Coagulopathy Case 1

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CLINICAL HISTORY

• A 4 year-old boy presented with a marked bruising tendency of the arms and legs. His mother mentioned that the bruising typically appeared without injury.

• Past medical history revealed that at 3 years of age the patient had an episode of epistaxis that required transfusion of one unit of blood.
• There was a family history of bleeding on the maternal side of the family. The patient’s mother and maternal grandmother had abnormal bleeding characterized by recurrent epistaxis and menorrhagia. The patient’s mother was transfused with 5 units of blood at the time of his delivery.

• The patient was on no medication at the time of evaluation.
• Physical examination revealed multiple ecchymoses over the extremities.
SCREENING COAGULATION LABORATORY RESULTS

- PT = 10 sec (Normal 8-14.6)
- aPTT = 37 sec (Normal 24-34.5)
- Plt = 250,000 /μL (Normal 130,000-350,000)
Coagulation cascade

**INTRINSIC**
(surface contact)

F XII → F XIIa

HMWK

KAL

F XI → F Xla

**EXTRINSIC**
(tissue damage)

F VII

Tissue factor

F VIIa

F X

F Va + PF-3

F VIIIa + PF-3

Prothrombin (F II)

Fibrinogen (F I)

Thrombin (F IIa)

Fibrin
Differential diagnosis for prolonged PTT

Mixing aPTT
- not corrected
  - Inhibitor
    - F IX low
      - Hemophilia, vWD
    - F VIII low
  - corrected
    - F VIII, F IX
      - F VIII and F IX normal
      - F XI, F XII, HMWK, Prekal
Further test results

• FVIII = 20% (ref 50-150%)
• vWF:Ag = 18% (ref 50-150%)
• vWF:RCo = 15% (ref 50-150%)
DIAGNOSIS

• von Willebrand Disease
Introduction

• Disorder of primary hemostasis first described in 1926 by Professor Erik von Willebrand: severe mucocutaneous bleeding in a 5 yr old Finnish girl from the Åland Islands; 4 sisters with hemorrhagic deaths before the age of 4; patient died at 13 with her 4th menstrual period

• 1971: the deficient protein was discovered and termed factor VIII-related antigen because it co-purified with factor VIII (FVIII)

• 1976: Zimmerman recognized FVIIIIR:Ag to be a distinct molecular entity and renamed it vWF protein

• Most common inherited disorder of bleeding in humans with an estimated prevalence of 1-3%
• vWD: associated with quantitative and/or qualitative defects of the vWF protein primarily and by deficiency of factor VIII coagulant activity secondarily
• Most types are inherited in a autosomal dominant fashion – males and females, all ethnic groups equally affected
• More than 100 mutations (chromosome 12) in many subtypes of VWD have been described
von Willebrand Factor

-Synthesized in endothelial cells and megakaryocytes

-vWF stored in Weibel-Palade bodies of endothelial cells & alpha granules of meggs/platelets

-vWF levels is higher in:
(a) African Americans, about 15% higher
(b) Chronic inflammation, acute infection, acute trauma
(c) Pregnancy, oral estrogen replacement, or oral contraceptive use
(d) Age, diabetes
(e) Malignancy, stress
(f) Surgery, exercise
vWF Function

ADHESION

PLATELET

GPIb

von Willebrand Factor

Endothelial Cells

Collagen

Glycosaminoglycans

AGGREGATION

PLATELET

GPIb

von Willebrand Factor

GPIIb/IIa

GPIIb/IIa

Symptoms

• Spectrum of clinical severity - many are subclinical
• Recurrent mucocutaneous bleeding, often spontaneous (menorrhagia, epistaxis, gingival bleeding, gastrointestinal/genitourinary bleeding)
• Excessive bleeding from wounds, bleeding following minor trauma, excessive bruising
• Do not have intramuscular or deep subcutaneous bleeding or hemarthroses
• All in the setting of normal platelet count
Type I

- Most common, 75-80% are Type I
- Autosomal-dominant with variable expressivity
- Clinical symptoms usually mild to moderate, sometimes asymptomatic
- Factor VIII activity (VIII:C), vWF antigen (vWF:Ag), and the ristocetin cofactor activity (vWF:RCoF) decreased proportionately
- Normal spectrum of multimers
- Mild cases respond to DDAVP (1-desamino-8-D-arginine vasopressin)
Type II

- Autosomal dominant
- Much less common with several variants
- Characterized by normal (or slightly-decreased) levels of dysfunctional protein
- Abnormal synthesis causing lack of larger multimers in plasma while retaining smaller multimers
Type IIA

- 10-12% of vWD patients
- Autosomal dominant
- Absence of **large** and **medium-sized** multimers in plasma
- Small multimers do not bind effectively to the GPIb receptor on platelets in the presence of ristocetin
- VIII:C ↓, vWF:Ag N/↓, vWF:RCoF ↓↓
- Clinical symptoms usually moderate to severe
- DDAVP ineffective
Type IIB

- 3-5% of vWD patients, much less common than Type IIA
- Autosomal dominant
- Absence of large multimers in plasma due to abnormally high affinity for platelet adhesion (via GP Ib) – creates secondary thrombocytopenia
- VIII:C N/↓, vWF:Ag N/↓, vWF:RCoF ↓↓
- Increased platelet aggregation with low conc of Ristocetin
- Adverse response to DDAVP due to release of abnormal large multimers
vWD: Types 2N (Rare)

• Also called vWD-Normandy and “autosomal hemophilia”

• 1%-2% of all vWD patients

• Results when a genetic defect prevents vWF from binding to FVIII, causing low level of F VIII

• vWF alleles:
  2N/2N (normal vWF level), or
  2N/vWD-type 1 (low vWF level)

• Often misdiagnosed as mild hemophilia A
vWD: Types 2M (Rare)

- Characterized by decreased binding to platelet GPIb
- 1%-2% of all vWD patients
- Autosomal dominant
- Normal multimeric pattern
Type III

- Rare (1-3% of vWD patients), very severe, autosomal recessive form
- Usually offspring of two parents with mild type I disease
- No detectable vWF or F VIII activity
- Severe & spontaneous mucosal bleeding, rarely with hemarthroses (similar to hemophilia)
- No response to DDAVP
Platelet Type (Pseudo) vWD

- Mutation in the GPIb gene that produces increased affinity of platelets to vWF
- Lack of large multimers secondary to clearance by platelet binding
- Clinical presentation and laboratory results are similar to those of Type IIB
Acquired vWD

- Extremely rare, fewer than 100 well-documented cases
- IgG autoantibodies to the VIII:vWF complex or absorption by malignant cells (e.g. essential thrombocythemia)
- Associated with immunologic disorders (lymphoma, SLE, MM, myeloproliferative neoplasm, benign monoclonal gammopathy), medications (valproate, ciprofloxacin),
- Inhibitors to vWF may develop following replacement therapy
- Treat the underlying disorder (i.e. corticosteroid therapy or chemotherapy/radiation), as well as acute symptoms of bleeding
<table>
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<th>Parameter</th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 3</th>
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Ristocetin Cofactor (VWF:RCo)

- Ristocetin (ristomycin) is an antibiotic from the vancomycin group, which is active against gram positive bacteria and mycobacteria. It was introduced for clinical use in 1956-7 and removed from use in 1960.
- VWF:RCo: quantitative assay that determines VWF function (activity) in patient’s plasma.
- A log-log relationship exists between degree of ristocetin-induced platelet aggregation of formalin-fixed platelets and concentration of VWF in patient’s plasma.
Normal tracing using platelet rich plasma (PRP)
vWF:RCo Standard Curve

Tan(α)

0.0 0.25 0.50 0.75 1.0

25 50 75 100 vWF:RCo (%)
Multimer analysis
Special testing for vWD-N and pseudo-vWD

- vWD-N: FVIII-vWF binding assay
- Pseudo-vWD: patients’ platelets will aggregate with cryoprecipitate (containing normal vWF)
Treatment

- **Type I** – DDAVP (1-desamino-8-D-arginine vasopressin), Stimate™- given intranasally or intravenously, 0.3 ug/kg BW over 30 min) usually sufficient for transient control of bleeding for minor surgical procedures. For severe cases, use vWF/FVIII Concentrates (Humate-P, half-life 12 hrs)
- **Type 2A** – vWF/FVIII Concentrates
- **Type 2B** – vWF/FVIII Concentrates, DDAVP contraindicated
- **Type 2N** - vWF/FVIII Concentrates
- **Type 3** – vWF/FVIII Concentrates
- **Pseudo vWD**- platelet concentrates
FVIII/vWF dosing

• Loading dose of 50-75 IU/kg body weight
• Then, 40-60 IU/kg body weight every 8-12 hours for 3 days
• Then, 40-60 IU/kg body weight daily for 7 days
Targeted levels for bleeding patient

- FVIII: 50%-100%
- vWF:RCo: 50%-100%

- Note that cryoprecipitate should not be used (infection risk) if vWF/FVIII concentrates are available