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. Overactive clotting can also cause problems; thrombosis, where blood clots form abnormally, can potentially cause embolisms, where blood clots break off and subsequently become lodged in a vein or artery. 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 modelling. 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/mm³.

Management is by platelet infusion, which carry 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/mm³.
• 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 life span 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. Spontaneous bleeding occurs mainly with platelet counts < 20 000 cells/mm³. In adults, ITP more commonly affects females and may have an insidious onset. Unlike ITP in children, there is usually no history of a preceding viral infection. Patients aged > 65 years should have a bone marrow examination to exclude an accompanying B-cell malignancy. There is a greatly reduced platelet count and the bone marrow reveals increased megakaryocytes (platelets precursor).

**Management:** Most cases of childhood ITP are self-limiting and resolve within a few weeks. Indications for oral prednisolone include severe purpura, bruising or epistaxis, and a platelet count < 10 000 cells/mm³. Adults are also treated with prednisolone, although this is often less effective than in children. Intravenous IgG raises the platelet count and is indicated if the bleeding is immediately life-threatening. 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.
- Mucosal bleeding: 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 or hemarthrosis. Individuals with severe hemophilia experience recurrent hemarthrosis in large joints, which over time lead to secondary osteoarthritis. 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 recognition of hemophilia. Dental extractions lead to prolonged bleeding and, in the past, have been fatal. Laboratory findings are *all normal except* for the prolonged PPT 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 also widely available now and, although more expensive, are much safer than those derived from plasma. In mild hemophilia desmopressin and 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.

**Complications of therapy:**
*Before 1986, concentrates were not virally inactivated and many patients became infected with hepatitis B, hepatitis C and HIV.*

*Development of anti-factor VIII antibodies, which arise in ~20–30% of severe hemophiliacs. Such antibodies rapidly neutralize therapeutic infusions, making treatment relatively ineffective. Infusion of factor VIIa may stop bleeding.*

**Hemophilia B (Christmas disease):**
This is caused by 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, which is more stable than factor VIII with a half-life of 18-24 hours but often up to 2 days, so that replacement therapy can sometimes be given at longer intervals than in hemophilia A.

**Hemophilia C (Factor XI deficiency):**
Inherited as autosomal dominant disorder. Factor XI deficiency results in rapid fibrinolysis. Fresh-frozen plasma or factor XI is required.

**Ehlers–Danlos disease:**
Is a group of inherited connective tissue disorders characterized by production of abnormal collagen, the main structural component of the connective tissue.
The main clinical features are joint hypermobility, skin laxity and easy bruising. Vascular Ehlers–Danlos syndrome (type 4) is a rare autosomal dominant disorder caused by a defect in type III collagen which results in fragile blood vessels, and easy bleeding. The diagnosis should be considered when there is a history of bleeding but normal laboratory tests.

Acquired bleeding disorders

The main causes include; anticoagulant therapy and liver disease, vitamin K deficiency, disseminated intravascular coagulation, amyloidosis (deficiency of factor X) and autoimmune disorders (e.g. acquired hemophilia).

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 8-12 hours, is maximal at 36 hours and persists for 72 hours resulting in prolonged PT and INR.

Warfarin's effect may be enhanced by many drugs like aspirin, NSAIDs, tramadol, some antibacterial like amoxicillin, antivirals and antidepressants like selective serotonin reuptake inhibitors (SSRIs). 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 h of stopping it. The PT, PTT are prolonged. Most patients are monitored with the PTT and are maintained at 1.5–2.5 times the control value (the therapeutic range). 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. Factor VII and protein C have the shortest half-lives of these factors and therefore decrease first. Therefore, vitamin K deficiency manifests with prolongation of the prothrombin time first. With severe deficiency, the PTT will be prolonged as well.

**Disseminated intravascular coagulation (DIC):**

Can be initiated by a number of mechanisms. Examples include infections, malignancy, drug toxicity and burns. The generation of intravascular fibrin clots leading to multi-organ failure, with simultaneous coagulation factor and platelet consumption causing bleeding. This may be exacerbated by activation of the fibrinolytic system secondary to the deposition of fibrin.
Investigations: ● Thrombocytopenia. ● Prolonged PT and PTT due to coagulation factor deficiency. ● Low fibrinogen. ● Increased levels of D-dimer (a fibrin degradation product).

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, drug therapy (especially with penicillin), and in pregnancy. In contrast to congenital hemophilia, females are affected just as frequently as males. Specialist hematological attention is required before any operative treatment is considered.

Liver disease:
In severe parenchymal liver disease, bleeding may arise from many different causes. These include reduced synthesis of coagulation factors, DIC and thrombocytopenia secondary to hypersplenism. Cholestatic jaundice reduces vitamin K absorption and leads to 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.
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