Challenging Hemostasis Scenarios in Pediatric Patients - A Case Study-Based Discussion

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Objectives

• After attending this educational session, participants will be able to:
  • Describe common clinical and laboratory features of factor XI deficiency
  • Identify laboratory tests that are useful in the evaluation of lupus anticoagulant-hypoprothrombinemia syndrome (LA-HPS)
  • Discuss clinical features of and treatment strategies for LA-HPS
Case 1

• 8 year old Caucasian girl referred to pediatric hematologist for evaluation of abnormal bruising and prolonged APTT

• Complex past medical history
  • Selective antibody deficiency
  • Synringomyelia
  • Joint hypermobility syndrome
  • Asthma
Case 1

- Evaluated for joint pain 2 years prior to pediatric hematology evaluation

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Patient Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>13.4</td>
<td>12-15.5</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>61</td>
<td>32-48</td>
</tr>
<tr>
<td>APTT 1:1 mixing study (immediate)</td>
<td>40</td>
<td>32-48</td>
</tr>
<tr>
<td>DRVVT (s)</td>
<td>32</td>
<td>33-44</td>
</tr>
<tr>
<td>Thrombin time (s)</td>
<td>16.8</td>
<td>14.7-19.5</td>
</tr>
</tbody>
</table>

- PT and APTT repeated by primary pediatrician, APTT remained prolonged by report
Case 1

• Additional clinical history
  • Has “always bruised easily”, worsening over past 9 months
    • Spontaneous ecchymoses on legs (non-palpable)
    • No epistaxis
    • Gums bleed easily (subjectively)
  • Adenoidectomy and eye surgery without excessive perioperative bleeding
  • Naproxen twice daily for joint pain
## Case 1

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Patient Result- Heme Eval 1 (reference interval)</th>
<th>Patient Result- Heme Eval 2 (reference interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>10.5 (9-13.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>33 (23-34)</td>
<td>44.9 (23-36)</td>
</tr>
<tr>
<td>Factor VIII activity (%)</td>
<td>82 (50-150)</td>
<td>165 (76-199)</td>
</tr>
<tr>
<td>vWF antigen (%)</td>
<td>132 (50-150)</td>
<td>143 (62-180)</td>
</tr>
<tr>
<td>vWF ristocetin cofactor activity (%)</td>
<td>187 (50-150)</td>
<td>113 (52-176)</td>
</tr>
<tr>
<td>vWF collagen binding activity (%)</td>
<td>154 (50-150)</td>
<td>N/A</td>
</tr>
<tr>
<td>vWF multimers</td>
<td>Normal distribution (normal distribution)</td>
<td>N/A</td>
</tr>
<tr>
<td>Factor IX activity (%)</td>
<td>75 (60-150)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Factor XI activity (%)</strong></td>
<td>N/A</td>
<td>33 (70-138)</td>
</tr>
<tr>
<td>Factor XII activity (%)</td>
<td>N/A</td>
<td>127 (58-166)</td>
</tr>
</tbody>
</table>
Case 1

- Repeat evaluation of factor XI activity on a new plasma sample 2 weeks later
  - 32%
Case 1

• Learning Points of Interest for Laboratorians
  • Developmental Hemostasis
  • Variability of APTT reagents
  • Spectrum of factor XI deficiency phenotypes
Developmental Hemostasis

• (or, the hemostasis version of “Children are not little adults!”)

• Levels of various hemostatic proteins may vary with age
  • Based largely on the work of Andrew et al
  • Additional investigators continue to publish studies using current instrument-reagent combinations

• Age-appropriate reference intervals essential when evaluating pediatric bleeding disorders
APTT prolongation in pediatric patients

• May not always predict an underlying bleeding disorder
  • In one study of 90 patients, 48% had no identifiable underlying explanation\(^1\)
  • Clinically significant bleeding disorder unlikely in absence of bleeding symptoms and family history\(^1\)
• APTT prolongations in children as compared with adults may relate to a combination of mildly decreased factor activities\(^2\)

APTT reagent variability

- Different APTT instrument-reagent combinations may exhibit differing factor sensitivities
  - Preferable to have an APTT reagent that begins to show prolongation with factor activity of 30-40%
  - Although not a CLIA-required study, factor sensitivity studies are recommended as good laboratory practice
    - See CLSI H47-A2

Factor XI Deficiency

• Most common of the rare coagulation disorders
  • Initially described in a Jewish family
• Most often identified during evaluation for
  • Bleeding diathesis
  • Unexplained APTT prolongation
    • APTT may be normal in some cases, however
• Laboratory Diagnosis- FXI activity

Factor XI Deficiency

- Variable bleeding phenotype
  - Even heterozygous deficient patients may have bleeding, particularly perioperative and postpartum
  - May be influenced by other concomitant factors
    - Decreased von Willebrand factor
    - Platelet function defects
  - Factor XI activity not clearly predictive of bleeding risk

Potential New Antithrombotic Therapy Involving Factor XI!
Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D.,
David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D.,
Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D.,
for the FXI-ASO TKA Investigators*

Factor XI-Antisense Oligonucleotide (FXI-ASO)

• 2\textsuperscript{nd} generation anti-sense oligonucleotide that binds to factor XI (FXI) messenger RNA (mRNA) in hepatocytes
  • Leads to degradation of FXI mRNA by ribonuclease H-1
• Functional Consequences
  • Decreased FXI protein synthesis
  • Lower plasma FXI activity

Effect of FXI-ASO on the Coagulation System (Figure 1)

FXI-ASO

• Phase 2 study
  • 300 patients enrolled
  • Evaluated safety and efficacy of FXI-ASO in DVT prevention in adult patients post total knee arthroplasty

• Three treatment regimens compared
  • FXI-ASO 200 mg daily
  • FXI-ASO 300 mg daily
  • Enoxaparin 40 mg daily

• Thrombosis evaluation by venography 8-12 days post-operatively

FXI-ASO

• No significant difference in incidence of thrombosis between enoxaparin (30%) and FXI-ASO 200 mg (27%) (p = 0.59)

• Fewer instances of thrombosis with FXI-ASO 300 mg (4%) than enoxaparin (30%) (p<0.001)

FXI-ASO

• No significant difference in incidence of major or clinically relevant bleeding complications between
  
  • FXI-ASO 200 mg (3%) (p = 0.09)
  • FXI-ASO 300 mg (3%) (p = 0.16)

  and enoxaparin (8%)

FXI-ASO- Future Directions

• Further study needed to confirm
  • Similar findings with other surgical procedures
    • Relatively low risk of bleeding post-knee arthroplasty
    • Is there a higher risk in tissues with higher fibrinolytic activity?
  • FXI-ASO superiority to other prophylactic anticoagulants
  • Other potential clinical uses of FXI-ASO
  • Role of intrinsic pathway in thrombus formation
Case 2

- 4 year old girl presented with sudden onset of extensive bruising without precipitating trauma
- Family history of “bleeding disorder”
  - No further information available
- Recent possible cold though no specific infectious agent identified
- Physical examination
  - Diffuse ecchymoses
  - No petechiae
# Case 2

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Patient Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>15.2</td>
<td>10.0-12.8</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>65.4</td>
<td>23.9-32.6</td>
</tr>
<tr>
<td>APTT 1:1 mixing study (immediate)</td>
<td>58.2</td>
<td>23.9-32.6</td>
</tr>
<tr>
<td>Thrombin time (s)</td>
<td>14.9</td>
<td>8.0-15.0</td>
</tr>
<tr>
<td>Factor VIII activity (%)</td>
<td>67</td>
<td>50-150</td>
</tr>
<tr>
<td>Factor IX activity (%)</td>
<td>98</td>
<td>60-150</td>
</tr>
<tr>
<td>Factor XI activity (%)</td>
<td>212</td>
<td>60-150</td>
</tr>
</tbody>
</table>
## Case 2

**Lupus anticoagulant testing**

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Patient Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRVVT screen (s)</td>
<td>70.1</td>
<td>&lt;55.1</td>
</tr>
<tr>
<td>DRVVT confirm (s)</td>
<td>44.2</td>
<td>N/A</td>
</tr>
<tr>
<td>DRVVT ratio</td>
<td>1.4</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>Hexagonal phospholipid neutralization (delta s)</td>
<td>56</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Factor II activity (%)</td>
<td>20</td>
<td>75-135</td>
</tr>
<tr>
<td>Antiprothrombin IgG (G units)</td>
<td>65</td>
<td>&lt;21</td>
</tr>
<tr>
<td>Antiprothrombin IgM (M units)</td>
<td>13</td>
<td>&lt;21</td>
</tr>
</tbody>
</table>
Case 2

• Laboratory Result Summary
  • APTT with non-correction of immediate 1:1 mixing study
  • No decrease in factor VIII, IX, XI activity
  • Lupus anticoagulant detected with both DRVVT- and APTT-based test systems
    • Marked decrease in factor II activity
    • Positive antiprothrombin IgG antibody
Case 2

• Diagnosis
  • Lupus anticoagulant with hypoprothrombinemia (Lupus anticoagulant-hypoprothrombinemia syndrome (LA-HPS))

• One of the few situations in which LA may be associated with clinical bleeding
  • Others include
    • Significant concurrent thrombocytopenia
    • Concomitant factor VIII inhibitor
Lupus anticoagulant (LA)

- Lupus anticoagulants are a heterogeneous group of antibodies
  - May occur spontaneously and transiently
    - In pediatric patients, LA detected in 0.7-2.4% of asymptomatic pediatric patients
  - May be associated with antiphospholipid syndrome (APS)
    - Less common in pediatric patients than transient LA

LA-HPS- Clinical Features

• Initially described in 1960
• Occurs in a minority of patients with LA
  • Up to 10% of LA patients by some reports
• In one pediatric study of 95 patients with LA
  • Only 8 had severe concurrent hypoprothrombinemia
    • Of these, only 5 had significant clinical bleeding

BMJ Case Rep. Published online [2013 Jan 7]. doi:10.1136/bcr-2012-007948.
LA-HPS- Risk Factors

- Recent antecedent infection is important risk factor (particularly for children)
  - Adenovirus (most commonly implicated)
  - EBV
  - CMV
- Other risk factors
  - Autoimmune disease, medications, lymphoproliferative disorders

BMJ Case Rep. Published online [2013 Jan 7]. doi:10.1136/bcr-2012-007948.
LA-HPS- Pathogenesis

• Antibodies directed against prothrombin (factor II) or antiphosphatidylserine/prothrombin complex arise in association with LA
  • Non-neutralizing antibodies

LA-HPS- Presentation

• Widely variable bleeding phenotype
  • Minor (gingival bleeding, ecchymoses, epistaxis)
  • Major (GI or GU mucosal bleeding, cerebral hematoma, intramuscular hematoma)

LA-HPS- Laboratory Diagnosis

• LA detected (using current laboratory guidelines)

• Factor II activity decreased
  • Factor II inhibitor assays (Bethesda titer) expected to be negative

• ELISA-based antiprothrombin antibody assays may be positive
  • Though not all patients with positive antiprothrombin ELISA will show hypoprothrombinemia or bleeding symptoms
Conclusion

- Interpretation of hemostasis assays in pediatric patients requires attention to developmental issues in addition to usual considerations for good laboratory practice.
- Certain disorders (e.g., LA-HPS) disproportionately affect the pediatric population.
- Stay tuned for more information on factor XI as a potential antithrombotic therapeutic target.
Thank you for your attention!

Questions?