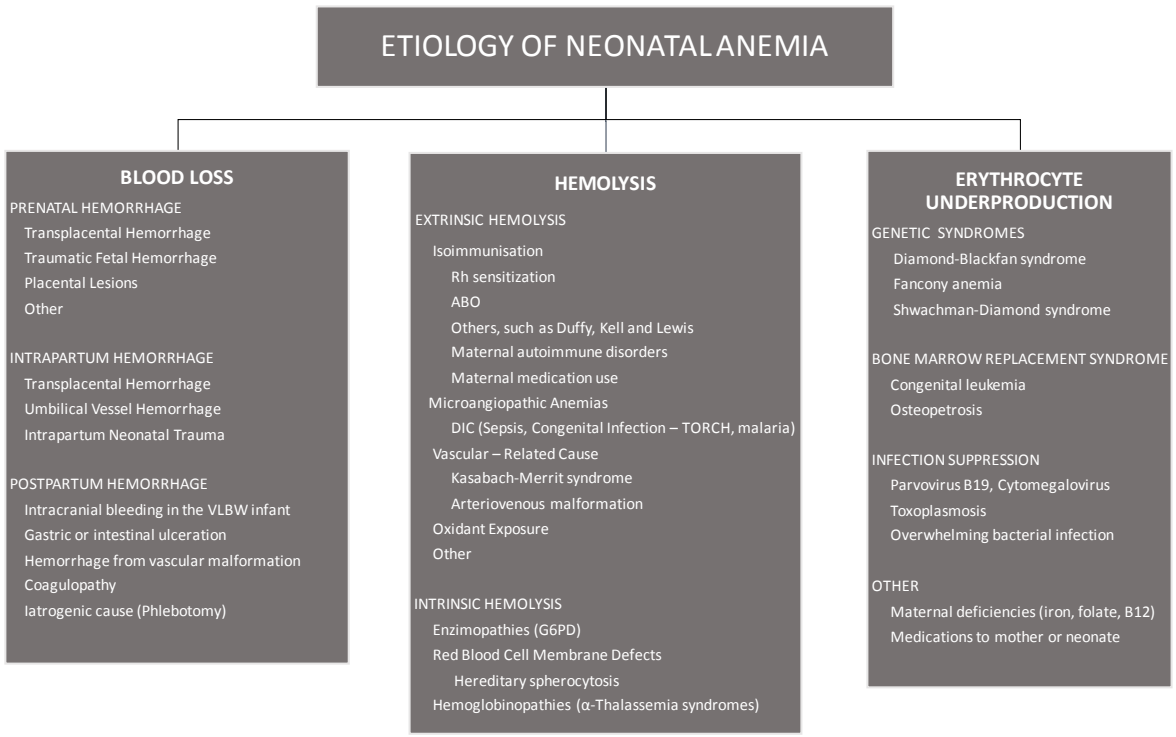
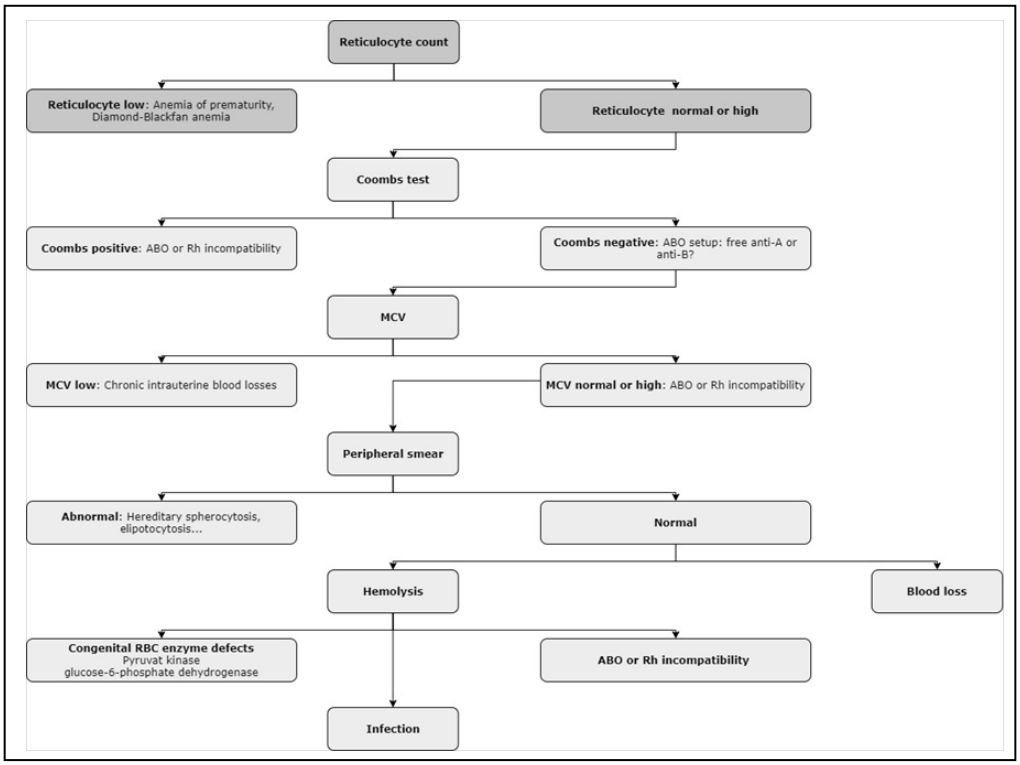


Figure 2. Neonatal anemia – diagnostic algorithm.



Mashewari A., Carlo WA. Anemia in the Newborn Infant. In: Kliegman, Robert., et al. Nelson Textbook of Pediatrics. Edition 20. Phialdelphia, PA: Elsevier, 2016.

Table 1. Causes of neonatal neutropenia.

Decreased neutrophil production	Increased neutrophil destruction or utilization	Excessive margination of neutrophils in the microvascular endothelium
Bone marrow failure syndromes (Kostmann syndrome, Barth syndrome, Schwachman-Diamond syndrome, Reticular dysgenesis, Cyclic neutropenia…)	Alloimmune neonatal neutropenia	Idiopathic neutropenia of prematurity
Infants of hypertensive mothers	Neonatal autoimmune neutropenia	Pseudoneutropenia
Viral infections	Autoimmune neutropenia of infancy	Drug-induced neutropenia
Donors of twin-twin transfusion	Sepsis, Necrotising enterocolitis	
Inherited errors of metabolism (Organic acidemias, Glycogen storage disease type 1b)		

Del Vecchio A, Christensen RD. Neonatal neutropenia: what diagnostic evaluation is needed and when is treatment recommended? Early Hum Dev. 2012 May;88 Suppl 2:S19-24.

Hb<13.5 g/dL is considered pathologic [16]. Anemia can occur due to blood loss, decreased production or increased destruction (hemolysis) of erythrocytes. The most common causes are listed in figure 1, [17] however this article focuses on hemolysis. Diagnostic algorithm displayed in figure 2 is based on reticulocyte count, MCV, antiglobulin (Coombs) tests and peripheral blood smear. In the case of suspected hemolysis (normocytic anemia with high reticulocytes and raised indirect bilirubin level) further diagnostics is needed. Child's and mother's blood types and antiglobulin tests should be done. If isoimmunisations is excluded, other causes of hemolysis should be considered, such as disseminated intravascular coagulation (DIC), vascular related causes like Kasabach-Merritsyn drome or arteriovenous malformations, and intrisic hemolysis caused by enzimopathies, red blood cell membrane defects or hemoglobinopathies (α-Thalassemia syndromes). Clinical and laboratory monitoring is crucial for therapy decision; phototherapy and/or exchange transfusion [17, 18].

Declarations

Authors' Contributions: The idea for the article came from Kranjcec Izabela. All authors contributed to literature search and interpretation. The first draft of the manuscript was written by

Kranjcec Izabela, Matijasic Nusa and Pavlovic Maja. All authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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