Patients with Factor VII or Factor XI deficiency: do they need treatment prior to surgery?

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WFH Global Survey 2011 data

- GT, 1884, 10%
- F1, 1196, 7%
- FII, 244, 1%
- FV, 1420, 8%
- FV+VIII, 385, 2%
- FVII, 5357, 30%
- FXII, 1054, 6%
- FXI, 4759, 27%
- FX, 1317, 7%
- BSS, 325, 2%

Graph showing the distribution of different factors with the following levels:

- F1: 1196, 7%
- FII: 244, 1%
- FV: 1420, 8%
- FV+VIII: 385, 2%
- FVII: 5357, 30%
- FX: 1317, 7%
- FXI: 4759, 27%
- BSS: 325, 2%
- GT: 1884, 10%

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The problem: unpredictable bleeding risk

- The RBDs cannot be classified by severity in the same way as haemophilia A and B
- Inadequate good level evidence because of rarity
- Data analysis based on European registry, data from UKHCDO, N American Registry and Indian registry at CMC Vellore

(SSF of ISTH: Communication on RBDs JTH 2012: 10; 1938-1943)
Classification of Rare Bleeding Disorders

<table>
<thead>
<tr>
<th>Coagulant factor</th>
<th>Laboratory phenotype</th>
<th>Coagulant activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Undetectable clot</td>
<td>0.1–1 g L(^{-1})</td>
</tr>
<tr>
<td>FII</td>
<td>Undetectable activity</td>
<td>\leq 10%</td>
</tr>
<tr>
<td>FV</td>
<td>Undetectable activity</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>FV + FVIII</td>
<td>&lt; 20%</td>
<td>20–40%</td>
</tr>
<tr>
<td>FX</td>
<td>&lt; 10%</td>
<td>10–20%</td>
</tr>
<tr>
<td>FXI</td>
<td>Undetectable activity</td>
<td>&lt; 30%</td>
</tr>
</tbody>
</table>

FXI no relationship between bleeding and factor level
(JTH 2012: 10; 1938-1943)
In vivo properties
(1:Rizza 1982, 2: Mannucci 2004)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Haemostatic level iu/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>10-20</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>40</td>
</tr>
<tr>
<td>Factor V</td>
<td>10-15</td>
</tr>
<tr>
<td>Factor VII</td>
<td>5-10</td>
</tr>
<tr>
<td>Factor X</td>
<td>10-15</td>
</tr>
<tr>
<td>Factor XI</td>
<td>?20-30</td>
</tr>
</tbody>
</table>

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Factor VII deficiency

• A very heterogeneous disorder and poor correlation with factor levels
• Registry data:
  – Griefswald Registry
  – Seven Treatment Evaluation Registry (STER)
  – International FVII Registry (IF7)
• Total 1343 patients
• Major bleeding predicts for further bleeding
• Those with level <0.1iu/ml are more likely to bleed
• 19% heterozygotes presented with bleeding
Suggested classification by symptoms rather than factor level

Ranking of symptoms by age at presentation

Mutational analysis of 98 homozygous subjects (15 asymptomatic) Showed that subjects with the SAME mutation were in all three clinical classes of severity

(Lapecorella and Mariani, Haemophilia 2008; 14: 1170-1175)
Patterns of lab results in Factor VII deficiency % (Iranian/Italian study)

<table>
<thead>
<tr>
<th>VIIC - rabbit</th>
<th>VIIC - human</th>
<th>VIIC - bovine</th>
<th>VIIAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>37</td>
<td>130</td>
<td>240</td>
</tr>
<tr>
<td>&lt;1</td>
<td>27</td>
<td>90</td>
<td>224</td>
</tr>
<tr>
<td>&lt;1</td>
<td>24</td>
<td>100</td>
<td>156</td>
</tr>
<tr>
<td>&lt;1</td>
<td>17</td>
<td>70</td>
<td>106</td>
</tr>
<tr>
<td>&lt;1</td>
<td>22</td>
<td>80</td>
<td>130</td>
</tr>
<tr>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>77</td>
</tr>
<tr>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Do values with human thromboplastin predict bleeding better?
Other issues

• Neonatal ICH - reported in 2-60% of cases
  – High morbidity and mortality
  – Be prepared
• Women have menorrhagia and chronic iron deficiency
• Thrombosis? Mechanism not clear*
• NA registry – 36% heterozygotes had bleeding, mainly skin and mucous membranes

*See Marty et al. Haemophilia 2008, 1-7 (11 events)
UKHCDO new guidelines for RBDs - FVII

- Cases with FVII <0.1 iu/ml or bleeding history are at higher risk
- Mild bleeding/minor surgery in higher bleeding risk cases consider antifibrinolytic therapy
- Severe bleeding or major surgery in higher bleeding risk cases consider rVIIa 15-30 ug/kg repeated if required every 4-6 h, usually for a minimum of 3 doses

• Consider long term prophylaxis for cases with personal or family history of severe bleeding or FVIIIC <0.1 iu/ml using 20-40 ug/kg three times a week adjusted to maintain clinical response

• Consider short-term prophylaxis for neonates without a bleeding history but FVIIIC 0.01 to 0.05 iu/ml up to 6-12 months of age

• Women with level <0.2 iu/ml in 3rd trimester who require caesarian section consider rVIIa 15-30 mg/kg every 4-6 h for at least 3d. For other women consider rVIIa only in response to bleeding
Factor XI deficiency

• Rosenthal (1955) described American Jewish family
• 2 sisters and their maternal uncle bled after dental extractions and tonsillectomy
• Common disorder in Ashkenazy Jews - gene frequency about 8%
• Autosomal inheritance
Relationship between factor XIC level and bleeding tendency in people from 54 UK families

(Assessors were not told the FXI levels)

Total: 249 individuals
45/128 with partial deficiency have a bleeding tendency

The APTT-based assay does not reflect FXI contribution to haemostasis

Data from European Network of RBDs showed no association between FXIC level and bleeding

Peyvandi et al. JTH 2012; 10: 615-621

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The balance of haemostasis and variable bleeding risk

• Blood group influences vWF and its clearance

• Factor VII gene mutations affect severe haemophilia A phenotype

• FV Leiden affects severe haemophilia A phenotype

• Low levels of several factors together within the normal range may affect bleeding risk
  – Chauleur et al JTH 2008;6:2067
  – Gudmundsdottir et al. JTH 2007;5:274

• Variation in platelet poly P?
Can we predict bleeding? 1

- 24 patients with FXI deficiency
  - 9 severe bleeding
  - 15 mild or non-bleeding
- Thrombin generation in PRP using low TF 0.5pM and corn trypsin inhibitor to block contact activation
- Bleeders had dramatically impaired TG independent of FXI level

Two patients with severe bleeding history

FXI C <1 iu/dl

Mild FXI deficiency FXIC 40 iu/dl

Can we predict bleeding? 2

- 43/89 pts FXIC <50 iu/dl
- Bleeding score (Tosetto 2006) and bleeding history – averaged
- Several coagulation factors, TAFI and PFA (26 parameters measured)
- Thrombophilia profile (too few patients)
- Global tests of haemostasis
  - ROTEM
  - Thrombin generation

Gueguen et al. BJH 2011; 156:245-251
Results (Study 2)

• Small study group
  – 15 bleeders
  – 24 non-bleeders

• Significant difference in levels of von Willebrand factor (RiCoF and ag) and thrombomodulin levels between bleeders and non-bleeders but all within NR

• Thrombin generation – no significant differences (TF 1 or 5pM, in both PPP and PRP no CTI)
Can we predict bleeding? 3

• TG studied in 16 unrelated patients with FXI deficiency and 14 controls
• PPP, TF 1pM, without CTI
• TG peak of non-bleeders was normal
• Peak was reduced in bleeders unrelated to FXI level
• Conclude that this would predict for surgery and enable selection of patients for less aggressive management

Livnat et al. ASH abstract 2013
Bleeding and Surgery: Management options

1. Watch and wait
2. Fibrinolytic inhibitors
3. Fresh frozen plasma
4. Factor XI concentrate
5. Fibrin glue – limited experience
7. rFVIIa

The nature of the haemostatic challenge is an important determinant of the management strategy

(Salomon et al. Haemophilia 2006;490-493)
FFP - cautions

• Large volumes may be required leading to cardiac failure in elderly patients
• Risk of transmission of infectious agents
  – Should use virally inactivated FFP
• Allergic reactions
Factor XI concentrate - 1

• 1984 onwards British concentrate available on named patient basis
• High concentration of antithrombin (mean 102 u/ml)
• Dry heated at 80°C for 72 hours
• 31 procedures in 30 patients aged 7-70 years, no significant adverse events (reported 1992)
• Recovery 91%, half-life 52 hours
Factor XI concentrate - 2

• French product available since 1991 - Hemoleven
• 3-5 u/ml of heparin
• 2-3 u/ml of antithrombin
• S/D viral inactivation and filtration at 15nm
• C1 inhibitor added
Factor XI concentrate – adverse events

• British concentrate - adverse events

• 4 patients with serious thrombotic events
  – pulmonary embolism - full recovery
  – 2 fatal myocardial infarctions
  – 1 fatal CVA

• All elderly patients with pre-existing cardiovascular disease

(Reported in letter to Lancet 1994)
Increased evidence of thrombosis

• Since 2002, 12 TE events reported to LFB after treatment with Hemoleven
  – 11 since 2007
  – 5 fatal
• 7 pulmonary emboli, 2 fatal
• 3 fatal CVA
• 1 TIA
• 1 DIC
• Background = about 140 treatments per annum
• No new TE reported with BPL product since 1996 when heparin was added

(Bolton-Maggs et al, Haemophilia 2014, 20 e336-358)
Thrombosis – risk factors

- 50% were more than 78 yrs old
- All but one had other risk factors
- Doses all <30u/kg except one
- No measurable FXIa in batches used
- PE developed very early after surgery (15-36h) with no evidence of VT
- 4 patients had received VTE prophylaxis
Revised guidance

• Manage in haemophilia centres
• Consider risk vs benefit and look at alternatives
• Avoid prophylaxis before surgery if possible and have FXI concentrate or FFP on standby
• Initial dose of Hemoleven no more than 10-15u/kg
• Registry of treated patients
• Thromboprophylaxis
Fibrinolytic inhibitors

• Factor XI deficient patients most likely to bleed from areas of high fibrinolytic activity

• Oral tranexamic acid alone was sufficient for dental extractions
  – 19 patients with severe deficiency
  – 14 had previously bled after surgery and 5 after trauma
  – only 1 had some oozing on day 3 which stopped

(Berliner et al 1992 Blood Coagul Fibrinolys 3: 465)
UKHCDO new guidelines for RBDs - FXI

• Cases with FXI <0.1 iu/ml and additional coagulopathy or bleeding history are at higher risk
• Screen for FXI inhibitors if FXI <0.1 iu/ml
• Mild bleeding/minor surgery in higher bleeding risk cases consider antifibrinolytic therapy
• Severe bleeding or major surgery in higher bleeding risk cases consider an initial dose of FXI concentrate 10-15 u/kg without antifibrinolytics
• An alternative is SD-FFP 15-25 ml/kg with antifibrinolytic
UKHCDO new guidelines for RBDs - FXI

• For delivery in women with levels <0.15 iu/ml and history of bleeding or no previous challenges consider SD-FFP and antifibrinolytic therapy at established labour or before CS
• For delivery in women with levels 0.15-0.7 iu/ml and a history of bleeding or no previous challenges consider antifibrinolytics
• For delivery in women with levels 0.15-0.7 iu/ml and no bleeding despite previous challenges only consider FXI conc or antifibrinolytics if bleeding occurs
Inhibitors in factor XI deficiency

- Inhibitors are reported in congenitally deficient patients
  - about 33% of Type II homozygotes (Glu117stop)
- Some may still respond to plasma products
- Some may need therapeutic management similar to factor VIII antibodies
  - Prothrombin complex concentrates
  - rFVIIa (single doses 15-30 mcg/kg)
  - Low dose rFVIIa followed by continuous infusion

Management of Factor XI deficient patients

- Individualise
  - for the patient
  - for the circumstances
- Choose least risky treatment
- Specialist centres
- Thrombin generation tests may help predict bleeding risk and enable better selection of therapy