

Evaluation of a Child with Purpura

Roganovic Jelena*

Department of Pediatrics, Clinical Hospital Center Rijeka, Faculty of Medicine of the University of Rijeka, Rijeka, Croatia

***Corresponding Author:** Roganovic Jelena, Full Professor Tenure, Department of Pediatrics, Clinical Hospital Center Rijeka, Rijeka, Croatia.

Received: April 10, 2018; **Published:** May 11, 2018

Abstract

The presentation of a child with purpura commonly causes anxiety to both parents and pediatricians. Purpura results from a hemorrhage into the skin or mucosal membrane. Purpura is not a disease per se but is a sign of various underlying causes of bleeding. It may be caused by disruption in vascular integrity (trauma, infection, vasculitis, drugs, vitamin C deficiency, and collagen disorders), platelet disorders (thrombocytopenia due to increased platelet destruction, decreased platelet production or sequestration; platelet function abnormalities) and clotting factor deficiencies. The initial approach should be dictated by the general appearance of a child and presenting vital signs. The key point is to differentiate a child with purpura who is in life threatening condition and one who is relatively well. The type, location and the extent of the purpuric rash may help guide the evaluation. A family history of a bleeding can indicate an inherited bleeding disorder. A thorough physical examination is important to forming a differential. Ultimately, clinicians who care for children must consider physical abuse if bruises are widespread or found on body areas not normally subjected to injury.

Keywords: *Purpura, Children, Hemostasis, Platelets, Investigation*

Abbreviations

ITP: Immune Thrombocytopenia; TTP: Thrombotic Thrombocytopenic Purpura; DIC: Disseminated Intravascular Coagulation; NAIT: Neonatal Alloimmune Thrombocytopenia; TAR: Thrombocytopenia with Absent Radii; ADP: Adenosine 5'-Diphosphate; VWD: Von Willebrand Disease; VKDB: Vitamin K Deficiency-Related Bleeding; PT: Prothrombin Time; INR: International Normalized Ratio; aPTT: Activated Partial Prothrombin Time

Introduction

Purpura refers to red or purple discolored spots of the skin and mucosal membranes due to bleeding from small blood vessels. Based on size, purpura is traditionally subdivided into petechiae (pinpoint hemorrhages < 2 mm in greatest diameter), purpura (2 to 10 mm in diameter), and ecchymoses (confluent lesions >10 mm in diameter). Ecchymoses are usually called bruises. A cardinal sign of purpuric rash is that it does not change color or blanch on pressure, in contrast to erythematous or vascular lesions [1].

Purpura is not a diagnosis but a sign that may be an innocent finding related to viral infection or the presenting feature of life threatening conditions such as meningococemia. Therefore, it is very important to identify pediatric patients who require rapid evaluation and management.

What can cause purpura?

Normal hemostasis requires a complex interaction of vascular endothelial cells, platelets, plasma coagulation factors and fibrinolytic proteins, all working together to stop bleeding at the site of an injury while maintaining normal blood flow elsewhere in the circulation. Purpura may result from loss of vascular integrity, platelet disorders, clotting factor deficiencies or miscellaneous conditions [2].

Vascular factors

Acquired causes of vascular purpura include trauma, Henoch-Schönlein purpura, infections, drug use, vitamin C deficiency and psychogenic conditions. Trauma is the most common cause of purpura in preschool and school-age children. Small bruises are usually restricted to lower limbs. Although there is a wide inter-individual variation in tendency to bruise after injury, in general hemorrhage is worse in areas where the skin is lax, such as the skin around the eye or genitalia. In infants some bruising may be found from time they begin to crawl, usually on body prominences including the knees and elbows, and the forehead. Physical child abuse should be suspected if skin bleeding (usually bruising) is widespread or present on body areas not normally subjected to injury. Increased venous back pressure following severe coughing or vomiting may cause purpura in the head and neck area [3]. Henoch-Schönlein purpura (IgA vasculitis) is the most common vasculitis in children, characterized by the classic tetrad of purpura, abdominal pain, arthritis and nephritis. The hallmark is palpable purpuric rash mainly on buttocks and lower extremities. Purpura fulminans is a life-threatening condition of intravascular thrombosis and hemorrhagic infarction of the skin that is rapidly progressive and is accompanied by vascular collapse and disseminated intravascular coagulation. It may be classified as infectious, neonatal and idiopathic. Drugs such as sulphonamide, penicillins, chloralhydrate, phenytoin, and atropine may cause vasculogenic purpura. Drug-induced vasculitis usually develops within 7 to 21 days of starting a drug, and subsides when the drug is discontinued. Dietary deficiency of vitamin C (scurvy) results in impaired collagen synthesis, and may present with gum and skin bleeding [1,4]. Psychogenic purpura (Gardner-Diamond syndrome or autoerythrocyte sensitization syndrome) is characterized by recurrent episodes of painful ecchymoses. Although the condition is usually seen in adult women with psychologic instability, pediatric cases have been reported [5].

Congenital causes include Ehlers-Danlos syndrome and hereditary hemorrhagic telangiectasia. Ehlers-Danlos syndrome comprises a group of inherited heterogeneous connective tissue disorders (13 types). Vascular type is characterized by thin and extremely fragile skin that bruises easily. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is an autosomal dominant disorder of vascular dysplasia, potentially resulting in skin and mucosal bleeding [2].

Platelet disorders

A number of acquired and inherited conditions which result in low platelet count or platelet function abnormalities may present with purpura. In most cases, thrombocytopenia is acquired. Spontaneous bleeding does not usually occur until the platelet count is less than $20 \times 10^9/L$ [1].

Thrombocytopenia may be a result of increased platelet destruction, decreased platelet production, or sequestration.

Increased Platelet Destruction: Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children. ITP is an acquired autoimmune disorder typically presenting with isolated thrombocytopenia and sudden onset of a purpura in an otherwise healthy child, often after antecedent viral infection. A benign and self-limited course is common, and major bleeding is exceptional [6]. Hemolytic uremic syndrome is an acquired disease characterized by a triad of microangiopathic anemia, thrombocytopenia, and acute renal injury. Children rarely manifest purpura. Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy outlined by a pentad of severe thrombocytopenia, microangiopathic hemolytic anemia, fever, renal dysfunction, and

neurologic abnormalities. TTP is specifically related to a severe deficiency in ADAMTS13 (the specific von Willebrand factor-cleaving protease), which is most frequently acquired via ADAMTS13 autoantibodies, but rarely is inherited via mutations of ADAMTS13 gene [7]. Disseminated intravascular coagulation (DIC) is a serious condition characterized by systemic activation of coagulation, leading to microvascular thrombi in various organs. Ongoing consumption of platelets and coagulation proteins may cause profuse hemorrhagic complications. DIC is always secondary to an underlying condition [8]. Neonatal alloimmune thrombocytopenia (NAIT) results from maternal immunization against specific platelet alloantigens paternally inherited by the fetus. Although many cases are mild, NAIT can cause significant morbidity including intracranial hemorrhage [9]. Drugs may cause thrombocytopenia acting as haptens with platelet surface antigens with subsequent formation of antiplatelet antibodies and increased platelet destruction. These include penicillin, sulfonamides, chloramphenicol, valproic acid, carbamazepine, cimetidine, and heparin [1,2].

Decreased Platelet Production: Bone marrow infiltration in children with acute leukemia, neuroblastoma, histiocytosis, myelofibrosis and storage diseases may result in thrombocytopenia and purpura. Most common drugs reported to cause thrombocytopenia by suppressing platelet production are alkylating agents, antimetabolites, anticonvulsants, chlorothiazide diuretics and estrogens. Viral and bacterial infections, especially septicemia, may cause thrombocytopenia by direct bone marrow suppression. Common viruses include hepatitis B and C, human immunodeficiency virus, Epstein-Barr, cytomegalovirus (CMV), parvovirus B19, rubella, mumps and varicella-zoster virus. Intrauterine TORCH infection, which includes Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, CMV, and Herpes infections, may lead to neonatal thrombocytopenia [10].

A number of rare congenital syndromes are associated with thrombocytopenia: congenital amegakaryocytic thrombocytopenia, thrombocytopenia with absent radii (TAR) syndrome, Wiskott-Aldrich syndrome and Fanconi anemia. Acquired aplastic anemia is a rare bone marrow failure syndrome characterized by pancytopenia and bone marrow hypoplasia. Immune destruction of hemopoietic stem cells plays an important role in pathogenesis. In 5% to 10% of patients, aplastic anemia is preceded by seronegative hepatitis. However, most patients do not have a history of identifiable infectious or chemical exposure before onset of pancytopenia [11].

Sequestration: Increased splenic platelet sequestration may occur in numerous disorders that cause splenomegaly. Splenomegaly causes mild or moderate reduction in platelet count rather than severe thrombocytopenia, and purpura is very rare. Platelet trapping can also occur in large hemangiomas. The combination of giant hemangioma, thrombocytopenia and consumptive coagulopathy is termed Kasabach-Merritt syndrome [1,2].

Platelet function abnormalities: Inherited platelet function disorders are rare cause of purpura. They are classified according to platelet function into adhesion, activation, secretion, and aggregation defects. This heterogeneous group of disorders includes Bernard-Soulier syndrome (platelet adhesion disorder), Adenosine 5'-diphosphate (ADP) receptors defects (platelet activation disorders), platelet secretion disorders (Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Gray platelet syndrome, Quebec platelet disorder), Glanzmann's thrombasthenia (platelet aggregation disorder), and platelet procoagulant function disorders. Acquired platelet function abnormalities are much more frequently encountered in clinical practice. Causes include drugs (aspirin, nonsteroidal anti-inflammatory drugs, clopidogrel, antihistamines, phenothiazines, valproic acid), systemic disorders (myeloproliferative and myelodysplastic disorders, uremia, macroglobulinemia, systemic lupus erythematosus) and procedures (cardiopulmonary bypass, extracorporeal membrane oxygenation). Aspirin and nonsteroidal anti-inflammatory drugs prevent cyclooxygenase-mediated production of thromboxane A₂. This effect can last 5 to 7 days [12].

Clotting factor deficiencies

Purpura can be the presenting sign of congenital or acquired deficiency of clotting factors. Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with the prevalence between 0.1 and 1% in general population (including all forms). Quantitative defects include type 1 VWD (partial deficiency of von Willebrand factor) and type 3 VWD (complete deficiency of von Willebrand factor). Type 2 VWD includes qualitative defects and functional anomalies of von Willebrand factor (2A, 2B, 2M, 2N). Patients with VWD usually

present with easy bruising, mucous membrane bleeding (epistaxis, menorrhagia), or prolonged bleeding following surgical procedures. Because bleeding symptoms in VWD are generally mild, the diagnosis is often delayed [13].

Hemophilia A and B are X-linked recessive bleeding disorders caused by deficiencies in the activity of clotting factors VIII and IX, respectively. Hemophilia A occurs in approximately 1 in 5000 male births and is five to six times more common than hemophilia B. The severity of hemophilia depends on the level of circulating functional coagulation factor. Both hemophilia A and B occur in mild (factor level > 5% to 35% of normal), moderate (factor level 1% to 5% of normal) and severe (factor level < 1% of normal) forms. Patients with mild hemophilia usually bleed after trauma or major surgery, those with moderate hemophilia may bleed excessively after injury, while those with severe hemophilia experience frequent spontaneous bleedings or excessive bleedings after minor trauma. Although hemorrhage can occur at any site, joint bleeds predominate with ankles, knees and elbows being most frequently affected. Male newborns with hemophilia may present with prolonged bleeding at circumcision or blood draws to screen for other conditions. Easy bruising may occur at the start of primary dentition. Parents may first notice symptoms when a boy begins crawling or walking, and develops large bruises or swollen joints [14].

Other coagulation factor deficiencies are diagnosed very infrequently. Deficiencies of the following coagulation factors may result in clinical bleeding: II, V, VII, X, XI, XIII and fibrinogen. They are all autosomal dominant disorders, and homozygous forms may result in severe bleeding. The diagnosis requires specific factor assays.

Vitamin K deficiency: Vitamin K is a fat-soluble vitamin required for the hepatic synthesis of clotting factors II, VII, IX and X. Deficiency of vitamin K is probably the most frequent acquired bleeding condition in children. It is most commonly caused by liver disease, gastrointestinal disorders (malabsorption, chronic diarrhea) and drugs (antibiotics, oral anticoagulants). The bleeding may vary from minor bruising to severe hemorrhage. Newborns are prone to vitamin K deficiency due to both endogenous (insufficient intestinal colonization by bacteria) and exogenous (poor placental transport and low concentration in breast milk) factors. Vitamin K deficiency-related bleeding (VKDB), previously called "hemorrhagic disease of the newborn", is rare and potentially life-threatening disorder in early infancy. According to the age of onset, early VKDB presents within 24 hours of birth and is almost exclusively seen in infants of mothers taking drugs which inhibit vitamin K. Classical VKDB presents between 24 hours and 7 days of life and is associated with delayed or insufficient feeding. Late VKDB occurs between 2 weeks and 6 months of life, and is associated with exclusive breast-feeding [15].

Clinical and laboratory evaluation

The initial approach to a child with purpura requires skill and knowledge, and should be determined by the general condition of the child and the presenting vital signs. Ill-appearing or febrile child with purpura requires rapid evaluation and treatment for serious hemorrhage. Children with abnormal vital signs warrant urgent attention and resuscitation efforts. Well-appearing child with purpura should go through a detailed history, physical exam, and screening laboratory studies. Careful past medical history and complete family history should be sought. The site and type of bleeds, as well as any other associated symptoms or signs should be noted.

A full clinical assessment is followed by laboratory evaluation. Initial screening tests in a child with purpura should include a full blood count with a peripheral smear, prothrombin time (PT) with an international normalized ratio (INR), and activated partial prothrombin time (APTT). With few exceptions, these studies identify most hemostatic defects. A complete blood count helps to determine hematological causes of bleeding. A low hemoglobin level is indicative of blood loss, hemolysis or bone marrow failure syndromes. The presence of schistocytes points to microangiopathic diseases. Neutrophilia, increased number of band forms and toxic granules suggest systemic bacterial infection. Isolated thrombocytopenia is typically associated with immune thrombocytopenia, drug-induced thrombocytopenia and inherited disorders. A blood film allows morphological examination of platelets. Mean platelet volume may be helpful [1,16].

When interpreting coagulation results, it is important to be aware of physiological differences between hemostatic systems of children and adults, most pronounced in young infants. A prolonged PT indicates deficiencies involving coagulation factors II, V, VII, X or fibrinogen, vitamin K deficiency and liver disease. Currently, PTT is accompanied by INR, which compares it to the laboratory's baseline normal. A prolonged aPTT is found in deficiencies of coagulation factors II, V, VIII, IX, X, XI, XII or fibrinogen. In general the deficient factor has to be less than 40% of normal before PT or APTT is prolonged. Warfarin typically prolongs PT alone and heparin typically prolongs aPTT alone. Lupus anticoagulant more commonly causes isolated prolonged aPTT. If there is a prolongation of either PT or aPTT, the 1:1 mixing study should be done to differentiate between a coagulation factor deficiency and a circulating inhibitor. The patient's plasma is mixed with equal volume of normal plasma, and the test is repeated. If the mixing of normal plasma corrects abnormal PT or aPTT, a factor deficiency is suggested. Further investigation warrants the use of sensitive assays for specific coagulation factors. In addition, normal clotting assays do not exclude factor XIII deficiency, type 1 von Willebrand disease, mild factor XI deficiency and platelet function disorders [1,3].

Pseudothrombocytopenia is a laboratory artefact secondary to platelet clumping and has no clinical significance. The phenomenon is consistently observed in 1 in 1000 individuals. The most common cause of pseudothrombocytopenia is a naturally occurring ethylenediaminetetraacetic acid-dependent agglutinin, which causes platelet clumping that can be confirmed by a peripheral blood smear. Large platelet aggregates are frequently not included in the platelet window of automated cell analyzers, leading to falsely low platelet counts. Platelet counts in citrate- and heparin-anticoagulated blood are usually, but not always, normal. Pseudothrombocytopenia may also result from *in vitro* platelet adherence ("satellitism") to leukocytes, and improper blood sampling techniques or delayed mixing with anticoagulant in the test tubes. If unrecognized, pseudothrombocytopenia may trigger unnecessary further investigations and clinical concern [17].

Management

Management of a child with purpura should always be directed to the underlying cause. In general, children with bleeding tendencies should not participate in vigorous physical activities or contact sports. Intramuscular injections should not be given routinely. The use of aspirin and non-steroidal anti-inflammatory drugs (indomethacin, ibuprofen, naproxen) should be avoided. Majority of children remain under the care of a pediatric hematologist.

Conclusion

The numerous causes of purpura may be broadly grouped into vascular disorders, platelet defects, and coagulation factors deficiencies. The initial evaluation of a child with purpura should be dictated by the general appearance and the presenting vital signs. The site and the type of bleeding may help establish the diagnosis.

Conflict of Interest

I have no conflict of interest to declare.

Bibliography

1. Rafini L. "Evaluation of purpura in children". Fleisher GR, ed. Waltham, MA: UpToDate Inc. (2017).
2. Leung AK., *et al.* "Evaluating the child with purpura". *American Family Physician* 64.3 (2001): 419-428.
3. Khair K., *et al.* "Bruising and bleeding in infants and children – a practical approach". *British Journal of Haematology* 133 (2006): 221-231.
4. Nagala S., *et al.* "Recent advances in understanding and management of acquired thrombocytopenia". *F1000 Research* 7 (2018): 68.
5. Jafferany M., *et al.* "Psychogenic Purpura (Gardner-Diamond Syndrome)". *The Primary Care Companion for CNS Disorders* 17.1 (2015): 10.

6. Roganovic J. "Immune thrombocytopenia in children". *Rad Croatian Academy of Sciences and Arts: Medical Sciences* 524.42 (2015): 59-72.
7. Joly BS, et al. "Thrombotic thrombocytopenic purpura". *Blood* 129.21 (2017): 2836-2846.
8. Levi M., et al. "How I treat disseminated intravascular coagulation". *Blood* 131.8 (2018): 845-854.
9. Roganovic J, et al. "Neonatal Alloimmune Thrombocytopenia". *International Journal of Pediatric Health Care and Advancements* 2.1 (2015): 4-6.
10. Gauer RL, et al. "Thrombocytopenia". *American Family Physician* 85.6 (2012): 612-622.
11. Scheinberg P, et al. "How I treat acquired aplastic anemia". *Blood* 120.6 (2012):1185-1196.
12. D'Andrea G., et al. "Inherited platelet disorders: thrombocytopenias and thrombocytopathies". *Blood Transfusion* 7.4 (2009): 278-292.
13. Sharma R., et al. "Advances in the diagnosis and treatment of Von Willebrand disease". *Blood* 130.22 (2017): 2386-2391.
14. Hoots WK, et al. "Clinical manifestations and diagnosis of hemophilia". Leung LLK, ed. Waltham, MA: UpToDate Inc. (2017).
15. Lippi G., et al. "Vitamin K in neonates: facts and myths". *Blood Transfusion* 9.1 (2011): 4-9.
16. Anderson JAM., et al. "Investigating easy bruising in a child". *British Medical Journal* 341 (2010): 827-829.
17. Choccalingam C., et al. "Estimation of Platelet Counts and Other Hematological Parameters in Pseudothrombocytopenia Using Alternative Anticoagulant: Magnesium Sulfate". *Clinical Medicine Insights: Blood Disorders* 10 (2017): 1.6.

Volume 7 Issue 6 June 2018

©All rights reserved by Roganovic Jelena.