Hemophilia A, Hemophilia B, Congenital von Willebrand Disease, and Acquired von Willebrand Syndrome

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Hemophilia A

Hemophilia A is a X-linked disorder due to congenital deficiency of factor VIII (FVIII). The frequency of Hemophilia is estimated to be approximately 1/5000 male births across ethnic group. The degree of bleeding severity with rare exception is directly related to patient's baseline FVIII level and can range from mild to life-threatening [3]. Although Hemophilia A affects mostly male, in rare occasion the disease can manifest in female via chromosome lionization [4–6]. In addition, approximately 30 % of Kemophilia A can present as de-novo mutation. Therefore, diagnosis of Hemophilia A should be considered even in the absence of a strong family history [7–9].

Factor VIII Protein

Unlike most other plasma coagulation proteins, which are produced by hepatocytes, FVIII is mainly produced by liver endothelial cells [10, 11]. This is likely the reason for elevated FVIII even under liver failure.

Factor VIII protein is produced as a six-domain protein, A1-A2-B-A3-C1-C2 [12–14]. In the Golgi compartment, FVIII is cleaved within the B domain to form the mature FVIII heterodimer that consists of the 200 kDa A1-A2-B heavy chain and the 80 kDa A3-C1-C2 light chain [15]. Once FVIII is released into circulation, it binds to von Willebrand factor (VWF) which serves to increase FVIII survival and regulate FVIII activity. Upon activation by thrombin, FVIIIa serves as a co-factor for Factor IXa in the activation of factor X to factor Xa and ultimately generation of thrombin [15–18]. Hemophilia A has been linked to a variety of well-known molecular mutations including inversions, large deletion, frameshift, nonsense, and missense defects [19, 20]. The severity of the disease can often be predicted by the site and type of mutation in the FVIII gene [21–24].

Diagnosis of Hemophilia A

The diagnosis of Hemophilia A begins in recognizing the X-linked inheritance pattern of an unexplained and isolated prolongation of PTT that is corrected in mixing study [25]. Subsequent laboratory workup should then identify a FVIII deficiency. However, it is important to note that an initial finding of an isolated prolonged PTT with mixing study correction does not immediately imply Hemophilia A [26]. Other PTT pathway factor deficiencies such as Factor IX (FIX) and Factor XI (FXI) deficiencies or even non-clinically significant Factor XII deficiencies will present with the same initial laboratory finding [27]. Therefore, it is important to order FIX and FXI along with FVIII to rule out other potential congenital bleeding disorders. Specifically important is to consider the von Willebrand disease (VWD), when considering the diagnosis of Hemophilia A, as carrier defect (Type 2N) or deficiency (Type 1 and 3) of VWF will result in decrease of FVIII. The diagnosis of these specific VWD will be discussed later in this chapter.

Severity of Hemophilia A is directly related to the degree of deficiency of FVIII activity as measured by one-stage assay, Mild Hemophilia is defined by FVIII activity between 5 snd 40 %, moderate disease is activity 1–5 %, while severe Hemophilia is below 1 %. Although FVIII activity via one-stage assay in general can predict bleeding phenotype, in very rare situation, there can be discrepant clinical bleeding symptoms with FVIII activity via one-stage assay. In such scenario, a two-stage FVIII assay may be used to better define patient's disease [28, 29].

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Hemophilia B

Like Hemophilia A, Hemophilia B is also a X-linked bleeding disorder affecting around 1 in 25,000 male births. In Hemophilia B, factor IX (FIX) is deficient which results in lifelong bleeding symptoms. The severity of bleeding is directly related to the degree of FIX deficiency. Approximately, one third of all cases arise from spontaneous mutation [30]. Therefore, like Hemophilia A, a lack of family history does not exclude the diagnosis.

Factor IX Protein

FIX protein is a 57 kDa multi-domain protein produced in the liver by hepatocyte. FIX is a vitamin K-dependent protein, requiring gamma-carboxyglutamation to be fully functional. FIX can be activated into FIXa via the intrinsic pathway by FXIa or the extrinsic pathway by tissue factor and FVIIa [31]. FIXa in the presence of calcium, FVIIIa, and phospholipids in turn activates FX into FXa and ultimately thrombin. Hemophilia B has been linked to a number of mutations, especially frameshift, missense, or nonsense mutations within the CpG dinucleotide mutation hotspot. Large and short deletions and insertions complete the genetic mutation profile for Hemophilia B [30].

Diagnosis

A deficiency in FIX may indicate vitamin K deficiency instead of Hemophilia B, especially in neonates [32]. Since FVII is also a vitamin K-dependent factor, an isolated prolonged PTT without prolongation of PT makes Hemophilia B likely as half-life of FVII is shorter than FIX. Like FVIII in Hemophilia A, severity of Hemophilia B is directly related to the degree of deficiency of FIX activity. Mild Hemophilia B is defined by FIX activity between 5 and 40 %, moderate disease is activity 1–5 %, while severe Hemophilia B is below 1 %.

Congenital von Willebrand Disease

VWD remains the most common congenital bleeding disease worldwide across all ethnic groups. Unlike Hemophilia, VWD is an autosomal disorder; therefore it affects both sexes equally and this inheritance pattern helps to distinguish it from Hemophilia A. Bleeding characteristics and severity are greatly affected by its subtypes and can range from joint and muscle bleeding (Type 3) to menorrhagia to mild oral and mucosal bleeding [33, 34]. Due to the variation of clinical presentation, a complete and accurate laboratory workup is important for the subtyping of VWD [35]. The laboratory workup for VWD will be discussed in detail in Chapter XX.

von Willebrand Factor

Unlike most other coagulation proteins, VWF is not produced by the liver which also helps to explain elevated FVIII and increased thrombotic risk in the setting of liver dysfunction. VWF is produced by both megakarocytes and endothelial cells (Fig. 7.1) as a 2813 amino acid long prepropeptide (Fig. 7.2) in the endoplasmic reticulum, which is then dimerized into 800kD dimers. These dimers are then polymerized into mature VWF multimers up to 20,000kD in length and VWF propeptide dimmers (VWF:pp) are cleaved from the mature multimers as they travel through the golgi. Finally, both the mature VWF and VWF:pp are packaged and stored in Weibel–Palade body of endothelial cells or alpha granules of platelets. Upon activation, mature VWF and VWD:pp are released from storage into circulation; once released, VWF multimers are cleaved at specific site in the A2 domain into multimers of variable sizes by a metalloprotease, ADAMTS13 [36–38]. Under normal physiological condition, VWF exists as large, intermediate and low molecular weight multimers in a balanced distribution. However, when this normal size distribution is disturbed, it will result in disease conditions such as thrombotic thrombocytopenic purpura when there is ultra large multimers [39] or bleeding when there is absence or decrease in large multimers [40].

Circulating VWF plays an important role in both primary and secondary hemostasis. In primary hemostasis, VWF serves to support platelet adhesion to the site of vascular injury via binding to sub-endothelial collagen and to glycoprotein Ib-V-X complex (GPIb) on platelet surface. This interaction is important in recruiting and activating platelets at site of vascular injury [41]. In terms of secondary hemostasis, VWF serves as a carrier protein for FVIII, which both protects FVIII from proteolysis and localizes FVIII to platelet surface [42, 43].

von Willebrand Disease

As discussed previously, VWD can present with widely different bleeding phenotypes depending on the underlying pathophysiology. In general, VWD (Table 7.1) can be broadly divided into two types of VWF defects, quantitative (type 1 and type 3) and qualitative (type 2). It is important to

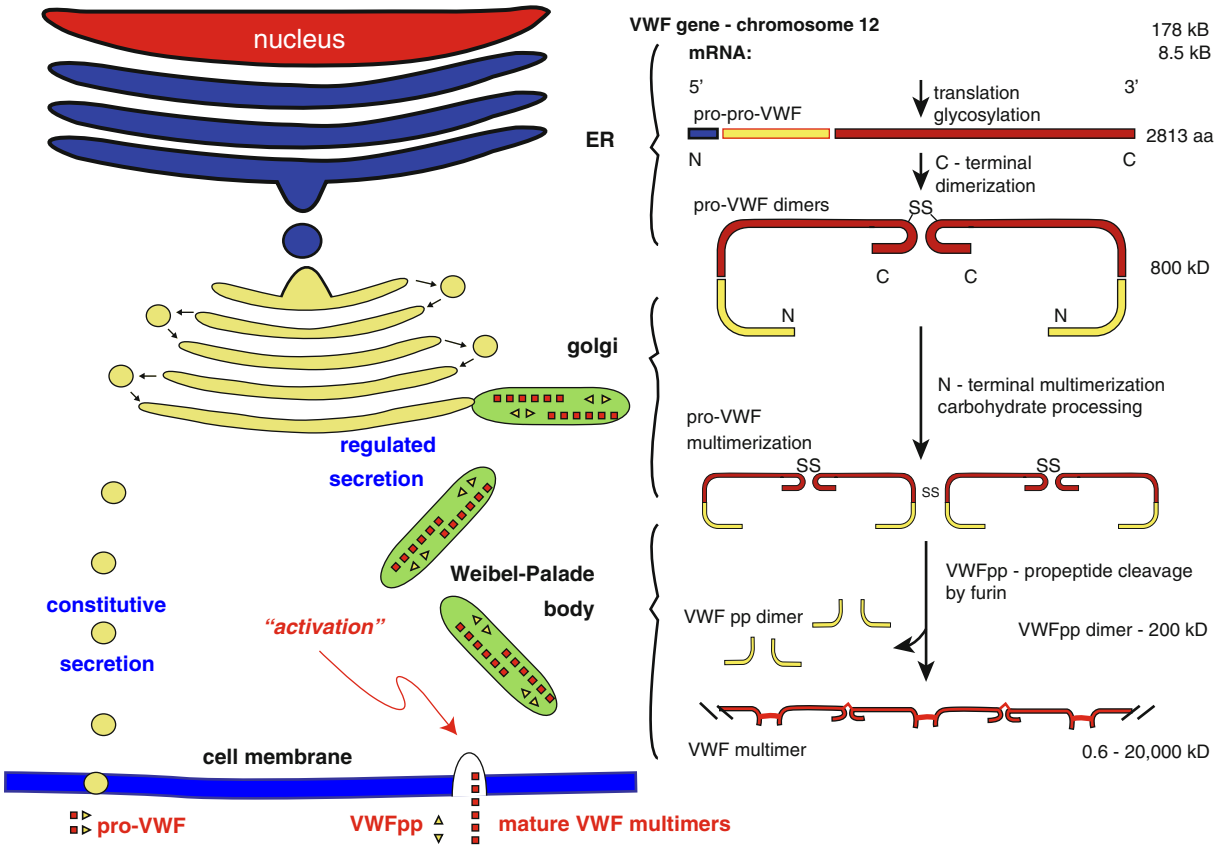

Fig. 7.1 demonstrates the production of VWF multimers in endothelial cells. Matured VWF and propeptide are stored within Weibel-Palade bodies ready for release upon activations. From Haberichter SL, Regulated release of VWF and FVII and the biologic implications, Pediatr Blood Cancer, 2006 May 1: 46(5):547–53

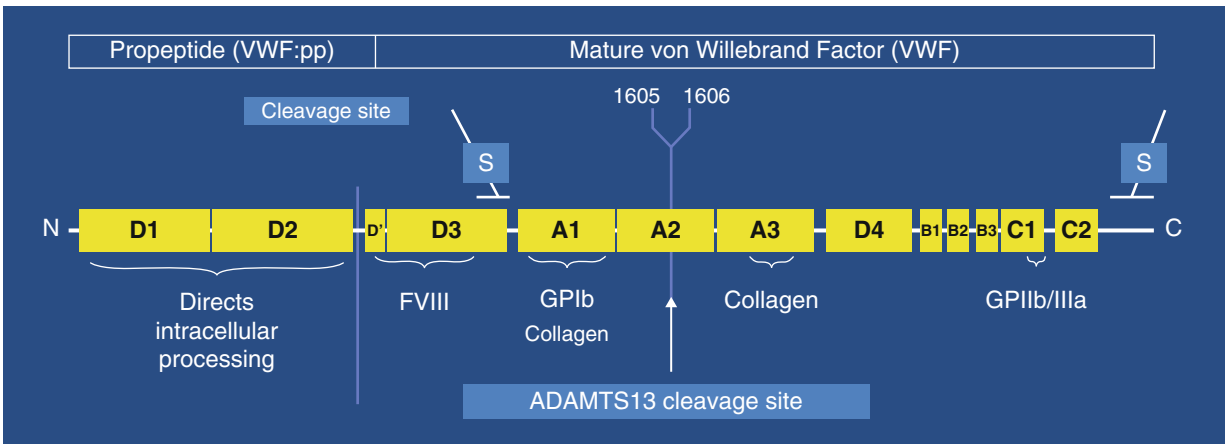

Fig. 7.2 showed the various known VWF domains and their respective contributions to the VWF function

Table 7.1 Various VWD subtypes and their expected laboratory findings

Condition	VWF:Act	VWF:Ag	FVIII	VWF:Act/Ag	VWF:MA
Type 1	<30	<30	L to N	>0.7	Normal but light
Type 2A	<30	<30–200	L to N	<0.7	Missing large multimer
Type 2B/PT-VWD	<30	<30–200	L to N	<0.7	
Type 2M	<30	<30–200	L to N	<0.7	Normal
Type 2N	30–200	30–200	Significantly lower	>0.7	Normal
Type 3	<3	<3	<10	–	–
"Low VWF"	30–50	30–50	Normal	>0.7	Normal
Normal	50–200	50–200	Normal	>0.7	Normal

distinguish the various subtypes of VWD via an algorithmic laboratory approach, as it can greatly impact the management of the patient. Various laboratory workups and algorithm is found in details in Chapter **.

Type 1 VWD

Type 1 VWD account for the majority of VWD (80 %). It is a quantitative defect defined as either VWF antigen (VWF:Ag) or VWF activity (VWF:Act) between 1 and 30 % without any observable VWF function defects that VWF activity to antigen ratio (VWF:Act/Ag) should be >0.5–0.7 [44]. In addition, VWF multimer analysis (VWF:MA) should show a normal size distribution with decreased intensity. Mechanism for type 1 VWD is due to decreased synthesis of VWF; however, type 1 variants (type 1C and type 1 Vicenza) have been shown to have increased clearance and decreased VWF half-life. It is important to rule out such type 1 variants as desmopressin treatment will not be an effective treatment as the therapy yield only short-lasting effect [45]. In both type 1C VWD and type 1 Vicenza, desmopressin challenge is expected to show good 1 h post-administration response with a decreased 4 h post-administration response [46]. Compared to other type 1 VWD, VWF propeptide to antigen ratio (VWF:pp/Ag) is increased, which is the defining characteristic of these type 1 variants [47]. It is important to note that FVIII in type 1 VWD is proportionally decreased as VWF is a carrier protein for FVIII, thus VWD workup should be performed in initial diagnosis of Hemophilia A. Furthermore, Hemophilia A can coexist with other subtypes of VWD. Lastly, laboratory diagnosis of VWD is proven challenging as VWF is an acute phase protein. Since the level can be increased several folds from baseline, a one-time normal VWF:Ag and VWF:Act cannot definitively rule out type 1 VWD [48]. Furthermore, FVIII is not an effective marker for acute phase as its level is directly affected by VWF:Ag level. Concurrent fibrinogen level or C reactive protein level may be used as potential acute phase markers, but neither of them has been universally validated. Until a better marker can be established, the most effective method to distinguish acute phase from baseline study remains to be repeat testing.

Low VWF

It is important to discuss "Low VWF" in the discussion of quantitative type 1 and type 3 VWD. As normal VWF:Ag and VWF:Act level is usually defined as >50 % and type 1 VWD is <30 %, the gray-zone area between 30-50 % can be difficult to define [44]. This "in-between" VWF:Ag and VWF:Act can fall within type 1 VWD in European region as type 1 VWD is defined as <45 % [49]. However, in the United States, type 1 VWD is strictly reserved for patient with VWF:Ag or VWF:Act <30 % without functional defects. Hence, individuals with repeat VWF level between 30 and 50 % should be considered as having "low VWF" and not VWD. Of note, blood group O individuals are more likely to have "low VWF' than other blood groups [50], which may be related to post-translational modification [51]. Individuals with "low VWF" should be made aware of increased risk for bleeding, but should not be considered as having true VWD.

Type 3 VWD

Type 3 VWD accounts for less than 1 % of VWD. It is a severe quantitative defect defined as absence (<1 %) of both VWF:Ag and VWF:Act [44]. As FVIII level can fall within moderate Hemophilia A range, it is important to rule out type 3 VWD.

Type 2A VWD

Type 2A VWD accounts for approximately 10 % of all VWD. It is characterized by the absence of both high and intermediate molecular weight VWF secondary to decreased synthesis or increased proteolysis by ADAMTS13 [44]. Therefore, laboratory workup demonstrates a qualitative defect of decreased VWF:Act but relatively normal VWF:Ag, which results in decreased VWF:Act/Ag ratio at <0.5–0.7. Of note, unlike type 2B VWD, mild thrombocytopenia is not an expected finding. Type 2A VWD is often considered as a diagnosis of exclusion.

Type 2B VWD

Type 2B VWD accounts for approximately 3-5 % of all VWD. Although its laboratory finding is similar to type 2A VWD with decreased VWF:Act/Ag ratio and loss of high molecular weight multimer, the mechanism for disease is entirely different [44]. Type 2B VWD is due to gain of function mutation in the platelet GPIb binding to A1 domain of the VWF protein, which results in increased and spontaneous binding of VWF to platelets without shear stress [52]. This abnormal interaction results in loss of both high molecular weight VWF and platelets, which explains the pathognomonic findings of thrombocytopenia in type 2B VWD. This gain of function mutation makes desmopressin a contraindication for type 2B VWD as it may result in thrombotic complications. Therefore, it is important to distinguish type 2B from other type 2 VWD; ristocetin-induced platelet aggregation study (RIPA) is only abnormal in gain-of-function VWD which includes Type 2B VWD.

Pseudo-VWD/Platelet-type VWD

As in type 2B VWD, the pathogenesis of platelet-type VWD (PT-VWD) is due to abnormal spontaneous interaction between platelet GPIb and VWF [44]. However, in contrast to type 2B VWD, the gain of function mutation is in the platelet GPIb receptor [53]. Overall, initial laboratory workup is indistinguishable from type 2B VWD, including decreased VWF:Act/Ag, loss of high molecular VWF, thrombocytopenia, and even abnormal RIPA. Specialized laboratory test, 2B binding assay can be used to differentiate PT-VWD from type 2B VWD. As in type 2B VWD, desmopressin is contraindicated for treatment of PT-VWD.

Type 2M VWD

Type 2M VWD accounts for only 1–2 % of VWD. The initial laboratory workup, similar to type 2A, 2B or PT-VWD, showed decreased VWF:Act/Ag [44]. Like type 2B VWD, pathogenesis for type 2M VWD also lies in the A1 domain of VWF, but it is a loss-of-function mutation where the interaction between platelet GPIb receptor and VWF is decreased [54]. Therefore, multimer analysis for type 2M VWD is normal and does not demonstrate loss of high or intermediate molecular weight VWF. It is the presence of normal multimer distribution with decreased VWF:Act/Ag that makes up the defining laboratory characteristic of type 2M VWD.

Type 2N VWD

Type 2N VWD is qualitative VWF disorder that accounts for 1–2 % of all VWD [44]. However, its functional defect lies not in VWF function as a coagulation protein, but its FVIII carrier function. Mutations within the D' and D3 domain of VWF molecule render the binding of VWF to FVIII defective [55]. As the coagulation function of VWF is unaffected, the VWF laboratory workup is unremarkable at first glance; normal VWF:Ag, VWF:Act, VWF:Act/Ag, and even normal multimer analysis. However, FVIII activity can be decreased to as low as 5–15 %, making 2N VWD sometimes difficult to differentiate from Hemophilia A. The inheritance pattern of 2N VWD is autosomal in contrast to X-linked in Hemophilia A. FVIII binding assay (Discuss in Chapter **) can be used to distinguish type 2N VWD from Hemophilia A. It is important to note that like other VWD subtypes, 2N VWD can coexist in patients with Hemophilia A. Therefore, concurrent 2N VWD should always be considered and ruled out as it can affect patient's response to recombinant FVIII infusion.

Acquired von Willebrand Syndrome

Acquired von Willebrand Syndrome (aVWS) is a collection of acquired bleeding disorders (Table 7.2), secondary of loss of VWF quantitative or qualitative functions [56]. Dozens of diseases have been associated with aVWS; nonetheless, laboratory findings often mimic subtype of congenital VWD, especially type 2A VWD with decreased VWF:Act/Ag and loss of high to intermediate molecular weight VWF. The loss of high molecular weight VWF can be secondary to either pathological high shear stress as in aortic stenosis [57], presence of autoantibodies against VWF [58], or even direct absorption by tumor cells [59]. Less commonly, aVWS may result from decreased overall VWF production as opposed to selective loss of high molecular weight VWF as in the case of hypothyroidism [60]. Bleeding diathesis of aVWS may vary, but bleeding symptoms and VWF laboratory abnormalities usually resolve upon resolution of underlying disorders.

Management of Hemophilia A, Hemophilia B, and von Willebrand Disease for Invasive Procedure, Surgery, and Pregnancy

The management of patients with Hemophilia A, B, and VWD can be complex; however, there have been established recommended guidelines (Table 7.3) that can provide some important standard of care guidance in managing these patients

Table 7.2 Shows the various disorders that have been reported to be associated with aVWS

Underlying disorders	Previous literature, ISTH-SSC and German registry 1968–2011 ($n=1292$)	
Cardiovascular	*414*	*32 %*
Aortic stenosis	201	16 %
Cardiac assist device	110	9 %
AV septal defects	21	2 %
Myeloproliferative	*350*	*27 %*
Essential thrombocythemia	212	16 %
Polycythemia vera	88	7 %
CML and myelofibrosis	64	5 %
Lymphoproliferative	*321*	*25 %*
MGUS	193	15 %
MM and WMg	80	6 %
NHL, HCL, and ALCL	28	2 %
Systemic diseases (hepatitis C, cirrhosis, hypo-thyroid, hemoglobinopathies, uremia, diabetes)	*87*	*7 %*
Drugs (valproate, hydroxystarch, etc.)	*40*	*3 %*
Neoplasia	*32*	*2 %*
Immune	*21*	*2 %*

Table 7.3 Published recommendations for peri-operative management of Hemophilia A, B, and VWD patients

	Hemophilia A [61, 62]	Hemophilia B [61, 62]	von Willebrand disease [62]
Dental procedure	50–100 % prior + antifibrinolytic × 7–10 days post	50–100 % prior + antifibrinolytic × 7–10 days post	60 % prior
Surgery (minor)	80–100 % prior + >50 % × 5–7 days	80–100 % prior + >50 % × 5–7 days	60 % prior + >30 % × 2–4 days
Surgery (major)	80–100 % prior +	80–100 % prior +	100 % prior + >50 % × 5–10 days
	80–100 % × 1–3 days	80–100 % × 1–3 days	
	60–80 % × 4–6 days	60–80 % × 4–6 days	
	+40–60 % × 7–14 days	+40–60 % × 7–14 days	
Delivery	>50 % prior [64] × 3–4 days [63]	>50 % prior [64] × 3–4 days [63]	80–100 % prior + >30–50 % × 3–4 days, up to 2 weeks [63]

around time of procedures, surgeries, or deliveries. It is important to note that factor concentrates should be used in place of plasma products as replacement of choice since the concentration is much higher and infectious risk is significantly less. DDAVP may be used in patients with mild Hemophilia A, mild VWD, or Hemophilia A carrier in place of factor replacements; however, a trial should be performed to ensure effectiveness prior to use in surgerical settings. Antifibrinolytic may be used in conjunction with standard factor replacement [61]; however, this practice has not been well-standardized beyond dental procedure, but should be considered if risk is high or if replacement therapy alone is ineffective.

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