Bleeding Emergencies in Inherited Coagulation Disorders

Giancarlo Castaman

Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy
Hemorrhagic emergencies

1. Bleeding potentially life-threatening or dangerous for function integrity

2. Clinical and laboratory situation with high risk of potential life-threatening bleeding (hemostatic emergency)

Both with the characteristics of «sudden and unexpected»
Causes of bleeding

- Clotting abnormality:
  - Congenital
  - Acquired
  - Secondary to other disorder(s)
  - Apparently idiopathic

- Quantitative/qualitative platelet defects

- Acquired hemostatic defects

- Trauma or surgery
**Coagulation process**

- **FXI** → **FXIIa** → **FXIa** → **Ca^{2+}** → **FIX** → **FIXa**
- **FVII** → **TF** → **FVIIa** → **PL, Ca^{2+}** → **FX** → **FXa**
- **Prothrombin → FVa**
- **FV** → **Thrombin**
- **FVIII** → **FXIIa** → **FXIIIa**
- **Fibrinogen → Fibrin monomers** → **Fibrin XL** → **XL-FDP**

**Hemophilia**

Rare bleeding disorders

- **F = factor**
- **a = active**
- **PL = phospholipids**
- **XL = cross-linked**
- **FDP = fibrin degradation products**
Hemorrhagic emergencies in inherited coagulation disorders

1. Apparently **primitive** in a subject with a bleeding disorder not diagnosed yet

2. **Spontaneous** in a patient previously diagnosed with an inherited bleeding disorder

3. **Triggered** by trauma or surgery

4. **Inhibitor(s)**
Hemorrhagic emergencies in inherited coagulation disorders

1. Apparently primitive in a subject with a bleeding disorder not diagnosed

2. Spontaneous in a patient previously diagnosed with an inherited bleeding disorder

3. Triggered by trauma or surgery
Apparently primitive in a subject with a bleeding disorder not diagnosed

• **Neonatal cerebral bleeding**
  (FXIII> afibrinogenemia> FVII> severe hemophilia)

• **Umbilical stump bleeding**
  (FXIII> afibrinogenemia > FX)
Bleeding symptoms in FX deficiency compared to severe Hemophilia A

Uprichard et al, Blood reviews 2002
Rare Bleeding Disorders: the peculiarity of Afibrinogenemia and FXIII deficiency

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Afibrinogenemia</th>
<th>FXIII deficiency</th>
<th>Severe Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding from umbilical stump</td>
<td>50 %</td>
<td>73 %</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>Spontaneous cerebral bleeding</td>
<td>10 %</td>
<td>30 %</td>
<td>~ 10%</td>
</tr>
<tr>
<td>Factor half-life</td>
<td>~ 4 days</td>
<td>~ 14 days</td>
<td>12 hours</td>
</tr>
</tbody>
</table>
FVII deficiency: Bleeding symptoms (IF7 Database)

- More frequent bleeding
  - Menorrhagia 62.9 %
  - Epistaxis 60.9 %
  - Ecchymosis 45.4 %
  - Gum bleeding 30.2 %
  - Hemartrosis 18.4 %
  - G.I. bleeding 14 %
  - Cerebral bleeding 5.7%
  - Hematuria 8.2%
  - Post-surgery 23.8 %*

* Prevalence in patients undergone surgery
Screening tests for a (severe) bleeding disorder

- APTT
- PT
- Platelet count
- (PFA©-100 ADP/EPI)
It still happens...

• Male, born at another hospital, APGAR 10

• On 12th day, at home, bleeding from umbilical stump

• Large subcutaneous hematoma right arm from previous venipuncture. Hb 14.2 g/dL, PT, PTT and platelet count normal, sutured at the same hospital

• The day after, new admission because recurrence of bleeding from umbilical stump
At the end he arrives...

- Hb 9.6 g/dL, surgical necrosectomy, transfused with RBC (Hb 7.2 g/dL)

- Afterwards, large bruising from minor trauma

- When 14 month-old, trauma to upper right incisive with recurrent oozing for at least 4 days

- Admission at Pediatric Department of our hospital on pediatrician’s request
Do we need Hemophilia centers?

- No bleeding history in the family

- Monochloroacetic acid 1 % = positive (clot lysis < 10 min); 30 min from blood drawing

- FXIII < 1 U/dL

- FXIII A gene = 4 bp homozygous deletion in exon 11 (c. 1392-1395 delAATT)

- Unrelated parents heterozygous
Clinical Pharmacokinetics of a Placenta-Derived Factor XIII Concentrate in Type I and Type II Factor XIII Deficiency

Francesco Rodeghiero, Alberto Tosetto, Eros Di Bona, and Giancarlo Castaman
Department of Hematology and Hemophilia and Thrombosis Center, San Bortolo Hospital, Vicenza, Italy

Half-life FXIII ~ 14 days
Levels 2 – 4% sufficient to prevent spontaneous bleeding

FXIII concentrate = 10-20 U/Kg/ 4 weeks
Outcome

- Infusion of 500 U FXIII concentrate, bleeding immediately stopped
- Prophylaxis with 15-20 U/kg FXIII every 4 weeks
- No further bleeding episodes
### Screening tests for Rare Bleeding disorders

<table>
<thead>
<tr>
<th>Factor</th>
<th>PTT</th>
<th>PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>FII</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>FV</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>FVIII-FIX</td>
<td>↑↑</td>
<td>N</td>
</tr>
<tr>
<td>FX</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>FXI</td>
<td>↑↑</td>
<td>O</td>
</tr>
<tr>
<td>FVII</td>
<td>N</td>
<td>↑↑</td>
</tr>
<tr>
<td>FXII</td>
<td>↑↑↑</td>
<td>N</td>
</tr>
<tr>
<td>FXIII#</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

# A specific screening test required (Urea 4 M or monochloroacetic acid 1 %)
Hemorrhagic emergencies in inherited coagulation disorders

1. Apparently primitive in a subject with a bleeding disorder not diagnosed

2. Spontaneous in a patient previously diagnosed with an inherited bleeding disorder

3. Triggered by trauma or surgery
Clinical features of Rare Bleeding disorders: spontaneity of symptoms

Haemophilia (2000), 6, 705–708

Spontaneous intracranial bleeding in two patients with congenital asfibrinogenaemia and the role of replacement therapy

*Haemophilia Centre, St Bartholomew’s and The London NHS Trust, Royal London Hospital, London, and †Oxford Haemophilia Centre, Churchill Hospital, Oxford, UK

• ~5 - 10 % of severe Hemophilia patients may suffer from cerebral bleeding, even apparently spontaneous
Severe bleeding in hemophilia

- **Cerebral**
  - Headache
  - Dizziness
  - Drowsiness
  - Nausea or vomiting

- **Eye**
  - Pain
  - Swelling
  - Discoloration
  - Visual disturbances

- **Tongue, Throat**
  - Difficulty in swallowing
  - Discoloration
  - Swelling
  - Difficulty in breathing

- **Urinary Tract**
  - Lower back pain
  - Blood in urine

- **Digestive Tract**
  - Vomiting fresh or old blood
  - Dark tarry stools
  - Fresh blood in stools
  - Pallor
  - Weakness
  - Pain

- **Genitalia**
  - Swelling
  - Pain
  - Discoloration

Contact Hemophilia Center Immediately!
Clinical features of Rare Bleeding disorders:

spontaneity of symptoms

Ileopsoas hematoma in hemophilia

- Femoral nerve palsy
- Acute compartment syndrome
Clinical features of Rare Bleeding disorders: spontaneity of symptoms

• 3 year-old kid with severe hemophilia A, tonsillitis and fever 39.5°C

• Recovery after 3 days with antibiotics, no fever, but pale and letargic

• Hb 5.7 g/dL; continuous oozing from right tonsil

Occult throat bleeding/hematoma
Disordini ereditari dell’ interazione piastrine-parete vascolare e della funzione piastrinica

- Procoagulant surface
- Deficit di attività procoagulante
- Disordini ereditari della funzione piastrinica (Storage pool, Difetti di secrezione)
- M. Von Willebrand
- GP IIb-IIIa
- Piastrina
- Trombastenina di Glanzmann
- Sindrome di Bernard-Soulier
- GP Ib
- Adhesion
- Aggregation
- Secretion
- VWF
- Fibrinogen
- Disordini ereditari della funzione piastrinica (Storage pool, Difetti di secrezione)
### Bleeding symptoms (%) in Italian patients with von Willebrand disease

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Italian Registry Willebrand (n = 896)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>63</td>
</tr>
<tr>
<td>Gum bleeding</td>
<td>33</td>
</tr>
<tr>
<td>Easy Bruising</td>
<td>38</td>
</tr>
<tr>
<td><strong>Menorrhagia</strong></td>
<td>34</td>
</tr>
<tr>
<td>Muscle hematoma</td>
<td>14</td>
</tr>
<tr>
<td><strong>Gastrointestinal bleeding</strong></td>
<td>6</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>3</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Federici et al, 2005
Family S, Föglö Island

- **Severe bleeding**
- **Mild or trivial bleeding**
TYPE 3 VWD
(IVS46 +1, G>T n.7770+1)

FVIII:C 160 IU/dL
VWF:Ag 98 IU/dL

FVIII:C 131 IU/dL
VWF:Ag 140 IU/dL

FVIII:C 121 IU/dL
VWF:Ag 99 IU/dL

FVIII:C 86 IU/dL
VWF:Ag 30 IU/dL

FVIII:C 90 IU/dL
VWF:Ag 45 IU/dL

FVIII:C 72 IU/dL
VWF:Ag 82 IU/dL

FVIII:C 57 IU/dL
VWF:Ag 63 IU/dL

FVIII:C 61 IU/dL
VWF:Ag 35 IU/dL

FVIII:C 1.2 IU/dL
VWF:Ag 1.8 IU/dL

IVS 46 +1 G>T
Bleeding at menarche in severe von Willebrand disease women

- Severe bleeding at menarche age 13, 24 hour after starting admitted with Hb 5.2 g/dL, still bleeding
- Treated with RBC, antifibrinolytics, FVIII/VWF concentrates

<table>
<thead>
<tr>
<th>Menorrhagia Score</th>
<th>0 no or trivial</th>
<th>1 present</th>
<th>2 consultation/pill use/iron therapy</th>
<th>3 transfusion/hysterectomy/curettage/replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 VWD (n = 54)</strong></td>
<td>16 (29.6 %)</td>
<td>10 (18.5 %)</td>
<td>16 (29.6 %)</td>
<td>12 (22.3 %)</td>
</tr>
<tr>
<td><strong>Controls (n = 121)</strong></td>
<td>101 (83.5 %)</td>
<td>3 (2.5 %)</td>
<td>9 (7.5 %)</td>
<td>8 (6.5 %)</td>
</tr>
</tbody>
</table>

IMS, JTH 2005
Influence of sex on bleeding tendency and transfusion requirement in Glanzmann Thrombasthenia
(modified from Awidi, Am J Hematol 40, 1, 1992)

20 patients; mean follow-up 5.6 years (1 – 8.5; 140 pt/years)

<table>
<thead>
<tr>
<th>Sex and number</th>
<th>Mean RBC (Units)</th>
<th>Total RBC (Units)</th>
<th>Platelet concentrates (Total Units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n = 8)</td>
<td>5.8</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>Females (n = 12)</td>
<td>19.2</td>
<td>230</td>
<td>163</td>
</tr>
</tbody>
</table>

@ Menorrhagia: 8 pts: 140 U RBC + 80 PC
Gastrointestinal bleeding in von Willebrand disease

- Often elder, severe phenotype and/or lack of high molecular weight VWF multimers (Fressinaud, 1993; Castaman, 2012)

- Acquired (aortic valve stenosis, AVWS)

- Angiodysplasia over GI tract, often of difficult localization by diagnostic techniques

- High requirement for blood transfusion, treatment cumbersome (prophylaxis and high FVIII/VWF concentrate requirement, octreotide, talidomide, atorvastatin…)
Number and types of bleeding episodes in VWD during 24-month follow-up

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1 R1205H (n = 60)</th>
<th>Type 1 C1130F (n = 23)</th>
<th>Type 2 A (n = 46)</th>
<th>Type 2 M (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>2</td>
<td>0</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>2</td>
<td>6</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hemorrhoidal</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1</td>
<td>0</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Castaman et al, 2011; 2012
Hemorrhagic emergencies in inherited coagulation disorders

1. Apparently primitive in a subject with a bleeding disorder not diagnosed

2. Spontaneous in a patient previously diagnosed with an inherited bleeding disorder

3. Triggered by trauma or surgery
Hemorrhagic emergencies triggered by trauma or surgery

- In patients already diagnosed:
  - Inadequate anti-hemorrhagic prophylaxis
  - Anatomical reasons

- In patients with mild inherited bleeding disorder still undiagnosed and manifest after surgery or trauma (e.g., mild hemophilia)
Inhibitors in hemophilia

- IgG inhibiting clotting activity of FVIII/FIX
- Usually < 20 exposure days to concentrate, rare later
- ~25% severe hemophilia A patients, <5% severe hemophilia B (risk of severe allergic reactions)
- Often transient, sometimes occurring during hemostatic challenges (e.g. surgery)
Treatment at very early age
Intensive treatment
Concurrent disorders (immunity)

Expression of genes involved in immune response

«Null» gene mutations/major deletions

Risk of inhibitor

Expression of genes involved in immune response

Treatment at very early age
Intensive treatment
Concurrent disorders (immunity)

Type of concentrate (+/- VWF)
Precocious prophylaxis
Cumulative inhibitor incidence in 1112 nonsevere hemophilia A patients, according to cumulative exposure days to factor VIII concentrates

- Inhibitor occurs in ~10% of non-severe Hemophilia A, often after intensive treatment.
- Risk increases continuously with increasing exposure days.

Eckhardt C L et al. Blood 2013
Distribution of F8 missense mutations associated with inhibitor development

- Genotyping advised at diagnosis also in mild hemophilia A
- Use desmopressin
## Hemophilia B and inhibitors in Italy

<table>
<thead>
<tr>
<th>Mutation</th>
<th>ED at inhibitor onset</th>
<th>Peak (BU)</th>
<th>ANA</th>
<th>Immunotolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trp194Stop</td>
<td>15</td>
<td>140</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Trp194Stop</td>
<td>8</td>
<td>90</td>
<td>NO</td>
<td>YES, after 1,598 ED with rFIX</td>
</tr>
<tr>
<td>Arg248Stop</td>
<td>30</td>
<td>2.6</td>
<td>NO</td>
<td>YES, after 26 ED with pdFIX</td>
</tr>
<tr>
<td>Arg248Stop</td>
<td>8</td>
<td>1.6</td>
<td>YES</td>
<td>NO, by-passing agents</td>
</tr>
<tr>
<td>Arg252Stop</td>
<td>14</td>
<td>117</td>
<td>NO</td>
<td>YES, after 153 ED with rFIX</td>
</tr>
<tr>
<td>Arg252Stop</td>
<td>&gt;20</td>
<td>11</td>
<td>NO</td>
<td>YES, partial response with rFIX, still ongoing</td>
</tr>
<tr>
<td>Deletion exons A-H</td>
<td>&gt;30</td>
<td>25</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Deletion exons A-H</td>
<td>4</td>
<td>1.7</td>
<td>YES</td>
<td>NO, by-passing agents</td>
</tr>
<tr>
<td>Deletion complete</td>
<td>50</td>
<td>18</td>
<td>NO</td>
<td>On demand treatment</td>
</tr>
<tr>
<td>Deletion complete</td>
<td>31</td>
<td>6.4</td>
<td>NO</td>
<td>NO, by-passing agents</td>
</tr>
</tbody>
</table>

Castaman et al, 2013
Patient with exons A-H deletion

- 6 yr-old boy with FIX < 1 U/dL; no treatment before the age of 5

- April 2010 – Large left thigh hematoma: Benefix 1000 U/day for 3 days
- End of May: Inhibitor BU 0

- June 18: Left knee hemarthrosis: Benefix 1000 U
  - June 29: BU 1.7, recurrence of hemarthrosis
  - New treatment with rFIX in intensive care unit
  - After ~200 U, infusion discontinued because of:
    - Acute asthma with respiratory failure
    - Tongue and lips edema
    - Tachycardia
    - Peripheral cianosis
    - Epinephrine and hydrocortisone
High Responding / Low Responding Inhibitors

- **High responding:** >5 Bethesda Units (BU)
  - FVIII/IX concentrates ineffectual
  - Every treatment induces an increase of BU titer (anamnestic response)

- **Low Responding:**
  - Trues: < 5 BU even after reexposure to concentrate
  - Transient: < 5 UB disappears continuing treatment within 6 - 12 months

Can be treated with FVIII/IX by increasing the dose (neutralising dose)
Recommendations for the treatment of hemophilia with inhibitors (BU > 5)

Treatment or prophylaxis (invasive procedures, surgery)

Firstline with by-passing agents:

• **rFVII** 90 µg/Kg every 2-3 hr until bleeding stops or persistence of hemorrhagic risk. Partial or complete response 75-100%.

  *Thrombotic complications <1:10.000 infusions*

• **aPCC** 50-100 UI/Kg every 8-12 hr up to max 200 U/kg/day. Partial or complete response 85-100%.

  *Thrombotic complications 4-8:100.000 infusions*

Duration based on clinical ground, without specific laboratory monitoring
Treatment of hemarthrosis as emergency situation to minimize the disability of long-term hemophilic arthropathy
What happens with hemarthrosis: Hemophilic arthropathy

Synovitis
- Boggy
- Swollen

Synovial membrane
Synovial cells
Capsule
Cartilage

Muscle wasting
Morning stiffness
Chronic pain
Limited movement

Joint Destruction
Chronic crippling artropathy
Prompt and adequate treatment of hemarthrosis to minimize the disability of long-term hemophilic arthropathy

- **Quantity**: Adequate dose of factor concentrate ($\geq 25$ U/Kg)
- **Timely**: Home-Treatment
- **Prevention/rehabilitation**: Prophylaxis
Conclusions

• The management of patients with inherited bleeding disorders should foresee the risk of emergency bleeding

• Regular surveillance allows the identification of at-risk patients (e.g., inhibitor development)

• Surgery should be always coordinated with hemostasis staff to plan treatment for unexpected bleeding

• Treatment of hemarthrosis requires adequate dosage and should be timely to minimize long-term disabilities

• Prophylaxis is the gold-standard for children
What happens with hemarthrosis

Early
- Bubbling
- Tingling
- Heat

Late
- Swelling
- Heat
- Pain

Normal joint
- Synovial membrane
- Synovial cells
- Capsule
- Cartilage