Updates on Factor XIII Deficiency and Dysfibrinogenemia

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Updates on Factor XIII Deficiency and Dysfibrinogenemia

Financial Conflicts of Interest: None
Factor XIII Deficiency
Definition

- Congenital or acquired bleeding disorder

- Decreased factor XIII levels in plasma

- Decreased covalent cross-linking between fibrin and target proteins (fibrin, alpha-2-antiplasmin, fibronectin, collagen, etc.)

- Decreased fibrin clot stability
Coagulation Cascade – Tissue Factor Model

Propagation

FXI → FXIa

FIX → FIXa

FVIIIa, PS, Ca

FVIII

FX → FXa

FVa, PS, Ca

FV

FII

FXIIIa

Fibrinogen

Fibrin monomer

Fibrin polymer

Initiation

Tissue factor

PS, Ca

FXIIa → FVII

PS, Ca

Cross-linked Fibrin polymer

FXIIa

FXIIIa

FXIII

Ca
Transglutaminase Reaction:
1. Lys – Gln peptide bond
2. Cross linking of D domains

Fibrin Cross-Linking

Factor XIIIa
Factor XIII Structure

• FXIII is a tetrameric protein (330 kDa)
  2 catalytic A subunits (FXIII-A)
  2 carrier B subunits (FXIII-B)

• FXIII-A (83 kDa) - chromosome 6, hematopoietic cells, platelets and monocytes

• FXIII-B (80 kDa) - chromosome 1, liver, circulates in plasma in 50% excess of FXIII-A, therefore all FXIII-A is bound to FXIII-B
Activation of plasma factor XIII heterotetramer

Thrombin mediated cleavage of A subunit activation peptides

Separation of B subunits

Calcium and Substrate

Catalytic form of A2 protein
Congenital Factor XIII Deficiency
Epidemiology

• Incidence is 1 in 2 million per year
• Equal frequency in males and females
• Increased frequency in consanguineous cultures
Congenital Factor XIII Deficiency
Pathogenesis

- Mutations in FXIII-A gene or FXIII-B gene
- Autosomal recessive – homozygous or compound heterozygous
- FXIII-A deficiency (~ 95%; 112 mutations as of 2013)
- FXIII-B deficiency (~ 5%; 16 mutations as of 2011)
- All mutations cause decreased to absent synthesis (type 1 deficiency - quantitative)

Congenital Factor XIII Deficiency
Clinical Features

- Childhood presentation
- Bleeding
- Poor wound healing
- Spontaneous abortion
# Congenital Factor XIII Deficiency

<table>
<thead>
<tr>
<th>Bleeding Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical bleeding</td>
<td>74</td>
</tr>
<tr>
<td>Bruising</td>
<td>56</td>
</tr>
<tr>
<td>Skin hematoma</td>
<td>49</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>28</td>
</tr>
<tr>
<td>Mucosal bleeding</td>
<td>26</td>
</tr>
<tr>
<td>Joint bleeding</td>
<td>21</td>
</tr>
<tr>
<td>Muscle bleeding</td>
<td>19</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
</tr>
</tbody>
</table>

Analysis of all cases (104 mutations) registered in the Factor XIII database ([www.f13-database.de](http://www.f13-database.de)) up to Jan. 2010

## Congenital Factor XIII Deficiency

<table>
<thead>
<tr>
<th>Bleeding Severity</th>
<th>Frequency</th>
<th>Mean FXIII Activity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>39.3%</td>
<td>31% (10.8 - 51.3%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6.1%</td>
<td>17% (0 - 37.1%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6.1%</td>
<td>2.6% (0 – 23.1%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>48.5%</td>
<td>0% (0 – 10.9%)</td>
</tr>
</tbody>
</table>

Analysis of 33 cases in the European Network of Rare Bleeding Disorders database. Grade 1 = traumatic bleeding; Grade 2 = spontaneous minor bleeding; Grade 3 = spontaneous major bleeding.

Congenital Factor XIII Deficiency
Laboratory Diagnosis - ISTH Guidelines

- Common hemostasis screening tests are normal (PT, PTT, thrombin time, platelet count)
- Traditionally, the clot solubility test was used as the screening test
- Test principle is based on the denaturation of the fibrin clot by urea, acetic acid, or chloroacetic acid
- Only detects severe FXIII deficiency (FXIII activity < 5%)
- Will be falsely normal if FXIII activity is > 5%
- Clot solubility test is no longer recommended

Congenital Factor XIII Deficiency
Laboratory Diagnosis - ISTH Guidelines

- Quantitative FXIII activity assay
  Plasma and platelet

- Quantitative FXIII - A subunit antigen
  Plasma and platelet

- Quantitative FXIII - B subunit antigen
  Plasma

## Congenital Factor XIII Deficiency

### Laboratory Diagnosis - ISTH Guidelines

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>FXIII - A</th>
<th>FXIII - B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FXIII activity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FXIII-A antigen</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FXIII-B antigen</td>
<td>NL or ↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FXIII activity</td>
<td>↓</td>
<td>NL</td>
</tr>
<tr>
<td>FXIII-A antigen</td>
<td>↓</td>
<td>NL</td>
</tr>
</tbody>
</table>

Congenital Factor XIII Deficiency
Treatment

• Human FXIII concentrate
  Purified from human donors, heat treated
  10 - 35 units per kg every 4 weeks
  Target FXIII 5 - 20% (trough)

• Human recombinant FXIII – A subunit
  Produced in yeast
  35 units per kg every 4 weeks

• Cryoprecipitate: 1 unit per 10 kg every 4 weeks

• Fresh frozen plasma: 15 – 20 mL per kg every 4 weeks

Acquired Factor XIII Deficiency
FXIII Inhibitors (Autoimmune)

- Adult presentation
- Associated with autoimmune disease and medications (isoniazid, penicillin, phenytoin, procainamide)
- Bleeding
- Diagnosed by decreased factor XIII activity, non-corrected FXIII 1:1 mixing study (90% are subunit A autoantibodies)
- Treat with factor XIII replacement and immunosuppression
- Good prognosis (80% remission); 10% mortality

Acquired Factor XIII Deficiency
Non-Autoimmune

- Caused by diseases that increase consumption of factor XIII
- Major surgery, pulmonary embolism, stroke, Crohn disease, ulcerative colitis, sepsis
- Factor XIII activity typically > 20%
- Other clotting factors also consumed in these diseases

Factor XIII Deficiency
FXIII Gene Mutation Databases

www.f13-database.de


www.hgmd.cf.ac.uk
Factor XIII Deficiency
Reference Laboratories

Quantitative FXIII Activity Assays
ARUP Laboratories (www.aruplab.com)
Esoterix (www.esoterix.com)
LabCorp (www.labcorp.com)
Quest Diagnostics (www.questdiagnostics.com)

FXIII-A and B Antigen, FXIII-A and B Gene Mutation
Diane Nugent, MD, Children's Hospital of Orange County;
Univ. of California, Irvine Medical School;
Phone: 714-509-8744; email: dnugent@choc.org
• Testing provided free of charge through program sponsored by
  CDC Foundation and funded by Novo Nordisk; requests for
  testing must be received by October 31, 2017


Ichinose A, Souri M. As many as 12 cases with haemorrhagic acquired factor XIII deficiency due to its inhibitors were recently found in Japan. Thromb. Haemost. 2011; 105: 925 - 927.


Factor XIII Deficiency - References


Dysfibrinogenemia
Definition

- Fibrinogen disorder caused by structural abnormalities leading to fibrinogen dysfunction
- Congenital or acquired
- Bleeding, thrombosis, or both
- Decreased fibrinogen functional levels in plasma
- Normal fibrinogen antigen levels in plasma
Fibrin Polymerization

Fibrinogen

Thrombin

Fibrin Monomer

Fibrin Polymer

Fibrinopeptide A

Fibrinopeptide B
Fibrinogen Structure

Figure 10.27
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company
Dysfibrinogenemia
Epidemiology

- Incidence is unknown (rare)

- Prevalence of 0.8% among patients with history of venous thrombosis
Dysfibrinogenemia
Pathogenesis

- Mutations in FGA gene, FGB gene, FGG gene
- Autosomal dominant – heterozygous mutations
- Rarely, homozygous or compound heterozygous mutations
- More than 100 mutations in 400 families
- Genotype/phenotype correlations not well established for most mutations
Dysfibrinogenemia
Hotspot Mutations

• 85% of mutations in FGA (exon 2; E domain) and FGG (exon 8; D domain); first exons to examine in genetic screening

• FGA – Arg16 (delayed fibrinopeptide A release, decreased platelet binding, decreased fibrinolysis, thin fibers)

• FGG – Arg275 (delayed/inaccurate fibrin monomer polymerization, decreased FXIII cross-linking, thick fibers, increased branching)

• Broad range of clinical manifestations, bleeding and thrombosis

• Most patients are asymptomatic (73%)
Dysfibrinogenemia
Thrombotic Mutations

- 7 mutations clearly associated with thrombosis risk
- **FGA - Exon 5** (mature chain: R554C, S532C)
- **FGB - Exon 2** (mature chain: R14C, del9-72, R44C, A68T)
- **FGG - Exon 8** (mature chain: D364V)
- Mechanisms include:
  - Decreased fibrinolysis (impaired plasminogen or tPA binding)
  - Decreased thrombin binding to fibrin
Dysfibrinogenemia
Pathogenesis

Dysfibrinogenemia
Clinical Features

• Mean age at diagnosis is 29 years

• Two-thirds are women

• 50 – 60% of patients are asymptomatic at time of diagnosis

• Bleeding phenotype is variable and usually mild
  2.5 major bleeding events per 1000 patients per year
  19% cumulative incidence major bleeding by age 50 years

• Thrombosis is frequent, and can be venous or arterial
  18.7 events per 1000 patients per year
  30% cumulative incidence by age 50 years

Dysfibrinogenemia
Clinical Features

Dysfibrinogenemia
Laboratory Diagnosis

**Screening Tests**
- Thrombin time (↑)
- Reptilase time (↑)
- Prothrombin time (↑)
- Partial thromboplastin time (↑)

**Confirmatory Tests**
- Fibrinogen activity (↓)
- Fibrinogen antigen (NL or ↑)
- Fibrinogen Act:Ag ratio (< 0.7)

**Molecular Tests**
- FGA mutation
- FGB mutation
- FGG mutation
Dysfibrinogenemia
Treatment

• No prospective controlled studies; guidelines based on expert consensus

**Bleeding Phenotype**
- Fibrinogen concentrate
- Cryoprecipitate
- Fresh frozen plasma
- Target fibrinogen > 100 mg/dL (trough)
- Tranexamic acid

**Thrombosis Phenotype**
- Low molecular weight heparin
- Mechanical prophylaxis
- Avoid fibrinogen concentrate due to risk of thrombosis

Dysfibrinogenemia
Fibrinogen Gene Mutation Database

www.geht.org/databaseang/fibrinogen
Dysfibrinogenemia
Reference Laboratories

**Fibrinogen Gene Mutation Analysis**
Philippe de Moerloose, University Hospitals of Geneva and Faculty of Medicine, Hemostasis Unit, 1211 Geneva, Switzerland
email: philippe.demoerloose@hcuge.ch
References


