



Acquired Factor VIII inhibitor

Morning Report 2/4/09

Acquired Factor VIII inhibitor

- Often categorized as hemophilic or nonhemophilic associated inhibitors – different responses to different treatments
 - Hemophilic: allo-antibodies against recombinant F VIII
 - Non-hemophilic: auto-antibodies against own F VIII
- FVIII inhibitors are the most common autoantibodies that affect clotting and lead to a bleeding diathesis

Acquired inhibitors

- Acquired inhibitors are antibodies that either inhibit the activity or increase the clearance of a clotting factor.
- Some disorders may be associated with antibodies to several factors (ie in SLE, APLA against FVIII, IX, XI, XII, and XIII)

Epidemiology

This is in the nonHemophilic patient:

- approx 1.3 in 1,000,000 people
- Presenting mortality up to 40%
- Spontaneous hemarthroses uncommon with acquired disease
- Usually >50, mean age was 70, 68% were men. If female usually were postpartum

Epi continued.....

- Associated with:
 1. Rheumatologic Dz
 2. Malignancy
 3. Pregnancy
 4. Drug reaction
- Relation to malignancy:
 - One case series commented on ~50 cases
 - Over 1/2 of cases assoc with solid tumor (2/3 of these were adenoCA - lung/prostate most common)
 - Most common heme malignancy was CLL

Presenting signs/symptoms

- Patients present with extensive bleeding, (large intramuscular, retroperitoneal, limb, subcutaneous, GU, GI, or excessive postoperative or postpartum bleeding) often life threatening, before it is recognized.
- Bleeding often life threatening, before it is recognized.
- Postpartum inhibitors usually come to attention several months after delivery (2-5 mo), when bleeding symptoms supervene; rarely, the inhibitor may develop during pregnancy.

Diagnosis

- Sudden presence of large hematomas or extensive ecchymoses in an elderly individual without significant trauma or known bleeding disorder should always raise the clinical suspicion of an acquired factor VIII inhibitor.

Diagnosis

- In addition to the clinical features, factor VIII inhibitors are characterized by a **prolonged activated partial thromboplastin time (aPTT)** and a normal prothrombin time (PT).
- A prolonged aPTT is also seen in the antiphospholipid antibody syndrome, but these patients present with **thrombosis** rather than bleeding episodes

Normal PT with **prolonged aPTT**

- **Acquired:**
 - Inhibitors to coag factors VIII, IX, XI, XII
 - Heparin
 - Acquired vWD
 - Lupus anticoagulant
- **Inherited:**
 - Factor deficiency VIII, IX, XI
 - vWD (if concomitant FVIII deficiency)
 - Deficiencies in FXII, prekallikrein, HMW Kininogen – not assoc with diathesis

Mixing Study: Deficiency vs Inhibitor

- **Inhibitor Screen:**
 - If a prolongation present in PT or aPTT, can check a mixing study
 - mix patient plasma and that from a normal patient, then immediately recheck the PT or aPTT and then check again at 2 hours after incubation at 37 C
 - recheck at 2 hours because some inhibitors have slow reaction kinetics (ie FVIII are notorious for this)
- Correction of prolonged aPTT suggests a factor deficiency or VWD
- Persistent prolongation of the aPTT indicates the presence of an inhibitor.

Mixing study continued.....

- The next step is adding a source of phospholipid to the mixed plasma. Correction of the aPTT suggests the presence of antiphospholipid antibodies.

Mixing study continued.....

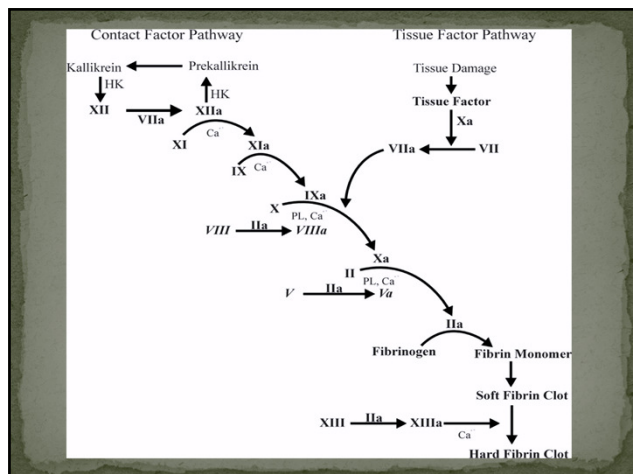
- If aPTT mix doesn't correct with phospholipid addition, check **Bethesda titer** for confirmation of diagnosis (FVIII inhibitor) as well as to quantify titer to evaluate efficacy of treatment

Bethesda Titer

- Bethesda titer - serial dilutions of plasma from patient and from normal pool - then check for FVIII activity
- Reciprocal dilution of patient plasma that results in 50% FVIII activity is defined as one Bethesda unit (BU)
- Stronger the inhibitor, greater the dilution required to allow for factor VIII activity

Treatment

- Control of bleeding:
 - If Bethesda titer <5, may use FVIII at high doses
 - If high titer: Recombinant human factor VIIa (Novo7)
 - Prothrombin complex concentrates
 - DDAVP
 - Others - plasmapheresis, immunoadsorption
- Immunosuppression:
 - Prednisone 1mg/kg/day
 - cyclophosphamide
 - Rituxan
 - IVIG



Natural History

- Factors positively associated with improved overall survival :
 - attainment of complete remission
 - age <65
 - post-partum status
- Although immunosuppression hastens time to complete remission, up to 36% of cases report spontaneous recovery (mean time 14 months)

References

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