THE RARE BLEEDING DISORDERS

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Overview

- Include fibrinogen, Factor II, FV, FV and FVIII, FVII, FX, FXI and FXIII deficiencies.
- Now a2-antiplasmin, PAI-1 and specific platelet disorders such as Glanzmanns and Bernard Soulier are considered rare bleeding disorders
- All separate disorders and females affected
- Usually transmitted in an *autosomal recessive* manner (therefore more common in populations where consanguinity is prevalent – India and Middle East)
- Considerable differences in bleeding patterns with range of severity from asymptomatic to *mild/moderate* bleeding to *life threatening* haemorrhage – which may not be related to levels

Overview

- Risks of adverse pregnancy outcomes
- Absence of clinical trials/studies means that recommendations regarding management are mainly based on *expert opinion/consensus*.
- This highlights the importance of registries to gather information.
- Often *no specific* replacement therapy (impact of the small market)
- Lack of established paediatric specific normal ranges can make diagnosis difficult
- Risks of inhibitor development and management are less well characterised due to limited information

Characteristics of rare bleeding disorders

Deficiency	Prevalence	Genetic	Clinical Features	Treatment
Fibrinogen	1:1,000,000	Chr 4	Usually mild except afibrinogenemia	Fibrinogen concentrate Cryo, FFP, Antifibs
Prothrombin	1:2,000,000	Chr 11	Usually mild (severe in homozygotes)	Prothrombin complex concentrate, FFP
Factor V	1:1,000,000	Chr 1	Usually mild	FFP or platelets
Comb FV/VIII	1:1,000,000	Chr 18 (LMAN1) Chr 4 (MCFD2)	Usually mild	FFP, Factor VIII, DDAVP
Factor VII	1:500,000	Chr 13	Severe with low lev	PD or rVII, PCC (min)
Factor X	1:1,000,000	Chr 13	Moderate to severe	FFP, PCC, FX conc
Factor XI	1:1,000,000	Chr 4	Mild to moderate	Antifibrinolytic drugs, FFP, PD FXI, rVIIa
Factor XIII	1:2,000,000	Chr 6 (F13A) Chr 1 (F13B)	Severe	FFP, cryo, PD or recomb FXIII
A2AP	<1:1,000,000			FFP, Antifibrinolytics
PAI-1	Unknown			FFP, Antifibrinolytics
Glanzmanns	1:1,000,000			Platelet Tx
BernardSoulier	1:1,000,000			Platelet Tx

Some considerations with RBD's

- Is regular prophylaxis indicated
- How are menstruation and pregnancy managed
- Surgical prophylaxis?

Decision based on severity of disease, type and site of bleeding and the minimal residual activity in the patients plasma. Also based on thrombosis risk

Fibrinogen (FI) deficiency

- Quantitative or qualitative deficiency /complete or partial
- Afibrinogenemia, hypofibrinogenemia – quantitative
- Dysfibrinogemia, hypodysfibrinogenemia – qualitative +/- quantitative
- Afibrinogenemia may have severe bleeding tendency (umbilical cord bleeding in 85%/skin, GI, GU or CNS bleeding, menorrhagia, first trimester abortions, post partum bleeding) Prophylactic treatment appears to be necessary for successful pregnancy – aim to maintain fibrinogen levels > 1 g/L and >1.5 g/L for labour). Fibrinogen concentrate the treatment of choice. Twice weekly dosing.
- Risks of thrombosis particularly with dysfibrinogenemia but also afibrinogenemia. In pregnant women with history of thrombosis or risk factors for VTE need to consider prophylaxis with LMW heparin in postpartum period if using replacement therapy.
- Surgical prophylaxis depends of major/minor procedure – but recommendations to keep fibrinogen level > 1.5 major/1.0 minor with varying durations of up to 2 weeks.

Prothrombin (FII) deficiency

- The rarest bleeding disorder
- Hypoprothrombinemia (activity and antigen levels low) and Dysprothrombinemia (dysfunctional protein produced)
- Complete FII deficiency incompatible with life
- Those with activity levels below 10% (homozygotes) have severe bleeding (joint, gut, intracerebral, gynaecological)
- Activity levels above 20% usually do not require replacement Rx
- Heterozygotes usually asymptomatic
- Prothrombin complex concentrates or FFP utilised. (NB risks of thrombosis with dysfunctional protein and risk of volume overload with FFP)
- Data about dosing and dosing intervals based on case reports - with prophylaxis recommended for those with history of severe bleeding and, for those with levels below 20%, the management of labour

Factor V deficiency

- Factor V is synthesised by hepatocytes (liver cells) and megakaryocytes (platelet precursor cells) and circulates in the plasma and is also **stored in platelets** (in α-granules)
- Most have reduced activity **and** antigen levels (type 1) but some have production of a **dysfunctional** protein (type2)
- Frequent symptoms are epistaxis and menorrhagia but joint and muscle bleeds can occur
- Life threatening bleeding is rare
- Bleeding tendency does **not** correlate well with the level
- Use FFP and/or platelet transfusion (specific concentrate is in development – super FVa)
- Limited information re management of pregnancy/labour – some use prophylactic FFP to maintain FV levels > 15%
- Similar guidelines for surgical prophylaxis – maintain levels > 15% for major procedures (often requires 12 hourly FFP dosing)

Combined FV and FVIII deficiency

- 2 types have been identified - with mutations which affect the intracellular transport of both factors
  - *So interestingly **NOT a deficiency** of factors but a **defect in transportation** that affects the levels of these 2 factors*
- Most frequent symptoms are easy bruising, epistaxis and dental bleeding
- Menorrhagia and post partum bleeding also
- More severe bleeding unusual so prophylaxis rarely required
- FVIII levels increase during pregnancy – not so FV – so bleeding manifestations at this time usually secondary to FV deficiency.
- Factor V can only be replaced by FFP/platelets
- Factor VIII – many options

Factor VII deficiency

- FVII is the most common rare bleeding disorder
- Symptom severity varies with poor correlation with plasma levels reported (except when levels are very low)
- Incidence of CNS bleeding reasonably high ?16%
- Epistaxis and menorrhagia are the most frequent symptoms
- Need for prophylaxis based on clinical bleeding phenotype
- Management with recombinant VIIa can be effective at low doses and with unusual efficacy given short half life.
- Interest in enhanced half life products and gene therapy.
- FVII levels increase during pregnancy but **not** in those severely deficient
- Surgical prophylaxis recommended – similarity to haem A with inhibitor

Factor X deficiency

- One of the more severe bleeding disorders
- Often have bleeding symptoms early in life (umbi stump, CNS or GI bleeding, haemarthroses.
- Strong association between levels and clinical bleeding severity (comparable to haemophilia)
- Long term prophylaxis and surgical prophylaxis recommended for those with severe bleeding symptoms
- Although FX levels increase in pregnancy, adverse outcomes (miscarriage, placental abruption, prem labour, post partum haemorrhage) are more frequent
- Management with FFP/PCC. There is a plasma derived FX concentrate (not in Australia)

Factor XI deficiency

- Deficiency or dysfunctional protein
- Ashkenazi Jews and French Basques have increased prevalence
- Unpredictable bleeding manifestations – and often relate to the site of injury. Sites with *high* fibrinolytic activity have *higher* risks of bleeding
- Menorrhagia common in females
- Risk of *thrombotic events* with use of FXI concentrates
- Antifibrinolytic agents very useful in these patients
- Surgical prophylaxis for patients with severe deficiency requires careful planning and thought – bleeding vs thrombotic risks. Consider site of surgery (high vs low fibrinolytic activity).

Factor XIII deficiency

- FXIII also known as fibrin stabilising factor – crosslinks fibrin, stabilising the clot against shear stress.
- Congenital disorders associated with high rates of morbidity and mortality. Acquired forms also occur.
- Umbilical cord bleeding, bruising, haematomas/muscle bleeds, delayed surgical bleeds/wound healing, recurrent miscarriage, CNS bleeds
- Not detected by routine clotting tests and factor assays
- Carriers often asymptomatic
- Regular prophylaxis advised in those who are affected because of the high risks of bleeding – fortnightly to monthly dosing due to long half life
- Successful pregnancy achieved with prophylaxis (only 9% achieved without prophylaxis)
- Surgical prophylaxis is essential
- Plasma derived and recombinant forms of FXIII available (also FFP)

Summary

- Rare bleeding disorders need to be considered as separate entities.
- More specific information is required about levels required for haemostasis, management of pregnancy and surgery - and levels to be achieved will be different for each bleeding disorder
- Age specific reference ranges need to be developed along with standardisation of factor assays
- Specific replacement therapy is required for some disorders
- Some of the novel therapeutics developed for the management of haemophilia may have applications in these disorders (including gene therapy)
- Importance of databases/registries collecting information about molecular genetics, phenotype, pregnancy outcomes, surgical outcomes


Confusion
is a
Prelude
to
Clarity