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Von Willebrand disease: 80 year-old without wrinkles

Introduction

In 1926 Erik von Willebrand described a novel bleeding disorder in a large family from Foglo on the islands of Aland in the Gulf of Bothnia. At variance with the well known X-linked inheritance of Hemophilia, the epitome of inherited bleeding disorders, both sexes were equally affected, suggesting an autosomal pattern of inheritance. Mucosal bleeding was the dominant symptom, while hemarthrosis and muscle hematoma were rare. The latter finding, together with the observation of a prolonged bleeding time with normal platelet count, led von Willebrand to surmise a functional disorder of the platelets, associated with systemic lesion of the vessel wall, as the possible cause of the disorder. Only in the 50s, was it demonstrated that in these patients the prolonged bleeding time was associated with reduced FVIII, but we had to wait until the 70s to clarify that the deficiency of a new factor, called von Willebrand factor (VWF) and different from FVIII, was responsible for von Willebrand disease (VWD). Surprisingly, the reduction of this factor caused low FVIII, pointing to the strict relationships between the two factors. The cloning in the 80s of VWF gene has settled the basis to unravel the molecular

causes of the disorder. In his paper, Federici summarizes the milestones in the history of von Willebrand disease. Despite the fact that the history of the disorder dates back to 1926,¹ several questions about molecular genetics, diagnostic criteria, laboratory methodology and clinical history remained and only recently important insights have been provided by relevant publications about these issues.

The bleeding tendency of VWD: from estimation to diagnostic utility

As reported by Federici, at least three major reports have contributed in the past in defining the main clinical features of patients with VWD. Until recently, however, no quantitative description of bleeding symptoms in VWD was available. This represents a diagnostic problem, since normal subjects may self-refer hemorrhagic symptoms quite frequently (Table 1)^{2,3} and thus discriminating between a significant bleeding history and trivial symptoms could help in designing a *risk profile* for VWD. The number and the perceived severity of symptoms, as reported by the patient, may be influenced by his/her education, family background (e.g., some symptoms may be underreported

by subjects belonging to a bleeding family) and personality, but also by the type of data ascertainment. For instance, using a self-reported questionnaire, Friberg *et al.* found that as much as 23% of Swedish girls reported three or more hemorrhagic symptoms.⁴

To overcome these problems, recently a physician-administered bleeding questionnaire has been developed to produce a severity score for each symptom.⁵ By this approach, less than 1% of normal controls reported three or more hemorrhagic symptoms compared to 50% of obligatory carriers of type 1 VWD.⁵ Furthermore, it appeared that the presence of 3 bleeding symptoms or a bleeding score (BS) of 3 in males and 5 in females was very specific for the bleeding history of type 1 VWD.⁵ Within the MCMDM-1VWD Project, it has been also demonstrated that bleeding history, as assessed by a modification of the original developed physician-administered questionnaire, was more severe in index cases than in affected relatives⁶ and its severity is probably greater in affected relatives with subtle multimeric abnormalities (but not typical for type 2 VWD) compared with those having normal VWF multimers in plasma.⁷ The symptoms that were mostly associated with VWD within these families were bleeding after minor wounds and cutaneous bleeding, whereas postpartum bleeding, bleeding from the gastrointestinal tract and oral bleeding had the same

frequency observed in unaffected family members. Likelihood ratios for type 1 VWD rose significantly with an increasing BS. There was a close correlation of severity of bleeding symptoms with VWF levels, and affected family members with more severe mucocutaneous symptoms had more bleeding complications after invasive procedures (tooth extraction or surgery). Thus, a standardized BS is potentially useful to further dissect the association between VWF function and bleeding, to establish an optimal diagnosis of type 1 VWD and to evaluate the bleeding risk in VWD patients.

The diagnosis of VWD: merely a question of levels?

In a subsequent paper within the MCMDM-1 VWD,⁸ it has been clearly shown that the probability of VWD was however markedly increased only for values below 40 IU/dL (positive LR: 95.1 for VWF:Ag), whereas intermediate values (40 to 60 IU/dL) of VWF only marginally indicated the probability of VWD. Taken together, these findings indicate that more stringent laboratory criteria should be adopted, possibly considering as a *significant* VWF reduction only for values below 40 IU/dL.

The molecular genetics of type 1 VWD

The relevance of the VWF level as a clue for the presence of VWD linked to VWF locus was emphasized by linkage studies and mutation screening in type 1 VWD. In about 70% of the families enrolled in the MCMDM-1VWD, linkage between the disease phenotype and the VWF was observed, but this figure dropped to 50% after exclusion of possible qualitative defects.⁹ Families with VWF levels < 15 IU/dL had the highest probability of co-segregation, unlike families with VWF levels > 45 IU/dL, as previously suggested in families enrolled in

Table 1. Frequency of hemorrhagic symptoms in normal subjects, as reported by Wahlberg *et al.*² and Mauser-Bunschoten *et al.*³

Investigated symptom	Frequency (%)
Profuse menstruation	44
Nosebleeds	5-36
Bleeding at delivery	19.5-23
Bleeding after tonsillectomy	2-11
Bleeding after surgery	6
Bleeding from small wounds	2
Various symptoms (1 or more)	40-50 in men 50-60 in women

an epidemiological investigation.¹⁰

These results were further reinforced by the observation that 50% of patients with VWF > 45 IU/dL had mutations in VWF, whereas 96% of those with VWF levels < 15 IU/dL had mutations. This also emphasizes the view of considering mildly reduced VWF as a *risk factor* for bleeding rather than a true genetic disorder.

The MCMDM-1 VWD demonstrated that the pattern of mutation observed in type 1 VWD differs from that observed previously in type 3 VWD,^{11,12} where about 80% of mutations are predicted to lead to null alleles, resulting from nonsense, splice, deletion and insertion mutations. Only a small proportion of such mutations were identified in this cohort (14/124 mutations, 11%). Thus, heterozygosity for a *type 3* VWD allele is not the main cause of type 1 VWD, as also suggested on the basis of the results of a multicenter study on heterozygous carriers of type 3 VWD.¹³

The results of gene screening, along with the results of the Canadian¹⁴ and UK studies¹⁵ in type 1 VWD, has significantly enlarged our comprehension of the molecular basis of type 1 and, surprisingly, have demonstrated that missense mutations scattered over the entire gene are the main responsible for a *quantitative* VWF defect.

The management of patients with VWD

Desmopressin and transfusional therapy with blood products represent the two treatment of choice in VWD.¹⁶ Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), a synthetic analog of vasopressin originally designed for the treatment of diabetes insipidus, increases autologous FVIII and VWF in plasmas and has become the treatment of first-choice in a large proportion of patients with VWD. This treatment increases plasma FVIII/VWF 3 to 5

times above the basal levels within 30-60 minutes with progressive returns to baseline within 6 to 8 hours. However, it has been recently reported that a subset of patients with complete immediate full normalization of FVIII and VWF levels may have an increased clearance of the moieties after DDAVP infusion, with half-lives as short as 1-2 hours.^{17,18} It is still not clear whether these patients should be treated differently. However, regardless of the knowledge of the causative mutation in a patient with a significant VWD, a test dose of DDAVP administered at the time of diagnosis helps to establish the individual response pattern and will permit planning future treatment.¹⁶ This suggestion is particularly reinforced by the fact that also some patients with type 2 VWD could respond to the compound.

In Western countries, virus-inactivated concentrates, originally developed for the treatment of hemophilia A, are the treatment of choice for VWD patients unresponsive or with contra-indication to DDAVP. These concentrates usually contains large amounts of FVIII and VWF which are both required for treatment. As clearly shown by Morfini, infused VWF stabilizes the endogenously synthesized FVIII with normalization of FVIII levels after 6-8 hours, so that no further infusion of FVIII containing concentrates is necessary. However, in the pharmacokinetic evaluation, Morfini clearly shows that carefully designed studies are required to estimate the true half-life of a given product according to the type of VWD of the patient. The dosages of concentrates recommended for the control of bleeding episodes are summarized in Table 2.^{11,16} Since commercially available intermediate and high-purity FVIII and VWF concentrates contain large amount of FVIII and VWF, high post-infusion levels of these moieties are consistently obtained. Moreover, there is a sustained rise in FVIII lasting for up to 24 hours, higher than predicted from the doses infused, lasting for up

Table 2. Doses of factor VIII-VWF concentrates recommended in VWD patients unresponsive to desmopressin.

<i>Type of bleeding</i>	<i>Dose (IU/kg)</i>	<i>Number of Infusions</i>	<i>Objective</i>
Major surgery	50	Once a day or every other day	Maintain factor VIII > 50 U/dl for at least 7 days
Minor surgery	30	Once a day or every other day	factor VIII >30 U/dL for at least 5-7 days
Dental extractions	20-40	Single	factor VIII >30 U/dl for up to 6 hours
Spontaneous or post-traumatic bleeding	20-40	Usually single	

to 24 hours. This pattern is due to the stabilizing effect of exogenous VWF on endogenous FVIII, which is synthesized at a normal rate in these patients. The cumulation of exogenous FVIII infused with the concentrates together with that endogenously synthesized and stabilized by infused VWF causes very high FVIII levels when multiple infusions are given for severe bleeding episodes or to cover major surgery. Recently, episodes of deep vein thrombosis have been reported in patients with VWD receiving repeated infusions of FVIII and VWF concentrates for maintaining clinical hemostasis especially following surgery.¹⁹ Thus, the risk of over-treatment should not be overlooked.

Even though these concentrates are not always effective in correcting the BT, since no concentrate contains a completely functional VWF, FVIII and VWF concentrates are successfully used for the treatment of VWD patients unresponsive to DDAVP, especially for soft-tissue and post-operative bleeding. For the rare patients with type 3 VWD who develop

anti-VWF alloantibodies after multiple transfusions, the infusion of VWF concentrates besides being ineffective, may cause post-infusion life-threatening anaphylaxis due to the formation of immune complexes (16). In these patients, recombinant FVIII or activated FVII concentrates have a role.

Conclusions

VWD is a fascinating bleeding disorders, whose complexity is still not completely clarified 80 years after its first description. Furthermore, several studies are still addressing the role of VWF in several other acquired hemostatic disorders. We are still waiting for further results from recently completed multi-center studies which, even though they will help in gaining additional advances in understanding the pathophysiology of VWD, nevertheless, and unavoidably, will open further rooms for research.

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