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Hemophilia

- Hemophilia A (factor 8 deficiency) & hemophilia B (factor 9 deficiency) are the **most common severe** inherited bleeding disorders. The incidence is about **1/5000 males** with no racial predilection.

Types

1. Hemophilia A (classic hemophilia, factor 8 deficiency, 85% of the total, X-linked recessive).
2. Hemophilia B (Christmas disease, factor 9 deficiency, 10-15% , X-linked recessive).
3. Hemophilia C (usually mild, factor 11 deficiency, 2%, autosomal recessive).

- Reduced levels of contact factors (factor 12, high molecular weight kininogen & prekallikrein) are associated with significant prolongation of APTT(PTT) but are not associated with hemorrhage.
- About **30%** of cases are due to **new mutation**.

Pathophysiology

- Factor 8 & 9 participate in a complex required for the activation of factor 10. Together with phospholipids & calcium, they form the "tenase" or factor 10 activating complex. Prothrombin time (PT) measures the activation of factor 10 by factor 7 & is therefore normal in factor 8 or factor 9 deficiency.
- After injury, the initial hemostatic event is formation of the platelet plug, together with the generation of fibrin clot, which prevent further hemorrhage. In hemophilia A & B, clot formation is delayed & is not robust. Inadequate thrombin generation leads to failure to form a tightly-cross linked fibrin clot to support the platelet plug leading to bleeding.

Clinical presentations

- Hemophilia A & B result in clinically indistinguishable bleeding disorders of variable severity according to the levels of factor 8 (F8) or factor 9 (F9) in the plasma.
- The severity of hemophilia is classified into 3 grades :

1. Mild: The concentration of the factor in the plasma >5U/dl (>5%), requires significant trauma for bleeding to occurs (dental work, surgery), the diagnosis may be delayed
2. Moderate: 1-5 U/dl (1-5%), requires mild trauma for bleeding to occurs.
3. Severe : < 1U/dl (<1%), spontaneous bleeding.

- **The hemostatic level** for F8 is >30-40% & that for F9 is >25-30%.
- **The normal level** is 100 % while the lower normal limit is 50%.
- Neither F8 nor F9 crosses the placenta, bleeding may present at birth or may occur in the fetus. Only 2% of neonates with hemophilia sustain intracranial hemorrhage & 30% of male infants with hemophilia bleed with circumcision. Obvious symptoms as easy bruising, intramuscular hematoma, & hemarthrosis begin when the child begins to cruise.
- Bleeding from minor traumatic laceration of the mouth (a torn frenulum) may persist for hours or days & may cause the parents to seek medical evaluation.

Although bleeding may occur at any area of the body, the hallmark of hemophilia is " **hemarthrosis"** i.e. bleeding into the joints. The earliest joint hemorrhages appear most

commonly in the ankle. In the older child & adolescent, hemarthroses of the knees & elbows are also common. Whereas the child's early joint hemorrhages are recognized only after major swelling & fluid accumulation in the joint space, older children are frequently able to recognize bleeding before the physician does. They complain of warm, tingling sensation in the joint as a first sign of an early joint hemorrhage. Repeated bleeding episodes into the same joint in a patient with severe hemophilia may lead to a **" target"** joint with recurrent spontaneous bleeding due to the underlying pathologic changes in the joint.

- Although most muscular hemorrhages are clinically evident by localized pain or swelling, bleeding into the **iliopsoas** muscle may be serious because patient may lose large volumes of blood into the muscle with hypovolemic shock with only a vaguee area of referred pain in the groin with flexion & internal rotation of the hip joint. The diagnosis is confirmed by U/S or CT.
- Other types of bleeding can be easy bruising, subcutaneous hematoma, mouth bleeds, & intramuscular hematoma.
- **life-threatening hemorrhage** as in bleeding into vital structures (CNS, upper airway) or by exsanguinations (external trauma, GIT or iliopsoas hemorrhages). If head trauma needs radiologic evaluation, factor replacement should precede that.
- Some female carriers may have mild bleeding (**lyonization** of X-chromosome), so level of factors should be done in all known or potential carrier to assess treatment in cases of surgery & clinical bleeding.

Differential Diagnosis

- In young infants with severe bleeding manifestations, the differential diagnosis includes: severe thrombocytopenia, severe platelet function disorders (as Bernard-Soulier syndrome & Glanzmann thromasthenia), type 3 (severe) von Willebrand disease & vitamin K deficiency.

Diagnosis

- **Prolonged PTT** (partial thromboblastin time). In sever hemophilia, the PTT value is usually 2-3 times the upper limit of the normal.
- **↓ F8 or F9** levels in the plasma.
- Normal platelet count, bleeding time, prothrombin time (PT) & thrombin time (TT)
- Unless the patient has inhibitors to F8 or F9, the **mixing** of normal plasma with patient's plasma results in correction of prolonged PTT.
- The mutation can be detected in the blood of patients or carriers & in the amniotic fluid by **molecular teqnique.**
- In the newborn, F8 may be artificially elevated due to birth process, while F9 is low.

Treatment

- Early appropriate therapy is the hallmark of excellent hemophilia care. When mild to moderate bleeding occurs, values of F8 or F9 must be raised to hemostatic levels (35-50%), while in life-threatening or major hemorrhage, the aim is 100% levels.
- Calculation of the dose: F8 = % Desired x body weight(Kg) x 0.5 (for F9: x 1.3)

1. Replacement therapy by F8 concentrate (250 or 500 IU/20 ml)

- **Hemarthrosis:** 50-60 IU/kg on day 1, then 20 IU/kg the following day. Consider every other day until joint function is normal or back to baseline. Consider prophylaxis.

Muscle or significant subcutaneous hematoma: 50 IU/kg; 20 IU/kg every other day may be needed until resolved.

- Mouth, deciduous tooth, or tooth extraction: 20 IU/kg; antifibrinolytic therapy; remove loose deciduous tooth.

- Epistaxis: apply pressure for 15-20 min, pack with petrolatum guaze; give antifibrinolytic therapy; 20 IU/kg if this treatment fails.
- Major surgery & life- threatening hemorrhage: 50-75 IU/kg; then initiate 25 IU/Kg q8-12 hr to maintain trough level >50% for 5-7 days; then 50 IU/Kg/day to maintain trough level >25% for 7 days: monitor F8 level.
- Iliopsoas hemorrhage: 50 IU/kg; then 25 IU/kg q12 hr until asymptomatic; then 20 IU/kg every other day for a total of 10-14 days with radiologic assessment.
- Hematuria: bed rest; 1.5 maintenance fluids; if not controlled in 1-2 days, 20 IU/kg; if not controlled, prednisolone (unless patient HIV infected).
2. Drug therapy: as **desmopressin** as intranasal spray (150 µg (1 spray) in <50 Kg & 300 µg (2 sprays) in >50 Kg) (useful in mild hemophilia A, not effective for hemophilia B).
- Mucosal bleeding may require adjunct use of **antifibrinolytics** (as aminocaproic acid or transexamic acid).
- Emicizumab is a monoclonal antibody can be used in treatment of hemophilia A with or without inhibitors as once-weekly prophylactic sc injection. F9 gene therapy is under study.
3. Local hemostatic measures:
- Application of a cold sponge & a pressure on the bleeding site.
- Hemarthrosis: immobilization of the affected joint for 2 days followed by gradual passive exercises. In severely painful joint with very tense overlying skin, aspiration of the blood after adequate F8 therapy will provide some relief.
4. Prophylaxis: for severe hemophilia, usually initiated with 1st or 2nd joint hemorrhage, effective & expensive, usually given every 2-3 days to maintain a trough level of 1-2% (20-40 IU/Kg F8 or 30-50 IU/Kg F9) . New long acting F9 may be given every 1-2 weeks.
5. Supportive care: avoid trauma as possible, anticipatory guidance (car seats, seatbelts, bike helmet, early psychological intervention, avoid aspirin & other NSAID, HBV vaccination, periodic screening for HBV, HCV, HIV, & LFT for patients exposed to plasma-derived products.
6. Comprehensive care: hemophilia care centers, family education, multidisciplinary team (physicians, nurses, orthopedists, physical therapists & psychosocial workers).
- The treatment of hemophilia B is F9 concentrate (30-50% higher doses than that for hemophilia A) & of hemophilia C is fresh frozen plasma.

Complications

1. Chronic arthropathy.
2. Inhibitors to F8 or F9: usually discovered with failure of the response to appropriate therapy or with routine follow-up screening, (25-35% in hemophilia A & 2-3% hemophilia B), treatment by desensitization programs (high doses of F8 or F9 to induce immune tolerance), alternate therapy as rituximab, emicizumab, steroids & other immunosuppressives (if this fails, recombinant activated factor 7 or activated prothrombin complex concentrate (may bypass the inhibitors but may increase the risk of thrombosis).
3. Infections as hepatitis B &C, AIDS & Creutzfeld-Jakob disease (↓ by the use of the recombinant F8 or F9.

Von Willebrand Disease (VWD)

- It is the **most common** hereditary bleeding disorder with an estimated prevalence from **1:100 to 1:10000 (males=females).** Patients typically present with mucosal bleeding
- VWF serves to bind platelets to injured sub-endothelium via binding sites for platelets & collagen for clot formation & serves as carrier protein for F8 protecting it from degradation in plasma.
- VWF is stored in endothelial cells & in platelets & circulates as large glycoprotein.

Clinical presentations

- VWD typically presents with **mucosal bleeding**, similar to other platelet defects. Epistaxis, easy bruising, menorrhagia, & surgical bleeding (particularly with dental extraction or adenotonsillectomy) are common. Symptoms are variable & do not necessarily correct well with VWF level. Severe type3 VWD may present with joint bleeds. Most patients have family history of bleeding.
- VWD may be caused by quantitative defects (mild-moderate: type 1 VWD, sever: type 3 VWD) or qualitative defects (type 2 VWD).

Types

- Type 1 VWD: most common type (60- 80%), caused by the quantitative defect in VWF, inherited as autosomal dominant inheritance. VWF level (VWF:Ag): <30 IU/dL proves the diagnosis, while level between 30-50 IU/dL is called (low VWF) with debate about regarding it as VWD (may bleed especially with surgery). 1C VWD is a subtype that is not responsive to desmopressin & need VWF- containing product. VWF increases with stress, exercise, pregnancy & blood group O (single normal VWF level does not exclude VWD). Some diseases as hypothyroidism & drugs as valproic acid can lower VWF in affected patients.

- Type 3 VWD: most sever type, symptoms as mild hemophilia (may be joint bleeds or CNS hemorrhage), VWF protein is completely absent, frequency: 1/million, VWF: <10 IU/dL (some gives prophylaxis). It is caused by the absence of VWF & treated with VWF-containing concentrates. It is inherited as autosomal recessive inheritance.

- Type 2 VWD (several varriants): rare , more severe than type 1, caused by qualitative defect of VWF, inherited as autosomal recessive inheritance.

- Type **2A** VWD: most common (10% of VWD cases), treated by desmopressin (mild) & VWF-containing concentrates (severe).
- Type **2B** VWD: thrombocytopenia may be present especially with stress (as surgery & pregnancy), desmopressin is relatively contraindicated.
- **Plate-type pseudo- VWD:** thrombobocytopenia (as type 2B VWD), treated generally by platelet transfusion.
- Type **2M** VWD: treated usually by VWF-containing concentrates but some minor bleeding may respond to desmopressin.
- Type **2N** VWD: some cases may misdiagnosed as mild hemophilia (high index of suspicion is required in patient with low F8 deficiency & absent family history.

Laboratory findings

- There is no reliable screening test for VWD.

- Platelet function analysis has been considered as a screening test for VWD but with suboptimal sensitivity & specificity. Also bleeding time is unreliable in diagnosis of VWD.

- There may be anemia (significant bleeding) or thrombocytopenia (type 2B VWD or plate-type pseudo- VWD).
- PTT may be prolonged (if F8 is low), but it is often normal (especially in type 1 VWD).
- No single test can diagnose VWD, so a panel of tests is usually required (VWF:Ag (quantity), VWF activity test (typically using ristocetin cofactor activity assay (VWF:RCo), F8 activity test, VWF:GPIbM test (measure VWF binding to platelet without ristocetin but it is not universally available), collagen binding test, multimer distribution test, & special tests for type 1C, 2B, & 2N VWD).
- Genetic diagnosis is not typically performed because of the large size of VWF gene & large number of benign sequence variations, however, it is increasing particularly for types 2A, 2B, 2M & 2N VWD.

Treatment

- Treatment depends on the type of VWD & the reason for treatment.
- **Desmopressin:** for most type 1 VWD & some type 2 VWD.
- **VWF-containing concentrates:** for type 2 VWD & type 3 VWD.
- **Careful monitoring of VWF & F8 levels** is recommended to tailor treatment for surgeries& major trauma.
- **Adjunct therapy:** for all types of VWD when possible, as antifibrinolytics for oral surgery, hormonal therapy for menorrhagia, local treatment of epistaxis (as nasal cautery or packing), & iron therapy for IDA.

Idiopathic (Autoimmune) Thrombocytopenia Purpura (ITP)

- The **most common** cause of acute onset of thrombocytopenia in an otherwise well child. The normal platelet count is 150–450 × 10^9/L. *Thrombocytopenia*; platelet count <150 × 10^9/L.

Etiology & Pathogenesis

- In about **1/20000** of children, 1-4 weeks after exposure to a common viral infection, an autoantibody directed against the platelet surface develops (for unknown reasons) with resultant sudden onset of thrombocytopenia.
- **A recent history of viral illness** is described in 50-65% of cases. Most common viruses have been described in association with ITP, including Epstein-Barr virus (ITP is usually of short duration & follows infectious mononucleosis) & HIV virus (ITP is usually chronic). In some patients, ITP appears to arise in children infected with *Helicobacter pylori* or rarely following the measles, mumps, rubella vaccine.
- The peak age is **1-4 yr**, although the age ranges from early in infancy to the elderly. Males and females are equally affected. It occurs more often in late winter and spring after the peak season of viral respiratory illness.
- After binding of the antibody to the platelet surface, circulating antibody-coated platelets are recognized by the Fc receptors on the splenic macrophage, this leads to ingestion & destruction of platelets.

Clinical manifestations

- The classic presentation of ITP is that of a previously healthy 1-4 yrs old child who has sudden onset of generalized petechiae & purpura.
- There may be bleeding from the gums & mucus membranes, particularly with profound thrombocytopenia (platelets count < $10x10^9$ /L).
- Findings on physical examination are normal, other than petechiae and purpura. Splenomegaly, lymphadenopathy, bone pain, and pallor are rare.
- A simple classification system has been proposed from the U.K. to characterize the severity of bleeding in ITP on the basis of symptoms and signs, but not platelet count:

1. No symptoms.

2. Mild symptoms: bruising and petechiae, occasional minor epistaxis, very little interference with daily living.

3. Moderate: more severe skin and mucosal lesions, more troublesome epistaxis and menorrhagia.

4. Severe: bleeding episodes—menorrhagia, epistaxis, melena—requiring transfusion or hospitalization, symptoms interfering seriously with the quality of life.

- The presence of abnormal findings as hepatosplenomegaly, bone or joint pain, remarkable lymphadenopathy, other cytopenia or congenital anomalies suggest other diagnosis (leukemia, syndromes).
- When the onset is insidious especially in adolescents, chronic ITP, or a possibility of systemic illnesses SLE is more likely.
- **Severe bleeding is rare (<3%** of cases in 1 large international study).
- About 70-80% of cases of acute ITP will have spontaneous resolution within 6 months from the onset.
- Therapy does not appear to affect the natural history of ITP.
- <1% of patients will develop intracranial hemorrhage (ICH). Those who favor interventional therapy argue that the objective of early therapy is to raise the platelet count to >20 x 10^9/L and prevent the rare development of intracranial hemorrhage. There is no evidence that therapy prevents serious bleeding.
- Approximately 20% of children who present with acute ITP go on to have chronic ITP. The outcome/prognosis may be related more to age, as ITP in younger children is more likely to resolve whereas the development of chronic ITP in adolescents approaches 50%.

Laboratory findings

- Severe thrombocytopenia (platelets count <$20x10^9$/L) is common & platelet size is normal or ↑ reflecting ↑ platelet turnover.
- In acute ITP, Hb, WBC count & differential should be normal (Hb may be ↓ with profuse epistaxis & menorrhagia).
- Bone marrow examination reveals normal granulocytic & erythrocytic series & characteristic normal or ↑ megakariocytes. Some of the megakaryocytes may appear to be immature and are reflective of increased platelet turnover.
- **Indications for bone marrow aspiration/biopsy** are abnormal WBC count or differential, unexplained anemia & history and physical examination findings suggestive of a bone marrow failure syndrome or malignancy.

- Other investigations according to the history & physical examination: Antinuclear antibody (ANA) for adolescent females to evaluate SLE. HIV studies should be done in at-risk

populations, especially sexually active teens. Direct Coomb's test for unexplained anemia to rule out Evan's syndrome (acute hemolytic anemia & thrombocytopenia which may be idiopathic or an early sign of SLE, autoimmune lymphoproliferative syndrome or common variable immunodeficiency syndrome. Platelet antibody testing is seldom useful in acute ITP.

Differential diagnosis

- Exposure to medications, splenic sequestration due to previous portal hypertension & rarely early aplastic process (as fanconi anemia) , TAR & MYH9 related thrombocytopenia.
- Other disorder which usually presents with other abnormal clinical or CBC findings: amegakaryocytic thrombocytopenia, HUS, DIC, SLE. HIV, common variable immunodeficiency, lymphoma, autoimmune lymphoproliferative disease & Wiskot-Aldrich syndrome.

Treatment

- A number of treatment options exist, but there are no data showing that treatment affects either short- or long-term clinical outcome of ITP. Treatment appears to be capable of inducing more rapid rise in platelet count to the theoretically safe level of >20 x 10^9/L, although no data indicate that early therapy prevent ICH.

1. No therapy other than education and counseling: of the family and patient with minimal or mild symptoms (no mucosal bleeding which predicts severe bleeding).This approach emphasizes the usually benign nature of ITP, is far less costly, and side effects are minimal.

2. IVIG or corticosteroids: particularly for mucocutaneous bleeding. A single dose of IVIG 0.8-1 g/kg/day or a short course of corticosteroids should be used as first-line treatment. IVIG at a dose of 0.8-1 g/kg for 1`-2 days induces a rapid rise in platelet count (usually >20 x 10^9/L) in 95% of patients within 48 hr. IVIG appears to induce a response by down-regulating Fc-mediated phagocytosis of antibody-coated platelets. It is expensive, time consuming & with high frequency of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis.

- Corticosteroid therapy: has been used for many years to treat acute and chronic ITP in adults and children. Prednisone of 1-4 mg/kg/24 hr appear to induce a more rapid rise in platelet count than in untreated patients, usually for short course until a rise in platelet count to >20x10^9/L to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis.
- Each of these medications may be used to treat ITP exacerbation, which usually occur several weeks after the initial course of therapy.
- I n the special case of ICH, multiple modalities should be used including platelet transfusion, IVIG, high dose corticosteroids & prompt consultation by neurosurgery & surgery.
- **Splenectomy** is done for 1. ≥ 4 yrs old patients with severe ITP that has lasted >1 yr (chronic ITP) and whose symptoms are not easily controlled with therapy & 2. life-threatening hemorrhage (as ICH) & not corrected by platelets transfusion, IVIG or steroids. Splenectomy is associated with a lifelong risk of overwhelming postsplenectomy infection caused by encapsulated organisms, increased risk of thrombosis and the potential development of pulmonary hypertension in adulthood.
- **Ritoximab:** as an alternative to splenectomy as (of label) use, 30-40% partial or complete remission.
- **Thrombopoiten receptor agonists:** to increase platelet count & approved for pediatric use.

- Platelet transfusion: usually contraindicated unless with life- threatening hemorrhage.

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