THROMBOCYTOPENIA- SHORT REVIEW OF THE ETHIOLOGIC AND THERAPEUTIC APPROACH

Adriana Mocanu[1], Anca Ivanov[1], Magdalena Starcea[1], Cristina Gavrilovici[1], Andra Elsayed[2], Mirabela Subotnicu[1], Ingrith Miron[1]

Abstract

Thrombocytopenia is defined as a platelet count less then150.000/mmm3. Thrombocytopenia can be often asymptomatic or may present as an incidental finding during routine evaluation or during laboratory investigations performed for other reasons. Clinically is suspected when a child develops symptoms like petechial rash, easy bruising or bleeding, or mucosal hemorrhage. Bleeding risk generally increases with a low platelet count, because circulating platelets fulfill many critical hemostatic functions :adhesion to sites of vascular injury, secretion of mediators of hemostasis (eg, thromboxane, adenosine 5 diphosphate, serotonin, and histamine) cause firm aggregation via fibrinogen binding and increase local vasoconstriction, platelets are also necessary for normal clot retraction. The system used most often to categorize the different causes of thrombocytopenia is based on the underlying pathologic mechanism leading to the thrombocytopenia, that is, either increased destruction or decreased production of platelets or increased splenic sequestration (capturing of circulating platelets in the spleen). An important role is attributed to the history of the disease, that should document the timing and severity of present and past bleeding symptoms. Other components of the history may provide clues to the underlying etiology of thrombocytopenia. Physical examination and laboratory findings complete and establish the etiology of thrombocytopenia. Management of thrombocytopenia in an individual patient should be guided by an understanding of its cause and predicted clinical course. Correction of the cause may not be possible (eg, congenital thrombocytopenias) or may not be necessary (eg, mild-to-moderate ITP).The principal management goal in all patients who have thrombocytopenia is to maintain a safe platelet count as to prevent significant bleeding, not to achieve a normal platelet count. What constitutes a safe platelet count in a particular patient varies, depending on the cause of the thrombocytopenia and consideration of all other aspects of hemostasis. For patients who have significant bleeding symptoms treatment is essential.

Key words: thrombocytopenia, child, etiology, bleeding, laboratory findings, treatment

Introduction

Thrombocytopenia is defined by the decreased number of blood platelets below the threshold of 150,000 per mm3. Thrombocytopenia may be the consequence of the following four pathogenic mechanisms:

- ***platelet production deficit***
- ***accelerated platelet destruction***
- ***abnormality of total platelet mass distribution***
- ***artefactual thrombocytopenia***

1***) Decrease in platelet production*** can be seen in the following situations:

- primary malignancies (leukemias), bone marrow infiltration, bone marrow insufficiency (aplastic anemia), viral infections (HIV, EBV, CMV, rickettsia, etc.), cyanogenic heart diseases, nutritional deficiencies; ineffective thrombopoiesis of genetic cause:

- thrombocytes with small dimensions: Wiskott Aldrich syndrome;

- platelets with normal dimensions: TAR (thrombocytopenia -absent radius), Congenital amegakaryocytic thrombocytopenia, familial platelet disorder with propensity to myeloid malignancy;

- giant platelets: Bernard-Soulier disease, MYH9-related disorders, Paris Trousseau syndrome, X Linked thrombocytopenia with dyserythropoiesis

2) ***Increased platelet consumption.***

a. ***Immune Causes:*** Immune Thrombocytopenic Purpura (ITP) - the most common cause of thrombocytopenia in children, Neonatal alloimmune thrombocytopenia, Evans Syndrome, collagenosis and autoimmune diseases

b) ***Non-immune causes:*** drug toxicity (heparin, vancomycin, trimethoprim-sulfamethoxazole), measles-mumps-rubella vaccine, platelet activation and increased consumption (disseminated intravascular coagulation, hemolytic and uremic syndrome, sepsis, thrombotic thrombocytopenic purpura, Kasabach-Merrit syndrome), mechanical destruction by hemodialysis, apheresis, cardiopulmonary bypass

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[1] Universitatea de Medicina si Farmacie "Grigore.T. Popa", Iasi, Romania
[2] Spitalul Clinic De Urgenta Sfanta Maria, Iasi Iasi, Romania
E-mail: adriana_baltag@yahoo.com, anca_vi@yahoo.com, magdabirm@yahoo.com, cristina.gavrilovici2012@yahoo.com, ingridmiron@hotmail.com

3) ***Platelet mass distribution abnormality (platelet sequestration)*** from hypersplenism encountered in infections, inflammation, red blood cell disease, storage diseases (eg portal hypertension in advanced liver cirrhosis, leukemia, lymphomas). This mechanism can also be seen in the case of hemangiomas or in the case of hemodilution (recent blood transfusion in large quantities).

4) ***Artifactual or false thrombocytopenia*** is a laboratory abnormality determined mainly by the presence of giant platelets or platelet agglutination (pseudo thrombocytopenia). Agglutination of platelets occurs in the presence of anticoagulant agglutinins (immunoglobulin A, M, G). This phenomenon is commonly encountered when blood collection is made in a container containing an EDTA-type anticoagulant.

Clinical manifestations and evaluation of thrombocytopenia in children

Evaluation of clinical manifestations/medical history

Anamnesis may provide important details on the timing / modality of occurrence and possibly the history of haemorrhagic events. The association of systemic signs and symptoms, family history, and personal pathological antecedents should be analyzed accurately. Drug history, any prodromal diseases (background diseases, history of respiratory infections), past blood counts, food survey, trips in endemic areas (malaria) may suggest the etiology of thrombocytopenia.

Clinical examination may reveal bleeding into the skin: skin purpura (petechiae, ecchymosis) - small dots, generally pinpoint, smooth, flat, painless, purple and do not blanch under pressure; rarely they can be pruritic; vibices - linear layout in the flexion folds, rarely hemorrhagic spots are filled with blood serosity, the rash having the character of serous bubbles. Bleeding in the mucous membranes (oral/nasal mucosa, soft palate, gums, lingual mucosa, conjunctival mucosa) such as epistaxis, gingivorrhagia, oral haemorrhagic blisters are common manifestations found in thrombocytopenia, regardless of etiology.

Clinical examination requires a correct inspection and classification of the haemorrhagic signs, their location and monitoring their dynamics. The presence of adenopathy, splenomegaly and / or hepatomegaly raises the suspicion of leukemia, lymphoma, chronic liver disease with Portal Hypertension, possibly viral infections. Sensorineural deafness-macrotrombocytopenia-cataract manifestations orientates towards the diagnosis of Fechtner syndrome, congenital leukoplakia- dyskeratosis.

The history of arthralgia / arthritis, prolonged febrile syndrome suggests a possible vasculitis or collagenosis (Systemic lupus erythematosus), and the association of skeletal abnormalities of absent radius type determines the diagnosis of TAR (Thrombocytopenia with absent radii) syndrome; the presence of skeletal abnormalities or spots café au lait in combination with thrombocytopenia, can be seen in Fanconi anemia. Other skin changes such as eczema accompanied by a history of recurrent infections (immune deficiency) determine the diagnosis of Wiscott-Aldrich syndrome; the presence of vascular tumors is encountered in Kasabach-Merritt's syndrome. Intracranial haemorrhage is the most serious consequence of thrombocytopenia and involves an increased risk of neurological complications

Laboratory evaluation of thrombocytopenia

Complete blood counts should be considered as a whole because the platelet count and the mean platelet volume(MPV) should be correlated with the white line and the red line.

Analyzing thrombocytopenia according to the mean platelet volume may reveal the following diseases:

- Low MPV(<7 fL): Wiscott Aldrich syndrome, X-linked thrombocytopenia
- normal MPV (7-11fL): Congenital amegakaryocytic thrombocytopenia, Thrombocytopenia with absent radii syndrome, Amegakaryocytic Thrombocytopenia associated with radioulnar synostosis, familial platelet disorder with propensity to myeloid malignancy
- MPV> 11fL: MYH9-related diseases; Bernard Soulier's syndrome, DiGeorge syndrome; ParisTrousseau syndrome; von Willebrand type 2B disease; X-linked thrombocytopenia with dyserythropoiesis / thalassemia.

Peripheral blood smear is a reference investigation on the estimation of platelet count, their morphology, the presence / absence of platelet aggregates; possible abnormalities of the white and red lines. The presence of blasts suggests a leukemic process; sometimes blasts are difficult to distinguish from atypical lymphocytes (sometimes present in immune thrombocytopenia or immune thrombocytopenic purpura) in the case of an infection in the near history.

The presence of small hypochromic red blood cells can be found in massive bleeding and the presence of schizocytes suggests a microangiopathic process (disseminated intravascular coagulation, hemolytic and uremic syndrome, thrombotic thrombocytopenic purpura), the presence of spherocytes is orientates to an autoimmune hemolytic anemia, which in the presence of immune-mediated thrombocytopenia establish the diagnosis of Evans syndrome.

A medulogram is not routinely recommended in the investigation of isolated thrombocytopenia if there is no suggestive symptom for infiltration / medullary insufficiency. This investigation is indicated in patients with chronic stable thrombocytopenia with a presumptive diagnosis of immune thrombocytopenic purpura at 6-12 months after debut.

Other tests such as coagulogram, Coombs test, D dimer, fibrin degradation products, antinuclear antibodies(AAN), anti-CMV antibodies, EBV, HIV, HCV, serum immunoglobulins, abdominal ultrasound / tomography, platelet kinetic studies / spleen scintigraphy are required in case of association of signs and symptoms specific to suspected etiology.

Both from the clinical and laboratory point of view, the elements of gravity which should be carefully analyzed can be determined,: the association at the onset or during evolution of haemorrhagic phenomena that interest the abdomen, oral haemorrhagic blisters, hematuria, retinal haemorrhage, meningocerebellar haemorrhage as well as the

association of hemostasis abnormalities or platelet counts below 10,000/mm3.

Platelet count is closely linked to the risk of bleeding, so it is imperative to correlate thrombocytopenia with the type of clinical manifestations. Thus, the absence of clinical manifestations necessitates a repeat of the complete blood count, and the harvesting method may detect the existence of technical errors or the use of EDTA (artefactual thrombocytopenia).

In general, the risk of bleeding does not increase until the platelet count falls significantly below 100,000/mm3. For example, surgical bleeding solely due to a decreased platelet count typically does not occur until the platelet count is less than 50,000/mm3 and spontaneous bleeding typically does not occur until the platelet count is less than 20,000/mm3.

Therapeutic approach of thrombocytopenia
General principles

The therapeutic management of thrombocytopenia should be individualized according to etiology and clinical evolution, and sometimes correction of the thrombocytopenia cause is not possible or not necessary.

The primary goal is to maintain platelet counts at a safe level to prevent bleeding, and the level of platelet safety varies from one patient to another and is dependent on the cause of the thrombocytopenia;

Patients at high risk for bleeding require immediate treatment, and in the case of asymptomatic thrombocytopenia or with minimal symptomatology, therapy may be required if the thrombocytopenia is severe or if the risk of bleeding is elevated.

Restriction of physical activity is indicated in moderate and severe thrombocytopenia, precautions are required for possible trauma, avoiding contact sports. Also, antiplatelet or anticoagulant medication (aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs) should be avoided.

Invasive procedures - a platelet count of more than 50,000 / mm3 is safe for most invasive procedures, but if the risk of bleeding is major, the safety level more than 100,000 / mm3. Corticotherapy in short dose (Prednisone 2mg / kgc, 7 days) or a single dose of IG IV (1g / kg) is sufficient to increase the number of platelets prior to procedures requiring haemostasis. Platelet concentrate administration in emergency situations is indicated because it provides prompt and satisfactory, but short-term hemostasis.

Critical bleeding management - Severe thrombocytopenia with massive bleeding requires a platelet concentrate, regardless of etiology. Intracranial haemorrhage is the most serious complication of severe thrombocytopenia with neurological symptoms and imaging is imperative, sometimes craniotomy being necessary. Patients with immune thrombocytopenic purpura and life threatening bleeding may receive pulse therapy with methylprednisolone (30mg / kg / day) besides platelet concentrate.

Therapeutic approach of neonatal thrombocytopenia.

Special attention should be paid to thrombocytopenia during the neonatal period.

In most cases, thrombocytopenia resolves spontaneously without any complications.

Platelet concentrate transfusion is reserved for cases with active bleeding or hemorrhagic signs: umbilical cord bleeding, numerous petechiae or extensive ecchymosis, cephalhematoma, or asymptomatic neonates with severe thrombocytopenia.

Newborns with allo-immune ITP have an increased risk for cerebral haemorrhage, (possibly intrauterine), which is why transfontanelar ultrasound is performed. The presence of intracerebral haemorrhage requires the administration of high doses of platelet concentrate, especially if platelets <100,000 / mm3. The administration of platelet concentrate is indicated in any required surgical intervention, even if the platelet values are more than 100,000 / mm 3; This intracerebral hemorrhage requires administration of high doses of platelet concentrate, in particular if the values of platelets <100,000 / mm3.

The risk of intracranial hemorrhage is greatly increased in the immediate perinatal period, it is necessary to maintain the values more than 50,000 / mm3 in the first 72-96 hours of life; after the first 96 hours of life, the decision for platelet concentrate transfusion depends on the clinical manifestations of each newborn.

Conclusions

1. Thrombocytopenia should be suspected in all patients with history of petechiae, bruising or bleeding, but can also be detected in asymptomatic patients.
2. Thrombocytopenia has as its mechanism in either increased destruction or removal of platelets from the circulation, or in the decrease in their production;
3. Physical examination corroborated with the history of the disease and the judicious use of laboratory data can accurately determine the etiology of thrombocytopenia;
4. Therapeutic management of thrombocytopenia is based on etiology and clinical evolution, the main aim being to obtain a safe level of platelets.
5. Neonatal thrombocytopenia resolves spontaneously, without complications, in most cases; establishing etiology requires specific treatment. Management of neonatal thrombocytopenia with high risk of life-threatening hemorrhage requires urgent administration of platelet concentrate, and diagnostic evaluation is continued thereafter.

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Correspondence to:
Adriana Mocanu
Universitatea de Medicina si Farmacie "Grigore.T. Popa",
Iasi, Romania
Email: adriana_baltag@yahoo.com