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FORUM

What can historical literature on von Willebrand disease teach us?

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Abstract

Dr Erik von Willebrand first described a family with bleeding symptoms in a Finnish publication in 1926. A closer look at this landmark publication sheds light on some pathophysiological aspects of von Willebrand disease that may be applicable even in the current era. We attempt to relay in this article how the teachings from this original description may provide a benchmark for further research in this condition.

KEYWORDS
bleeding, estrogen, history, von Willebrand disease

1 | INTRODUCTION

"Hereditär pseudohemofili," written in Swedish and published in Finska Läkaresällskapets Handlingar in 1926 by Dr Erik von Willebrand, changed the way we diagnose patients referred with bleeding symptoms [1]. Although he wrote further papers in German, which included a detailed summary of his first paper, an English translation as "Hereditary pseudohemophilia" by Professor Peter Wahlberg from Åland has helped us understand more about the intuitive, imaginative, and "consageous" nature of Dr von Willebrand [2–4]. Inga Marie Nilsson, in an accompanying commentary to the English translation, detailed "von Willebrand had *followed the literature of the day carefully*, and he knew the few *methods available at that time for investigation* of a patient with a haemorrhagic diathesis" [4].

2 | "FOLLOWING THE LITERATURE CAREFULLY"

Erik von Willebrand may be considered as someone who felt "standing on the shoulders of giants" as extremely important. He was clearly aware of the seminal work published in the decade before (1918) by Eduard Glanzmann, titled "Hereditare Hamorrhagische thrombasthenic. Ein Beitrag zur Pathologie der Blutplattchen" (Hereditary hemorrhagic thrombasthenia, A contribution to the pathology of blood platelets) in Jahrbuch der Kinderheilkunde (Yearbook of Pediatrics) [3,5]. Glanzmann had noted a close relationship between his cases and chronic Morbus Werlhof (currently known as immune thrombocytopenia) and considered the patients to be in a more severe state due to a hereditary constitutional defect in the thrombocyte system [3]. He, hence, gave the label "hereditary hemorrhagic thrombasthenia" to this new disease. [5]. In a similar manner, von Willebrand noted an analogy between the "bleeder cases from the islands" and those described by Glanzmann with respect to the course of disease, blood features, and mode of inheritance [3]. In addition to patients with Glanzmann thrombasthenia, von Willebrand attempted to compare his cases with those diagnosed with hemophilia, anaphylactoid purpura (previously known as Henoch–Schönlein purpura, now termed immunoglobulin A vasculitis), and chronic Morbus Werlhof. Based on a bleeding pattern similar to those with thrombasthenia, rather than hemophilia, he chose

to call the newly discovered condition "hereditary pseudohemophilia" [3]. This was based on the recommendations of E. Frank, who had just written an extensive treatise on hemorrhagic diatheses and suggested a completely new nosology rather than including them in a known group of hemorrhagic diatheses [3].

3 | "INVESTIGATIONS USING METHODS AVAILABLE AT THE TIME"

A connection between von Willebrand disease (VWD) and platelets (hereditary hemorrhagic thrombasthenia) or blood vessels (anaphylactoid purpura) rather than coagulation factors (hemophilia) was evident in the initial investigations conducted by von Willebrand [3]. He found the following results, which he tabulated along with the results of the other 3 hemorrhagic conditions described above: [3].

- Prolonged bleeding time, a measure of platelet function and vascular integrity.
- Normal clotting time, which was prolonged in hemophilia.
- Normal clot retraction, a process where outside-in signaling by platelet integrin αIIbβ3 orchestrates the contraction of the fibrin mesh, making the blood clot smaller [6]. Normal clot retraction may possibly occur in VWD since von Willebrand factor (VWF)–platelet interaction is not needed in this process.
- Positive capillary resistance test (Rumpel–Leede capillary fragility test or tourniquet test), which assesses the fragility of capillary walls [7].

These test results suggested a possible abnormality in platelet and vascular function in VWD. Von Willebrand put this conclusion quite elegantly as "The pathogenesis of the hemorrhages may in my opinion most easily be explained by a co-operation between these moments, i.e., a disturbed function of the thrombocytes and a general lesion of the capillary walls." [3]. Did other hematologists at the time come to a similar conclusion?

4 | OLDER STUDIES FOR DISTURBED PLATELET FUNCTION IN VWD

After hearing about the work of von Willebrand, Rudolf Jürgens, who had devised a capillary thrombometer along with Morawitz, tested the bleeding tendency of patients with VWD using his new device [8]. The thrombometer revealed a prolonged thrombosis time of up to 10 times the normal in some of these patients [9,10]. Jürgens concluded asthenic thrombocytes (platelet factor 3) as the causal agents of the pathogenesis of bleeding in these subjects [8]. In combination with the abnormal Rumpel–Leede test, which suggested a vascular defect, the condition was renamed "Willebrand-Jürgens" constitutional thrombopathy" (interestingly, the Willebrand-Jürgens-Syndrome was a terminology used as recently as 2001) [10,11]. Armand Quick, who is famous for introducing the prothrombin time test, described similar cases to von Willebrand and came up with the nomenclature "Minot-von Willebrand disease" or "pseudopathic purpura" based on his cases and an earlier description by Minot and Lee of a familial bleeding tendency resembling thrombocytopenia but with normal platelet count [9,12].

The existence of some platelet abnormality in VWD was suggested by 3 other observations: i) reduced platelet aggregation with adenosine diphosphate, ii) similar platelet counts in venous and capillary blood in VWD while in normal subjects, the count in capillary blood is lower, and iii) morphologically abnormal platelets when examined by an electron microscope [13,14]. Thus, von Willebrand's intuition of disturbed thrombocyte function in his patients and clinical similarity to Glanzmann thrombasthenia may have been right. How is all this relevant in the 21st century?

We now know how important VWF is in primary hemostasis for mediating platelet adhesion to damaged vascular subendothelium via glycoprotein Ib and the subsequent thrombus growth via glycoprotein IIb/IIIa to resist blood flow. It is also established that some patients with type 2B VWD have large platelets, which resemble that seen in patients with congenital thrombocytopathies [15,16]. More recently, some suggestions have been added into guidelines, and these state that patients with low VWF (borderline levels of VWF) should not be diagnosed with VWD but investigated for other reasons for bleeding, predominantly platelet function disorder [17,18]. The contribution of these other reasons for bleeding, even for VWD, needs additional exploration as bleeding phenotypes vary, even in type 3 VWD [19].

5 | OLDER STUDIES FOR DISTURBED VASCULAR FUNCTION IN VWD

Von Willebrand postulated a vascular problem in addition to platelet dysfunction in his patients. This vascular basis for VWD was given more thought by MacFarlane in 1941 [20]. Using microscopy work, he demonstrated irregularity and tortuosity of the nail bed capillaries and inadequate contraction on injury in these patients, which, according to him, explained the prolonged bleeding time [20]. In 1946, William Dameshek's group published a series of 11 patients who had increased bleeding time in the presence of a normal coagulation time and normal clot retraction and performed a literature search of 62 similar cases [21]. They concluded that these cases, all designated as pseudohemophilia, represent a particular disorder of the capillaries, in which capillary retractility following trauma may be inherently defective [21]. The terminology "hereditary capillary purpura" was suggested to avoid the "ill-defined" term "pseudohemophilia" by some researchers [22].

The vascular involvement in VWD soon took a different twist with the discovery of antihemophilic globulin (AHG) (factor VIII). In 1956, Erlandson et al. [23], based on the facts that the predominant laboratory finding in VWD is prolonged bleeding time and the AHG deficiency in their cases was less severe than in classical hemophilia, postulated the abnormality is in the vascular system. They performed capillary microscopy in their patients in 2 areas, the nail beds of the fingers and the bulbar conjunctivae, and found marked abnormalities in all cases [23].

This group went on to classify VWD into 2 types: "vascular hemophilia," manifesting the combined vascular defect and AHG deficiency, and "pseudohemophilia," manifesting only the vascular abnormality [23]. The association of a vascular defect with a deficiency of AHG was confirmed by other groups, which led to VWD being named "vascular hemophilia" (or "angiohemophilia") for a decade or 2. [23–25].

6 | CLINICAL EVIDENCE FOR VASCULAR DYSFUNCTION IN VWD

In the current era, we know more about the vascular effects of VWF. Qualitative or quantitative defects of VWF are associated with angiodysplasia in both congenital and acquired VWD [26]. Angiodysplasia in VWD occurs predominantly in the gastrointestinal tract and, more commonly, in type 2 and 3 VWD [27]. A search for pathophysiological mechanisms has demonstrated increased vascular endothelial growth factor–dependent angiogenesis and fragility of the neovessels in the experimental setting of deficient VWF [28]. Here, heparin/heparan binding domain in VWF A1 motif modifies local angiogenesis [29] and the bleeding phenotype. Another interesting clinical finding is the more than a coincidental concurrent diagnosis of hereditary hemorrhagic telangiectasia (HHT) in patients with VWD [30,31]. Both VWD and HHT show similarities in their presentation, with mucosal bleeding patterns affecting nasal passages and oral mucosa and gynecological bleeding being predominant.

7 | ESTROGEN, VASCULAR DYSFUNCTION, AND VWD

Estrogen therapy is clearly beneficial in those with heavy menstrual bleeding associated with both VWD and HHT. However, this hormonal therapy can also benefit troublesome epistaxis [32]. Pregnancy as well as exogenous estrogen use are well known to be associated with elevated levels of VWF (the so-called "gestational palliation effect") [33]. However, the clinical effects of estrogen therapy on ameliorating VWD symptoms may have been discovered by coincidence. Three women with type I VWD receiving estrogen for menopausal symptoms or contraception underwent major surgeries, such as lumbar disc laminectomy, cholecystectomy, and hysterectomy, with no excess bleeding even without cryoprecipitate or other blood component administration [34]. They had required blood products to stop bleeding from dental extractions or other surgical procedures prior to being on estrogen. Interestingly, angiodysplasia in VWD has also been treated with estrogen therapy, but more recently, the focus has been on targeting angiogenesis pathways using agents such as lenalidomide and bevacizumab [27,35–37]. Although estrogen can stimulate the release of VWF from endothelial cells, its effect in decreasing bleeding is independent of this effect and may be related more to its vasoprotective effect [38,39]. Vast research has targeted the understanding of the mechanisms by which estrogen improves endothelial function and promotes angiogenesis (summarized in a review [40]). In the current context, how are estrogen and vascular dysfunction connected with von Willebrand's original case description?

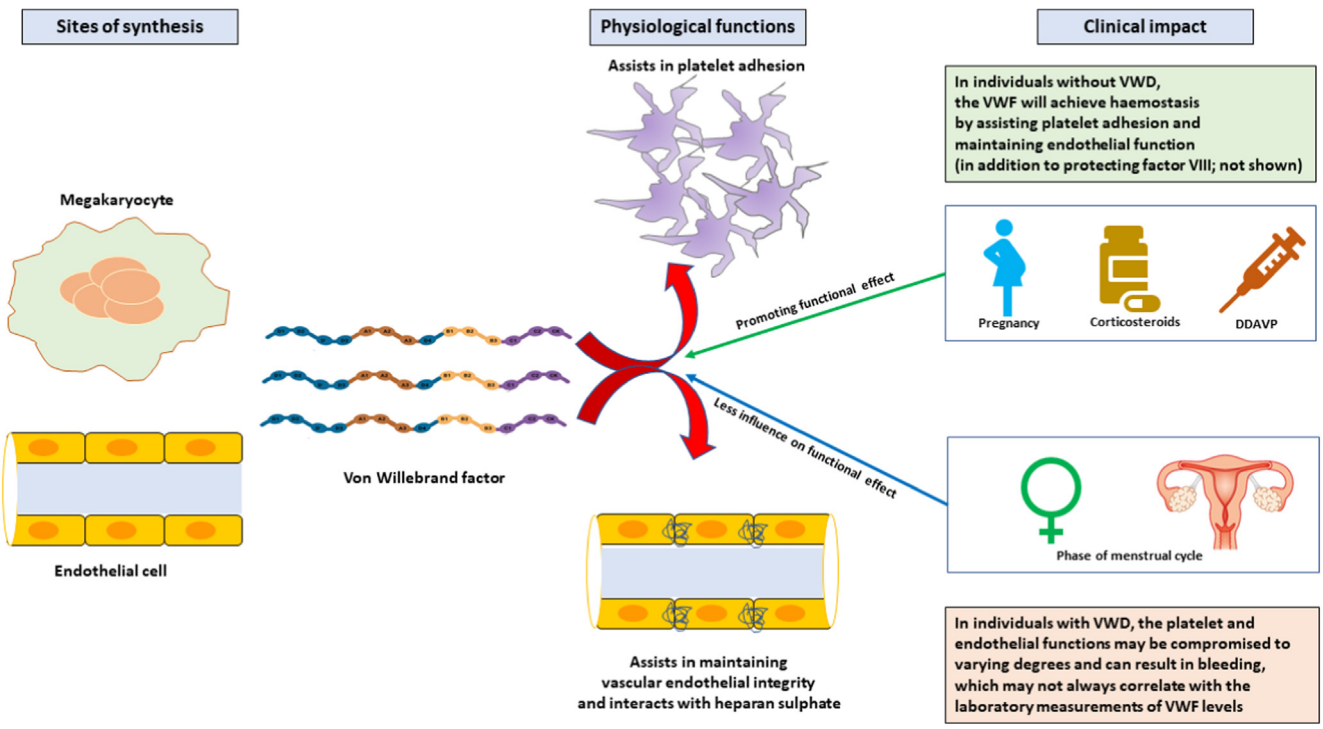

FIGURE Both megakaryocytes and endothelial cells release von Willebrand factor (VWF) into their vicinity and to the circulation. The released VWF affects platelets and vascular function in turn. These effects may be altered under physiological states like menstrual cycle and pregnancy but can also be modulated by hormonal therapies and desmopressin (DDAVP). In addition, endocrinological disorders like hypothyroidism may have an impact on the hemostatic system and vasculature. VWD, von Willebrand disease.

From an inheritance and epidemiology point of view, although VWD occurs with equal frequency among men and women, females are more often diagnosed with the condition, even from the times of its original description by Erik von Willebrand. In his Swedish paper, he recounted the 19 cases already described in the literature, including that of family I by Kehrer, whose paper was titled, "Die HaÈmophilie beim weiblichen Geschlechte'" (translated as "Hemophilia in the female sex") [3]. Von Willebrand correctly recognized this as being unlikely based on Nasse–Lossen's law, which states, "women never can become hemophiliacs," and considered these cases as certainly being due to the presence of earlier unknown disease [3]. In his detailed description of 66 members from the Åland islands, of the 23 patients, bleeding symptoms were more common among women, being observed in 16 of the 35 women examined but only in 7 of the 31 men [3]. Also, von Willebrand noted, "Within the Åland bleeder family, that five deaths from bleeding were known. They were all female bleeders." [3]. So why may VWD present more often and be more severe in women? Can there be an explanation other than women menstruate and give birth and thus are more likely to present with excess bleeding? One aspect is the recurrent and critical loss of red blood cells upon the already poor adhesive capacity to vascular wounds and collagen in VWD-impaired hemostasis [41]. But can sex-specific hormones play a role? It is well known that estrogen levels rise and fall twice during the menstrual cycle but drop precipitously after ovulation. It is possible that the vasoprotective effects of estrogen mitigate the vascular dysfunction in individuals with VWD, and for the same reason, relative deficiency of estrogen during certain periods of the menstrual cycle and in the postpartum period may impact bleeding symptoms in VWD. This postulate, however, requires further analysis. It is useful to note in this context that endometriosis, a condition where vascularized endometrial tissue grows outside the uterus, has been reported to be more frequent in women with VWD than in those without VWD [42].

8 | CONCLUSION

In summary, VWF produced by megakaryocytes and the endothelium function along with the platelets and vessel wall to coordinate the local hemostatic responses (Figure). von Willebrand knew about this platelet/vascular connection early on, as we can read and understand from his original paper. Several other eminent researchers have consolidated this finding with some elegant research in the following years, which are also detailed in this paper. The mere circulating VWF levels do not always reflect the bleeding phenotype of the patient. In this context, the following future approaches may be interesting:

- Examine how platelet function is impaired in the various types of VWD, including the contribution of blood flow and opening up of the platelet binding sites of VWF subjected to hemodynamic alterations, and how this may impact bleeding manifestations.
- Determine the degree of vascular dysfunction by clinical methods such as capillary microscopy and more targeted glycobiological, hemorheological [43], and vascular-specific tests to determine how much of the bleeding symptoms results from the reduced VWF impact on vascular function rather than VWF activity in isolation.
- Can we identify the risk of bleeding in those persons with low VWF based on their platelet/vascular effects?
- Does desmopressin (DDAVP), a derivative of vasopressin, work in certain types of VWD through its effect on platelets and the vasculature? Reports have already shown that DDAVP can induce the release of P-selectin, and endothelin-1 and impact platelet activation [44].
- Why is VWD more common in women? Do sex hormones play a role in the bleeding manifestations of VWD?
- How can we study the impact of estrogen on the platelet/vascular effects of VWF? Can estrogen be then considered as a treatment in settings where DDAVP may be contraindicated or VWF concentrates may be unavailable (eg, low-resource settings)?
- Similar effects to estrogen may be achievable by corticosteroids. The endothelial barrier protection function of corticosteroids may be exploited in VWD, similar to other conditions associated with bleeding, such as immune thrombocytopenia [45]. Corticosteroids are also known to elevate FVIII levels, which are associated with VWF in hemostasis [46].

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J.T. conceived the article and wrote the first draft. R.L. provided critical comments. Both authors approved the final submission.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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