Hemostasis and Bleeding Disorders (Part 2)

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Bleeding Disorders

If the blood does not clot sufficiently, it may be due to bleeding disorders. Hemostasis disorders can develop for many different reasons.

Disorders of primary hemostasis

Failure of platelet plug formation in primary hemostasis:

1. Diseases affecting the vessel wall
2. Platelet disorders
3. Von Willebrand disease

1. Vessel wall abnormalities

Hereditary hemorrhagic telangiectasia is a dominantly inherited condition characterized by abnormalities of vascular modeling. Patients present with recurrent bleeds (particularly epistaxis) or with iron deficiency due to occult GI bleeding. Treatment includes iron therapy and local cautery or laser therapy to prevent lesions from bleeding.

2. Platelet disorders

These are caused by platelet deficiency, abnormal platelet function or abnormal platelet distribution.

Thrombocytopenia (low platelets)

Mainly caused by:

• Decreased platelet production; bone marrow diseases (aplastic anemia, chemotherapy, radiotherapy or metastatic diseases), viral infections (HIV, CMV, rubella) or drugs.

• Increased platelet destruction; immunological (idiopathic thrombocytopenic purpura ITP), splenomegaly or disseminated intravascular coagulopathy (DIC).

Clinical features of platelet deficiency include; easy bruising and easy bleeding, petechia, ecchymosis that can be seen on the oral mucosa and on the skin of the extremities in addition to postoperative hemorrhage but not usually until the platelet count *falls < 20 000 cells/mm^3*.

Management is by platelet infusion, which carries the risk of infection with blood-borne agents. Where there is immune destruction of platelets (e.g. in ITP), platelet infusions are less effective.

Indications for platelet transfusion include:

● A platelet count < 10 000 cells/mm^3.

● Troublesome bleeding, such as persistent epistaxis.

● Life-threatening bleeding, such as GI hemorrhage.

Transfusions provide only temporary relief because the survival of the platelets in the circulation is a few days at most.

Abnormal platelet function

In **thrombasthenia** (Glanzmann syndrome) there is defective platelet aggregation, it is an autosomal recessive condition. This condition is usually managed by local mechanical measures, but antifibrinolytic such as tranexamic acid may be useful and in severe bleeding, platelet transfusion may be required.

Drugs associated with platelet dysfunction are NSAIDs, aspirin and clopidogrel (Plavix). All these drugs (with the exception of the NSAIDs), irreversibly and permanently affect the entire lifespan of the platelets which is about 7–10 days (average 7 days). The effect of NSAIDs is temporary and lasts about 24-48 hours. The platelet count is not affected by any one of these drugs.

Idiopathic Thrombocytopenic Purpura (ITP):

The presence of autoantibodies directed against platelets results in platelet destruction. In adults, ITP more commonly affects females and may have an insidious onset.

Management: Adults are treated with oral prednisolone. Persistent or potentially life-threatening bleeding should be treated with platelet transfusion. Splenectomy should be considered in patients with relapsing disease.

3. Von Willebrand disease (vWD)

Also called pseudohemophilia. It is the most common inherited bleeding disorder and it is due to deficiency of von Willebrand factor (vWF) which mediates platelet aggregation, platelet adhesion to damaged endothelium and acts as a carrier for factor VIII. It has an autosomal dominant inheritance.

Management

- Mild hemorrhage: desmopressin or tranexamic acid.
- Severe bleeding: factor VIII concentrates.
  - Desmopressin stimulates the release of von Willebrand factor (vWF) from the endothelial cells (with subsequent increase in factor VIII, 3 to 5-fold)

Congenital bleeding disorders

Hemophilia A (Factor VIII deficiency):

Is inherited as an X-linked recessive disorder; Affects males only, females are carriers. It is as about 10 times as common as hemophilia B. Factor VIII has a half-life activity of 8-12 hours, normal plasma contains 1 unit of factor VIII/ml, a level defined as 100%. Hemophilia can be classified as:

Mild when factor VIII level is 5-30% of the normal

Moderate when factor VIII level is 1-5% of the normal

Severe when the factor VIII level is less than 1% of the normal

Clinical features and investigations: The diagnosis is normally made after the age of 6 months when babies become more mobile and first experience bruising. Although joints and muscles are the most common sites for hemorrhage, bleeding can occur at almost any site. Intracranial hemorrhage is often fatal.

Abnormal bleeding after extractions has sometimes led to the recognition of hemophilia. Dental extractions lead to prolonged bleeding. Laboratory findings are *all normal except* for the prolonged PTT and reduced levels of factor VIII.

Management: Bleeding episodes should be treated early with intravenous factor VIII concentrate. Factor VIII concentrates prepared by recombinant technology are more expensive but much safer than those derived from plasma (Before 1986, concentrates were not virally inactivated and many patients became infected with hepatitis B, hepatitis C and HIV).

In mild hemophilia, antifibrinolytic agents such as tranexamic acid may be adequate. This is often sufficient to treat a mild bleed or cover minor surgery such as dental extraction. In case of severe bleeding, factor VIII should be given.

Hemophilia B (Christmas disease):

This is caused by a deficiency of factor IX and is also an X-linked condition. The disorder is clinically indistinguishable from hemophilia A but is less common. Replacement therapy is with synthetic factor IX.

Hemophilia C (Factor XI deficiency):

Inherited as an autosomal dominant disorder. Factor XI deficiency results in rapid fibrinolysis. Fresh-frozen plasma or factor XI is required.

Acquired bleeding disorders

The main causes include:

Anticoagulant therapy

These are given as prophylaxis or treatment of thromboembolic events; they are used to treat atrial fibrillation, IHD, MI, DVT, CVA and pulmonary embolism. The common anticoagulant drugs are warfarin for long-term treatment and heparin for short-term treatment.

Warfarin

Is the most commonly used oral anticoagulant. It is a vitamin K antagonist (warfarin inhibits the vitamin K-dependent synthesis of clotting factors II, VII, IX and X, as well as protein C and protein S). Its effect begins after 8 hours and persists for 72 hours resulting in prolonged PT and INR.

Warfarin's effect may be enhanced by many drugs like NSAIDs, some antibacterial drugs like amoxicillin. Reversal of warfarin's effect by discontinuing its use, or by administering vitamin K.

Aspirin

Is the most commonly used antiplatelet agent. Inhibits platelet aggregation and inhibits synthesis of prostaglandin by cyclooxygenase (Bleeding time increased).

Heparin

It is a natural product, present in granules of the mast cells that line the vasculature and is released in response to injury. It is also used as a parenteral anticoagulant given subcutaneously or intravenously, for acute thromboembolic episodes and for hospitalization protocols that include significant surgical procedures (to prevent DVT and pulmonary emboli).

Heparin acts immediately on blood coagulation to block the conversion of fibrinogen to fibrin. *Protamine sulfate* is a drug that reverses the anticoagulant effects of heparin by binding to it.

The anticoagulant effect of heparin is usually lost within 6 hours of stopping it. The PT, PTT are prolonged. Most patients are monitored with the PTT. Heparin is available as standard (unfractionated heparin UFH) or as low molecular weight heparin (LMWH), the latter has less frequent dosing and more predictable properties.

Clopidogrel (Plavix)

One of the commonly used antiplatelet agents. The mechanism of action of these agents is to prevent platelet aggregation.

Vitamin K deficiency

Vitamin K is a fat-soluble vitamin that plays an essential role in hemostasis. It is present in the diet and also synthesized by the intestinal flora. It is absorbed in the small intestine and stored in the liver. The three major causes of vitamin K deficiency are poor dietary intake, intestinal malabsorption, and liver disease. Factors II, VII, IX, and X, protein C and protein S all decrease with vitamin K deficiency.

Disseminated intravascular coagulation (DIC):

The generation of intravascular fibrin clots leading to multi-organ failure, with simultaneous coagulation factor and platelet consumption causing bleeding. It can be initiated by a number of mechanisms such as infections, malignancy, drug toxicity and burns.

Investigations: ● Thrombocytopenia. ● Prolonged PT and PTT due to coagulation factor deficiency.

Management: Therapy should be aimed at treating the underlying condition causing DIC (e.g. IV antibiotics for septicemia). Blood products such as platelets and/or fresh frozen plasma should be given to correct identified abnormalities.

Acquired hemophilia

A rare disorder due to circulating antibodies to factor VIII, which typically are of unknown origin but may rarely form in autoimmune disorders such as rheumatoid arthritis. In contrast to congenital hemophilia, females are affected just as frequently as males.

Liver disease:

In severe liver disease, bleeding may arise from many different causes. These include reduced synthesis of coagulation factors or thrombocytopenia secondary to hypersplenism. Cholestatic jaundice reduces vitamin K absorption leads to a deficiency of factors II, VII, IX and X. This deficiency can be treated with parenteral vitamin K.

Renal disease:

Advanced renal failure is associated with platelet dysfunction and bleeding, especially GI bleeding.

Scurvy:

Vitamin C deficiency affects the normal synthesis of collagen and results in a bleeding disorder characterized by petechial hemorrhage, bruising and subperiosteal bleeding. The key to diagnosis is the dietary history.

The end

Terms:

CMV: Cytomegalovirus

HIV: Human Immunodeficiency Virus (AIDS)

NSAIDs: non-steroidal anti-inflammatory drugs

Idiopathic: referring to a disease with no obvious cause

CVA: cerebrovascular accident

MI: myocardial infarction

IHD: ischemic heart disease

DVT: deep vein thrombosis