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Review Article

Approach to a Bleeding Child

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ABSTRACT

Bruising and bleeding are commonly seen in children. Reasonable differential diagnosis between bleeding disorders and non accidental injury is possible by careful history and examination. The lab tests can be screening tests and special tests. If the screening tests are normal, a thrombin time and platelet aggregation studies should be considered. In individuals with abnormal screening tests, further specific factor work-up should be undertaken for precise diagnosis. In a patient with an abnormal bleeding history and a positive family history, normal screening tests may need further laboratory evaluation. It is challenging for general pediatrician to interpret results of routine screening tests and make decisions to seek for specialist advice. An effort is made to approach a bleeding child by a practicing pediatrician with limited facilities for investigations and when to seek specialist advice.

Keywords: bruising, bleeding, children, investigation, non accidental injury.

INTRODUCTION

Hemostasis is an active process that clots the blood in areas of vessel injury and also limits clot size. Over the time clot is lysed and normal blood flow is restored. Hemostasis has 3 components - vascular component (vasoconstriction), platelet aggregation and clot formation. Vascular injury exposes sub endothelial matrix which will come in contact with blood. von Willebrand factor which come in contact changes its configuration and provide glue to platelets. Platelets aggregate and release ADP, serotonin and other proteins. Aggregation and recruitment of other platelets leads to the formation of platelet plug.

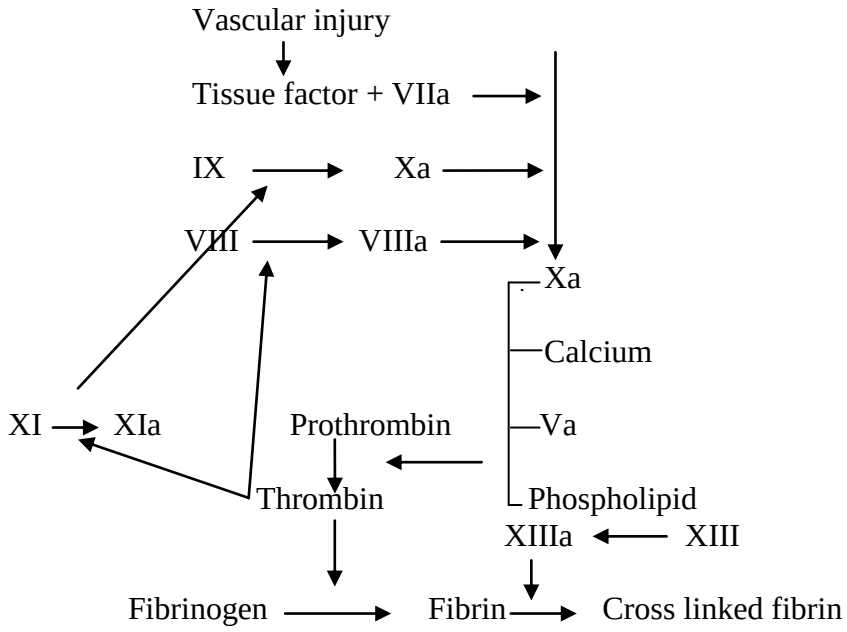
Tissue factor is released from sub endothelial matrix activates factor VII and starts coagulation cascade as shown on the fig in vivo. Factor VII releases small amount of VIIa by autocatalysis which will keep process going. Thrombin at the bottom of

cascade has multiple roles it activates V, VIII and XI, fibrinogen to fibrin. The stable fibrin-platelet plug is ultimately formed through clot retraction and cross linking of the fibrin clot by factor XIII.

Clot formation is regulated by antithrombin 3; protein C&S and TFPI (tissue factor pathway inhibitor). Antithrombin 3 regulates factor Xa and thrombin primarily and to a lesser extent factor IXa and XIa. Protein C&S inhibits Va and VIIIa. TFPI inhibits VIIa and tissue factor. [1]

Once clot is formed fibrinolytic system limits its extension and later lyses the clot. Plasmin formed from plasminogen by tissue plasminogen activator(TPA) lyses fibrin in to FDP. TPA is inhibited by plasminogen activator inhibitor(PAI). [1]

Figure 1 Blood coagulation in vivo



Bleeding and bruising is a common problem in childhood and a reasonable differential diagnosis is possible by careful history and examination.

Bruising due to accidental injury around one year is common when normally child attempts to walk [2] and falls but restricted to lower limbs and not associated with petechiae or purpura whereas bruising due to non accidental injury common over head face chest or upper arms.

Repeated bleeding from a single site is most often due to local pathology e.g. epistaxis or meckel's diverticulum. Bleeding in a child with a history of uncomplicated previous surgery or dental extraction suggest an acquired disorder than inherited disorder. Acquired disorder present later in life and family history bleeding may not be present.

History of bleeding in a well child with antecedent infection and purpuric rash commonly seen in Idiopathic thrombocytopenic purpura or rash associated with joint pains suggests Henoch Schonlein purpura (HSP). Petechie, purpura and mucosal bleeding with fever may be seen as part of serious illness like septicemia meningococcemia or viral hemorrhagic

fever. Purpuric rashes with icterus suggest liver failure, rash with diarrhea seen in Hemolytic uremic syndrome; Easy bruising can also be due vitamin C deficiency or with history of intake of drugs like analgesics, anticonvulsants or steroids.

Time of onset of bleeding: bleeding from umbilical cord or cephalhematoma without history of difficult labour or undue bleeding during fall of deciduous tooth or following a minor trauma or bleeding into joint or hematoma suggest a hereditary disorder. Family history important and it is important to know family pedigree including stillbirth, gender of affected member and details of bleeding. If only male are affected suggests XR disorder while both sex may be affected in AR or AD disorder.

Bruising in a neonate may be due to sepsis or vitamin k deficiency or a platelet disorder.

Site and type of bleeding: Petechiae and purpura –may be due to vasculitis or platelet disorder.

Petechie or purpura since birth suggests hereditary platelet disorder like TAR or BS syndrome. Mucous membrane bleeding- may be due to platelet disorder or von Wilebrand disease(vWD). History of menorrhagia in female patients suggests vWD. Bleeding into muscle or joint suggests coagulation factor deficiency. Easy bruising delayed wound healing with previous history of oozing from the umbilicus suggests factor 13 deficiency.

Easy bruising, scarring and delayed wound healing- seen in connective tissue diseases like Ehlers-danlo syndrome. Cigarette paper scar, hyper extensible joints suggest Ehler-Danlos syndrome.

Certain syndromes are known to be associated with bleeding disorders. Hereditary hemorrhagic telangiectasia is associated with characteristic telangiectatic lesions in the skin and mucus membrane may manifest with epistaxis, malena and bleeding per rectum. Presence of telangiectasia in the mucous membrane of nose, bulbar conjunctiva, tongue, lips and tips of fingers is the hallmark of diagnosis. Keloids may be seen in children with afibrinogenemia and factor XIII deficiency. Presence of syndactyly with history of bleeding episode is known to be due to factor V deficiency. Wiscott Aldrich syndrome is associated with thrombocytopenia, recurrent infection, otitis media, and eczema. Children with Albinism may have qualitative functional defects of platelets. Thrombocytopenia with absent radius (T.A.R.Syndrome) is easy to diagnose because of skeletal anomaly. Kasalbach-Merritt syndrome is characterized by giant hemangioma associated with evidence of clinical and sub clinical DIC and thrombocytopenia.

Is the bleeding due to vascular, platelet or a coagulation abnormality or a combination of these?

Though it is not always possible to categorically differentiate the nature of the bleeding, proper history and evaluation of presenting complaints, clinical findings provide valuable clue to decide the type of bleeding.

Bleeding manifestations in vascular disorder, thrombocytopenia or functional platelet disorders are usually in the form of spontaneous subcutaneous and mucus membrane bleeds like petechiae, purpura, ecchymoses, epistaxis, menorrhagia and these lesions are extremely rare in coagulation disorder except in Von Willebrand's disease. Purpuric spots appear and disappear in crops and may be associated with multiple superficial ecchymoses. Bleeding is usually precipitated by injury and it continues for hours (superficial bleeds). It is often controlled by pressure and once controlled, it usually does not recur.

However in patients with coagulation factor deficiency, hematomas are usually deep (in the muscles) and spreading, bleeding into cavities like joints, retroperitoneal space is known. Posttraumatic bleeds are often delayed, sometimes hours after the injury. This may recur and pressure may not control bleeding.

On examination petechie and purpura are seen in platelet disorders, purpura and mucus bleeds seen in vWD which may include recurrent epistaxis echymosis and menorrhagia in a teen age child. Child with hematoma, joint bleeding and extensive echymoses suggest coagulation disorder like hemophilia. Rashes, purpura and splenomegaly suggest infections, malignancy or collagen vascular disease. Eczema, recurrent otitis media and purpura suggest Wiskott Aldrich syndrome. Muco cutaneous bleeding can also be seen in Keselbach merit syndrome and hereditary telengiectasia. Purpura with absent radius suggest TAR syndrome.

Laboratory investigations:

Though history and examination suggest nature of bleeding disorder investigations are necessary to confirm the diagnosis. They can be divided into screening tests and special tests. [2] CBC and PS, Platelet count, PT, APTT are screening tests. If the results are normal, a thrombin time and platelet aggregation studies should be considered. In individuals with abnormal screening tests, further specific factor work-up should be undertaken for precise diagnosis. In a patient with an abnormal bleeding history and a positive family history, normal screening tests may need further laboratory evaluation. [3]

CBC and peripheral smear: CBC can identify degree of anemia and white cell count help to identify infection. PS also helps to identify aplasia or leukemia. Platelets in clumps rules out platelet deficiency whereas scanty platelets suggest thrombocytopenia. Absence of clumping suggests platelet function disorder. Large platelets simulating size of the lymphocytes suggest possibility of Bernard Soulier syndrome. Small platelets and thrombocytopenia suggest Wiskott Aldrich syndrome. Scanty and large platelets seen in ITP.

Platelet count:

It is simple step in evaluating bleeding. Thrombocytopenia is the commonest cause of bleeding in children. Platelet count above 50,000/mm^3 rarely has significant clinical bleeding. Bleeding with normal platelet count suggests a platelet functional disorder. Platelet count low in Infections, ITP, hypersplenism, drugs, malignancy, CHD, Fanconi anemia, TAR syndrome BS syndrome and WA syndrome

PT

The PT measures the extrinsic clotting system after the activation of clotting by tissue factor (thromboplastin) in the presence of calcium. Normal PT 10-13 seconds

PT measures extrinsic clotting system and the common pathway. PT is prolonged with deficiencies of plasma factor VII, X, V, II and fibrinogen and inhibitors of these factors. A prolongation of PT with normal PTT indicates factor VII deficiency that occurs with congenital deficiency or early during oral anticoagulant therapy, or Vit. K deficiency or liver diseases. The INR is used to determine similar degrees of anticoagulation with warfarin (Coumadin)-like medications.

APTT

APTT measures the initiation of clotting at the level of factor XII through sequential steps to the final clot end-point. The APTT employs a contact activator (silica, kaolin, or ellagic acid) in the presence of calcium and phospholipid. It does not measure factor VII, factor XIII, or anticoagulants. Normal APTT is around 25-40 seconds APTT is prolonged

during deficiency or abnormalities factor XI, IX, VIII, X, V, II and fibrinogen and by inhibitors of blood coagulation.

TT

The thrombin time measures the final step of the clotting cascade in which fibrinogen is converted to fibrin. The normal thrombin time varies between laboratories but is usually between 11-15 sec. Prolongation of the thrombin time occurs with reduced fibrinogen levels (hypofibrinogenemia or afibrinogenemia), with dysfunctional fibrinogen (dysfibrinogenemia), or by substances that interfere with fibrin polymerization, such as heparin or fibrin split products.

Table 1 Interpretation of coagulation screen tests and suggested further investigations.

PT	APTT	TT	Possible abnormality	Suggested investigation
↑	N	N	Factor VII def Vit k def Liver disease	Factor VII assay
N	↑	N	Factor VIII(hemophilia A or vWD)IX,XI deficiency, lupus anticoagulant or other inhibitors	Factor assays AVL and mixing studies
N	N	↑	hypo or dysfibrinogenemia	Reptilase time
↑	↑	N	def of factor II,V,X, liver disease, oral anticoagulants, massive transfusion.	Factor assays, INR
N	↑	↑	heparin	Reptilase time
↑	↑	↑	DIC, heparin overdose, afibrinogenemia	D dimmers, reptilase time
N	N	N	Consider diagnosis on table 2	

Bleeding disorders that may be present with normal platelet count and coagulation screen are Mild vWD, Mild deficiency of factors VIII,IX or XI, Factor XIII deficiency, Alfa 2 antiplasmin deficiency, PAI 1 deficiency, Glanzmann thrombasthenia, Platelet pool defect, Platelet release defect (gray Platelet syndrome), Collagen diseases and Vitamin C deficiency. [3]

Bleeding time: It is difficult to standardize bleeding time and values vary from lab to lab. Platelet counts less than 100,000/mm^3 are usually associated with prolonged bleeding times, disproportionate prolongation of the bleeding times may suggest a qualitative platelet defect or von Willebrand disease. Bleeding time also prolonged in HSP, CT diseases, scurvy, hereditary telangiectasia or drugs like aspirin or steroids. After the incision with the bleeding time device, blood is blotted from the margin of the incision at 30 sec intervals until bleeding ceases. Although each laboratory must establish its own normal range, bleeding usually stops within 4-8 min.

Reptilase time: Reptilase time uses a snake venom to clot fibrinogen. Unlike the thrombin time, the reptilase time is not sensitive to heparin and is prolonged by reduced or dysfunctional fibrinogen and fibrin split products.

Platelet function analyzer: Bleeding time is operator dependent and is difficult to perform in very young children. Although yet to be fully validated, new methods of in vitro bleeding time assay such as the PFA-100 may in time supersede these, and provide an easy method to exclude platelet function disorders. The PFA-100 instrument measures the time it takes flowing blood to block an aperture coated with collagen and adrenaline or ADP. Initial experience suggests that it is useful in detecting platelet function defects as well as most cases of von Willebrand's disease. [4]

Special studies

Platelet aggregation studies :

When a qualitative platelet function defect is suspected, platelet aggregation testing is usually ordered. Platelet-rich plasma from

the patient is activated with one of a series of agonists (ADP, epinephrine, collagen, thrombin or thrombin-receptor peptide, and ristocetin). Repeat testing or testing of other symptomatic family members can help determine the hereditary nature of the defect. Many medications, especially aspirin, other nonsteroidal anti-inflammatory drugs, and valproic acid alter platelet function testing. Some platelet aggregometers measure specific ADP release from the platelets, as reflected in generating luminescence (lumiaggregometer) and are more sensitive in detecting abnormalities of the platelet release reaction from storage granules. In Von Willebrand disease, aggregation to restocitin is lacking whereas aggregation to other agents may be normal. [5]

Correction studies:

In this, normal plasma is added to patient's plasma and APTT is carried out in this mixture. If the resulting APTT is normal (i.e., patients abnormal APTT is corrected) then deficiency state is present. If however mixture APTT remains prolonged, an inhibitor is present. Correction of abnormal APTT in mixing study in a patient with bleeding disorder indicates deficiency of Factor VIII, IX, XI and if not associated with clinical bleeding tendency, indicates deficiency of factor XII, Prekallikrein, high molecular weight kininogen. Mixing patient's plasma with known deficient plasma or artificially preparing deficient plasma can then confirm deficiency of particular factor. [5]

Adsorbed plasma is deficient in factor IX where as serum is deficient in factor VIII. If not corrected then it is due to factor that is deficient in this known deficient plasma / serum. Factor assay specific factor assay to know degree of deficiency.

Tests for fibrinolytic system:

The Euglobulin clot lysis time (ELT) is used to assess a reduction of fibrinolysis. More specific tests are available in most laboratories to determine the levels of plasminogen, plasminogen activator, and inhibitors of fibrinolysis. An increase in fibrinolysis may be associated with hemorrhagic symptoms, and a delay in fibrinolysis is associated with thrombosis.

SUMMARY

Whenever a child presents with bruising or bleeding needs to be differentiated from non accidental injury and to be evaluated further to find out the cause. We hope that this article will provide a systematic approach to a bruising or bleeding child by practicing pediatricians who have limited facilities for investigations and when to seek specialist advice for further management.

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