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PEARLS OF LABORATORY MEDICINE

von Willebrand Disease

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von Willebrand factor (vWF)

- Multimeric protein that mediates adhesion of platelets at sites of vascular injury
  - Collagen
  - Platelet glycoprotein Ib (GP1b) receptor
  - High-molecular-weight (HMW) multimers are more effective at binding platelets
- Carrier for coagulation factor VIII (FVIII)

von Willebrand disease (vWD)

- Deficiency (quantitative) and/or dysfunction (qualitative) of vWF
- Results in defective platelet adhesion and mucocutaneous bleeding pattern
- One of the most common inherited bleeding disorders
  - Usually autosomal dominant
- Rare acquired cases

vWD etiology

- Decreased production
- Abnormal secretion
- Increased degradation
- Abnormal multimeric pattern
- Abnormal platelet binding
- Abnormal collagen binding
- Abnormal FVIII binding

Quantitative: types 1and 3

Qualitative: type 2 subtypes

Initial hemostasis evaluation

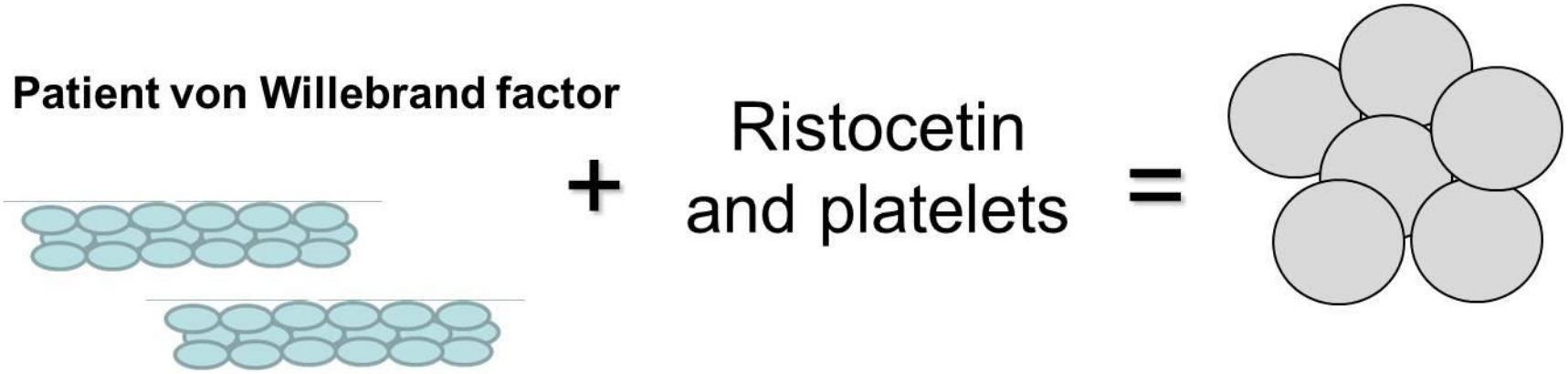
Test	Result in vWD
Platelet count	Usually normal
Prothrombin time (PT)	Normal
Activated partial thromboplastin time (aPTT)	Abnormal in severe vWD, often normal in mild/moderate vWD
Platelet function tests	Abnormal in severe vWD, often normal in mild/moderate vWD

Initial vWD evaluation

Test	Methodology
von Willebrand factor antigen (vWF:Ag)	Immunoassay
von Willebrand factor activity (Ristocetin cofactor activity, vWF:RCo)	Platelet agglutination
Factor VIII activity	Clot-based (aPTT)
Multimeric analysis	Gel electrophoresis; used for vWD subtyping; shows presence and relative concentration of various sizes of multimers

vWF:RCo

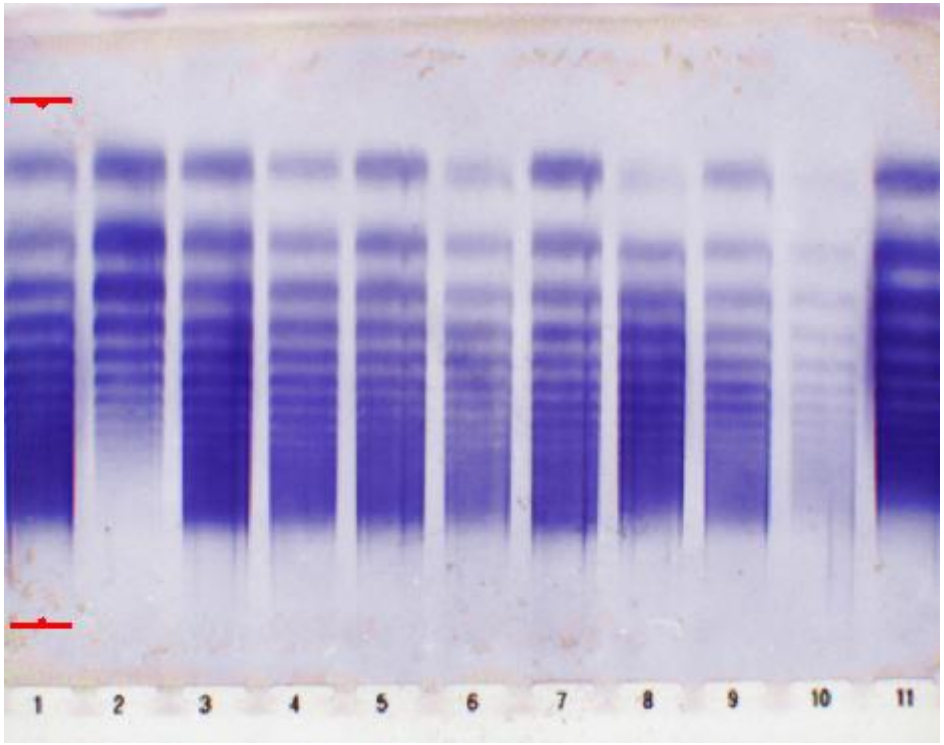
- Platelet agglutination method
  - Ristocetin causes patient HMW vWF to bind and agglutinate reagent platelets, decreasing turbidity



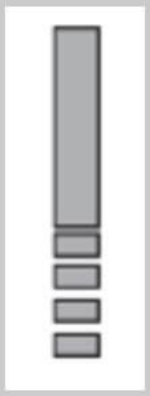
Multimeric analysis

LMW multimers

HMW multimers



Type 1

Test	Result
vWF:Ag	Decreased (variable severity)
vWF:RCo	Decrease proportionate to vWF:Ag
RCo:Ag Ratio	Normal (close to 1)
FVIII	Normal or decreased
Multimer Example: Normal multimer 	Normal 

Type 3

Test	Result
vWF:Ag	Absent
vWF:RCo	Absent
FVIII	<10% of normal
Multimer	Absent

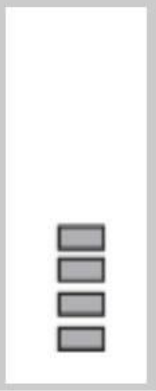
Type 2 subtypes

- Qualitative (protein functions abnormally)
- Mutations affect interaction with ligands
  - Missing large multimers (HMW and/or IMW)
    - 2A, 2B, platelet-type
  - Decreased platelet or collagen binding
    - 2M
  - Decreased FVIII binding
    - 2N

Type 2 – use of activity to antigen ratio

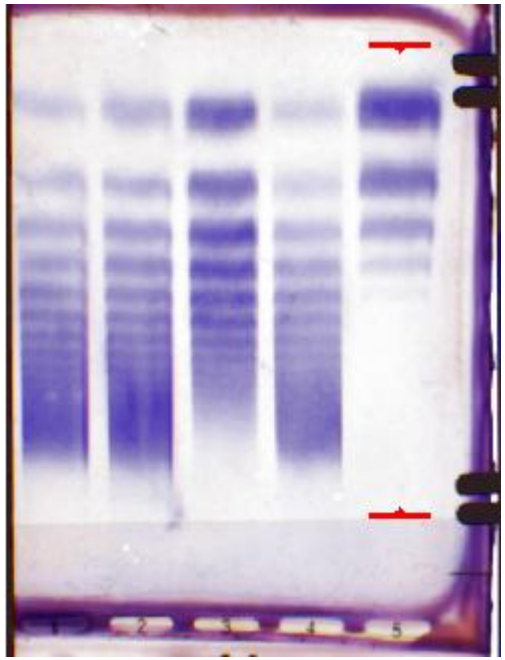
- Majority of type 2 cases (except 2N, some cases of 2M) demonstrate decreased platelet binding activity
  - Missing large multimers
  - Loss of function mutation affecting platelet binding domain
- Results in decreased activity:antigen ratio (such as RCo:Ag ratio) (< 0.5 - 0.7)

Example: Type 2A

Test	Result
vWF:Ag	Mild decrease
vWF:RCo	Moderate to severe decrease
RCo:Ag Ratio	Decreased
FVIII	Normal or decreased
Multimer Example: Normal multimer 	Missing HMW and IMW multimers 

Example: Type 2A

Test	Result	Reference Interval
vWF:Ag	46%	52-214%
vWF:Rco	<10%	51-215%
Rco:Ag Ratio	<0.2	>0.5
FVIII	60%	56-191%
Multimer	HMW/IMW multimers absent	Normal



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