Review Article

Diagnosis and management of von willebrand disease in Spain

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Abstract: The correct diagnosis and classification of von Willebrand disease (VWD) is difficult because of the variability of its clinical expression and limitations of laboratory methods. However, correctly diagnosing VWD is important for therapy and genetic counselling. A survey related to the referred VWD patients in Spain revealed local diagnostic problems in at least one third of the cases of VWD. Consequently, a Spanish multicenter study was carried out in which a cohort of 556 patients from 330 families was analyzed centrally. VWD was confirmed in 480 patients. Next generation sequencing (NGS) of the whole coding von Willebrand factor gene (*VWF*) was carried out in all recruited patients, compared with the phenotype, and a final diagnosis was established. A total of 238 different *VWF* mutations were found: 154 were not included in the Leiden Open Variation Database (LOVD). Of the patients, 467 were found to have a *VWF* mutation/s. A good phenotype/genotype association was estimated in 94.6% of the cases. One hundred and eighty patients had two or more mutations. Occasionally a predominant phenotype masked the presence of a second abnormality. One hundred and sixteen patients presented with mutations that had previously been associated with an increased VWF clearance. Ristocetin induced platelet agglutination (RIPA) unavailability,

central phenotypic results disagreement and difficult distinction between severe type 1 and type 3 VWD prevented a clear diagnosis in 74 patients. A local/central disagreement over diagnosis occurred in 42.3% of the whole cohort. The NGS study facilitated an appropriate classification in 60 of them. Based on these results, a proposal for a change in the VWD diagnostic paradigm, suggesting the inclusion of the analysis of *VWF* at the initial diagnostic process, has been made. An extension of this project to include 400 new VWD patients has begun. A diagnostic strategy has been developed, and a Spanish consensus guideline for optimal treatment of VWD was developed in Spain. Desmopressin (DDAVP) is the treatment of choice in responsive VWD patients. VWF concentrates (VWF/FVIII) are used in individuals unresponsive to DDAVP, when DDAVP is contraindicated, or in VWD types 2B and 3, and for long term management needs (e.g., post major surgery).

Keywords: Von Willebrand factor (VWF); von Willebrand disease (VWD); diagnosis; therapy; Spanish Registry

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Introduction

Information regarding the status of von Willebrand disease (VWD) in Spain was very scarce until 2011, when a survey related to the referred patients to each center was carried out with a good rate of response (66.6%) from 36 centers, including the five Spanish Hemophilia Treating Centers (1).

Regarding the diagnosis, the data obtained indicated that the more widely used tests were factor VIII (FVIII), von Willebrand factor (VWF) ristocetin cofactor activity (VWF:RCo) and VWF antigen (VWF:Ag), and to a lesser extent, VWF collagen binding (VWF:CB). Obviously due to the limited use of the ristocetin induced platelet agglutination (RIPA) assay it was expected that some patients with type 2B and pseudo-VWD were misdiagnosed. The VWF binding to FVIII (VWF:FVIIIB) measurement was carried out in only two centers, and eight requested this analysis from an external laboratory. Sixty-five percent of the participants never requested this assay, which suggested that some patients with this subtype (type 2N VWD) could be misdiagnosed as hemophilia A, or underdiagnosed.

Six centers had the methodology available to perform a multimeric analysis of VWF; however, one abandoned it in 2002 because the test was very cumbersome. Twenty hospitals requested this analysis from an external laboratory, although not for all patients. Seventeen percent of the participants never requested this assay. The low use of this method could lead to under-diagnosis of some patients, as may happen in heterozygous type 2A (IIC) patients.

At the time of the previous survey (1), the molecular study of the VWF gene (*VWF*) was carried out only in five centers, four by the Sanger sequencing method and one using a screening method, and nine centers requested this study from an external laboratory. Noteworthy, fifty per cent of the participants never requested this study. The complexity, the high cost and experience required to perform a molecular study constitute the reasons for its low use. Overall, then, the participants in this survey revealed local diagnostic problems in at least one third of the VWD patients (1).

Regarding VWD therapy, different international guidelines were followed by different treating centers and for that reason a Spanish consensus guideline was developed (2).

The Spanish project "Clinical and molecular profile of VWD in Spain (PCM-EVW-ES)" (Spanish VWD registry)

Motivated by the success and experience of the European Project "Molecular and Clinical Markers in the Diagnosis and Management of VWD Type 1" (MCMDM-1VWD) (3,4) in which Spain participated, a Spanish Registry on VWD was initiated in 2010 with the first data emerging in 2015 (5-8). The rationale for this project included: (I) different laboratory methodologies used and their standardization problem; (II) unavailability of certain assays (RIPA, multimeric analysis) in some centers; (III) the lack of detection of certain type of mutations (reflecting dysfunctional binding with collagen types IV and VI) by some routine assays; and (IV) the overall

Table 1 Modifications to the von Willebrand disease (VWD) revised ISTH classification (the following categories have been added)

Classification	Categories
VWD 1H (1 "Historical")	Type 1 diagnosis clear in the past and currently does not show von Willebrand factor (VWF) levels ≤30%, but has current bleeding symptoms. Most of these patients show some *VWF* mutation
VWD 2M (2CB)	Selective deficiency of VWF binding to collagens types I, III or IV and VI
VWD CL ("clearance")	VWD presenting with an increased clearance of VWF. Usually no good response to desmopressin acetate (DDAVP)
VWD 1 ("Smeary")	Type 1 with smearing profile of all the multimers
VWD 2A/2M	VWD that has been a matter of controversy receiving several different denominations showing multimeric smearing, with a variable proportion of high molecular weight multimers (HMWM). This is the case with p.Arg1374Cys and p.Arg1315Cys *VWD* mutation

cost of phenotypic studies. An additional aim was to further investigate the impact of the study of *VWF* in the diagnosis of VWD.

Study cohort

Patients of any age previously diagnosed locally with VWD or referred from any hospital department or from family care who fulfilled one or more of the following inclusion criteria: (I) VWF:Ag and/or VWF:RCo ≤30 IU/dL, observed on two or more occasions; (II) detection of multimeric abnormalities of VWF; (III) in case of isolated FVIII deficiency it was necessary to provide demonstration of a decreased VWF:FVIIIB; (IV) presence of *VWF* mutations; (V) presence of RIPA at a low ristocetin concentration. Exclusion criteria: presence of any data suggesting acquired von Willebrand syndrome (AVWS). The definitive diagnosis was performed centrally and an evaluation of phenotype/genotype congruence was made. Five hundred and fifty-six patients from 330 families previously diagnosed with VWD in 38 centers were investigated. Their bleeding history and bleeding score were also registered.

Methods

A main feature of the PCM-EVW-ES is that the phenotypic VWF and molecular *VWF* analysis, carried out in all the recruited patients, was centralized in three expert laboratories to achieve a more uniform characterization. The revised ISTH classification was used (9) although the inclusion of some new categories for the diagnosis, already suggested by several investigators, was made (10-12) (*Table 1*). The central phenotypic study included FVIII:C, VWF:Ag, VWF:RCo, VWF:CB (using type I/III collagen), VWF multimeric analysis and VWF:FVIIIB. The *VWF* analysis was made by next generation sequencing (NGS), and multiplex ligation-dependent probe amplification (MLPA) in cases with no mutations and a clear VWD pattern (6,7). In this regard *VWF* (exons 1 to 52, adjacent intronic regions and ~1,300 bp of promotor region) was analyzed by using a MiSeq Illumina Sequencer with NGS adapters, using a previous published protocol (6,7). Additionally, *GP1b* was sequenced by the Sanger method in some cases to avoid misdiagnosis of a potential pseudo-VWD.

Results

This patient cohort included 556 patients from 330 families. The distribution of the patients according to the local and central phenotypic diagnosis and after the final diagnosis, including the genetic results, are shown in *Table 2*. The higher number of patients at final diagnosis [480] with respect to the central phenotypic study [442] is explained, for example, by the presence of *VWF* mutations interfering with the VWF binding to collagens IV and VI, which are not detected by routine VWF:CB assays using only collagens I and III. It was noteworthy that there was a local/central diagnosis disagreement occurring in 42.3% of the patients.

The main findings of the study included VWD confirmation in 480 patients, 467 patients with mutation. In 174 patients, more than one mutation was detected. A total

Table 2 Comparison between the local, central phenotypic diagnosis and final assignment according to the genetic and phenotypic association

Classification	Local, n (%)	Central phenotypic, n (%)	Final, n (%)
Type 1	285 (51.2)	126 (28.6)	129 (26.9)
Type 1H*	0	22 (5.0)	30 (6.3)**
Type 3	41 (7.4)	44 (10.0)	42 (8.8)
Type 3 carriers	2 (0.4)	5 (1.1)	26 (5.4)
Type 2	33 (6.0)	–	–
Type 2A	73 (13.0)	59 (13.3)	111 (23.2)
Type 2B	16 (2.9)	23 (5.2)	35 (7.3)
Type 2M	15 (2.7)	32 (7.2)	39 (8.1)
Type 2A/2M	24 (4.3)	38 (8.6)	34 (7.0)
Type 2N	26 (4.7)	9 (2.0)	9 (1.9)
Type 2N carriers	0	10 (2.3)	11 (2.3)
Compound heterozygous	1 (0.2)	4 (0.9)	–
Uncertain classification	40 (7.2)	74 (17.2)	14 (2.9)
Total	556	442	480

*, 1H: type 1 historical (currently normal VWF properties but previously decreased); **, one patient without mutation and 21 with a mutation.

of 116 patients presented with a clearance type mutation. Occasionally a dominant phenotype masked a second abnormality (7).

A total of 704 variants (237 different) along *VWF* were identified, and 155 had not been previously recorded in the international mutation database. The potential pathogenic effect of these mutations was assessed by *in silico* analysis. Furthermore, four short tandem repeats were analyzed to evaluate the ancestral origin of recurrent mutations. The outcome of genetic analysis allowed reclassification of 79 patients, including the identification of 26 asymptomatic type 3 and 11 type 2N asymptomatic carriers, and (important for genetic counseling) and re-inclusion of 43 patients previously excluded by phenotyping results and the exclusion of 5 patients. Mutations were identified in all except 13 type 1 patients, yielding a high genotype-phenotype correlation.

The phenotype/genotype association was evaluated according to the following criteria: (I) excluded patients: none of the general inclusion criteria met, presence of a mutation not previously described with normal VWF and/or previously described mutation probably not causative (because associated with a normal phenotype); (II) definite patients: clear phenotype correlated with a previously described mutation or with clear type 1 phenotype without mutation but with family history; (III) candidate patients: clear phenotype associated with a variant not previously described. In this regard, a variant (as a genetic change) that was present in two or more patients with the same phenotype was considered to be probably causative. Furthermore, patients categorized into type 2A/type 2B VWD with a mutation outside of exon 28 were considered to be type 2A, because type 2B mutations are restricted to exon 28. (IV) Undefined patients: VWD phenotype difficult to assign associated with a variant not previously described.

According to these criteria, *Figure 1* shows the distribution of the cohort patients. Seventy-six patients were excluded: (I) because of a misdiagnosis of VWD (eight hemophiliacs and five carriers). The molecular study of these hemophiliacs and carriers by NGS detected a mutation on FVIII gene (*F8*). (II) Seven presented with a probable/confirmed acquired von Willebrand syndrome (AVWS), and (III) 56 were excluded because either there was no fulfillment of any recruitment criteria, or because the patient had a mutation not previously described with normal VWF levels and/or previously described mutation which was probably not causative (because it was associated with a normal phenotype).

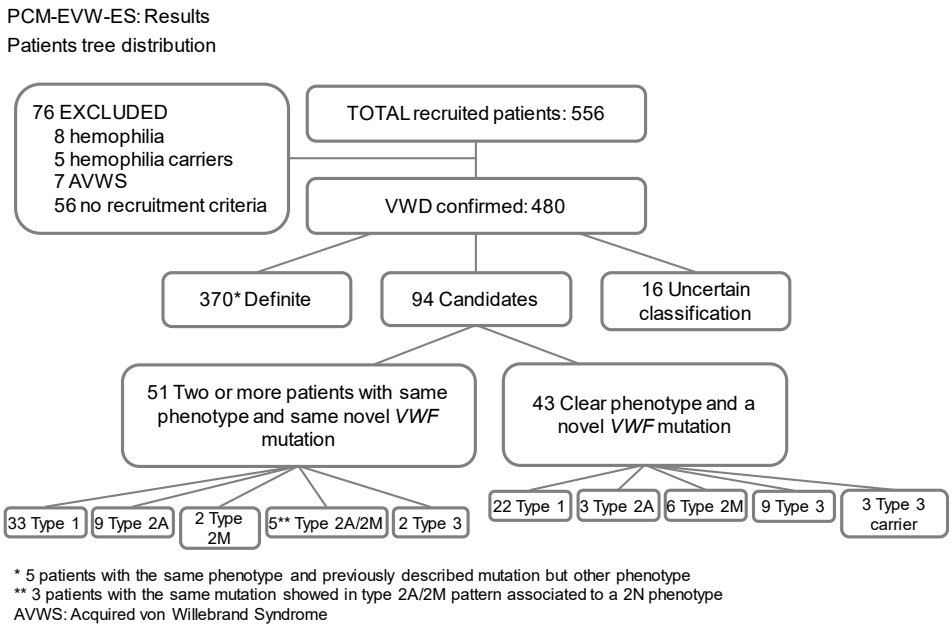

Figure 1 Classification of the patients' cohort according to the phenotype/genotype association. A tree distribution of the patient's cohort is shown. Despite the centralized study and the molecular study, 16 patients remain undefined. The distribution by types of the "candidate" patients is presented at the bottom.

Three hundred and seventy cases were considered "definite patients". Ninety-four were considered "candidates", 51 with a clear phenotype associated with a novel genetic change present in two or more patients with the same phenotype (considered as probably causative), and 43 with a clear phenotype that correlated with the location of the mutation.

Sixteen patients, that were considered as "uncertain classification", had a VWD phenotype difficult to assign associated with a novel genetic change.

Conclusions from the registry

Included all the following (5,7,8): (I) the sensitivity and specificity of NGS compared with the conventional method was 99% and 98%, respectively; (II) a good phenotype/genotype correlation was found in 77% for patients definite and 94.6% for patients definite plus candidates; (III) the cost of the *VWF* NGS study was found to be $60/sample, much cheaper than the conventional Sanger method, with very fast data produced; (IV) a centralized VWD diagnosis would be advisable.

These data will require confirmation in a much larger series of patients. However, they reinforce the importance and usefulness of molecular studies in VWD diagnostics supporting the possibility of a new diagnostic paradigm incorporating NGS in the first line of VWD diagnosis. In this regard, we have suggested an algorithm for the initial diagnosis of VWD based on the following parameters: (I) personal and family bleeding history; (II) a bleeding score assessment tool (BAT); (III) VWF:Ag; (IV) at least one test for VWF activity (VWF:RCo, VWF:GPIbR, VWF:GPIbM, VWF:Ab assays); (V) platelet count and peripheral blood smear; (VI) *VWF* NGS study. Phenotypic testing should use a VWF cut off level of ≤30 IU/dL for type 1 VWD. Afterwards, a mutation orientated specific test/s for confirmation can be implemented, if desired. This does not intend to suggest that molecular analysis is a surrogate approach for a phenotypic study, and both will continue to be complementary.

The generation of an algorithmic platform will be required. We are now developing one with a software based on these parameters that will help in the diagnostic process at the clinical setting. It includes a *VWF* mutations database that will be updated regularly, considering the *VWF* sequence variants that are known not to influence VWF or cause a clinical disease. This algorithm platform connected to the PCM-EVW-ES application will be validated by using data from this project. This has been tested on a prototype

with great rate of success on simulations based on data provided by some publications.

A summary of this project was presented at the International Society of Thrombosis and Haemostasis (ISTH) VWF Subcommittee (SSC) meeting in Montpellier, France (13). Recently the project has been granted to recruit 400 new additional patients with VWD.

A similar project has been carried out in Portugal (14).

Current Spanish strategy in VWD diagnosis

Awaiting the validation of the above mentioned new proposed VWD diagnostic paradigm, the diagnosis is based in two main aspects: the evaluation of the bleeding history to estimate the severity of the bleeding phenotype, and the laboratory data. The Spanish strategy in VWD diagnosis follows several international recommendations (15-26). However, certain aspects should be emphasized.

Bleeding history

A correct diagnosis of VWD is complex, and not always precise, due to the wide variety of the bleeding phenotype, the variability of the VWF levels and the great heterogeneity of VWD subtypes. The diagnosis is based in two main aspects: the evaluation of the bleeding history to estimate the severity of the bleeding phenotype, and the laboratory data. The bleeding history is the main aspect and suggests a diagnosis of VWD when at least three different bleeding symptoms are recorded or when a bleeding score >3 in males and >5 in females is obtained by using a standardized BAT (27). Considering that a mild VWF deficiency is associated with a mild bleeding risk the diagnostic effort must be invested in patients with a significant bleeding history to avoid the risk of over-medication of patients with a dubious or only a mild bleeding history (28).

Laboratory evaluation of VWD

Diagnosis of VWD is based on the presence of reduced VWF:RCo (and/or VWF:CB) (cut off level of ≤30 IU/dL), with a further characterization of VWD type based on the assessment of VWF:Ag, FVIII:C and multimer pattern. VWF levels ≤30 IU/dL have been shown to be strongly associated with a significant clinical severity and the presence of mutations in *VWF*. For that reason, VWF levels between 31–50 should be considered as low VWF associated with a mild bleeding risk. Due to the cost, the conventional molecular analysis of *VWF* by the Sanger method is generally advised in type 3 VWD or in the distinction of types 2A and 2B, as well as to differentiate type 2N from hemophilia A. *Figure 2* presents a suggested VWD diagnostic algorithm. *Table 3* shows the recommendations for the molecular study (29). This practical diagnostic approach in VWD has been previously published (30).

Therapy of VWD

Despite the existence of different treatment guidelines for VWD, controversial issues of concern for both patients and physicians remain. This being the principal reason for developing consensus recommendations on the treatment of VWD in Spain (2), which again follow several international recommendations (15-24,30-32). However, a number of aspects deserve a comment.

Optimal management of VWD requires: (I) a correct diagnosis because of its impact on patient outcomes (33); (II) knowledge of previous hemorrhagic history; (III) assessment of values of VWF and FVIII; and (IV) an assessment of the severity of the bleeding episode(s) to estimate the type, dose and duration of the treatment to administer. These guidelines are also suggested for patients without a definitive diagnosis of VWD with slightly decreased VWF:RCo (31–50 IU/dL) who may benefit from prophylaxis or treatment under certain clinical situations.

The goal of treatment is to correct the deficiencies of VWF and FVIII and is aimed at stopping or preventing bleeding during surgical procedures.

The following must be considered: (I) the decrease in FVIII is secondary to a defect of VWF; (II) restoration of normal levels of FVIII is usually accompanied by the control of non-mucosal and soft tissue bleeding after surgery, even in the absence of primary hemostasis correction; (III) the restoration of primary hemostasis to control severe mucosal bleeding is necessary; and (IV) VWF replacement therapy restores the plasma compartment, but not the platelet compartment. Therapy should be primarily planned through drug administration and treatment of bleeding sites. When these are not effective or sufficient, concentrated hemostatic replacement therapy should be used instead.

Persistence of bleeding despite adequate correction of VWF and FVIII requires an assessment of the patient to rule out other causes of bleeding, including anatomical lesions or surgical problems.

As in all patients with congenital bleeding diathesis, it

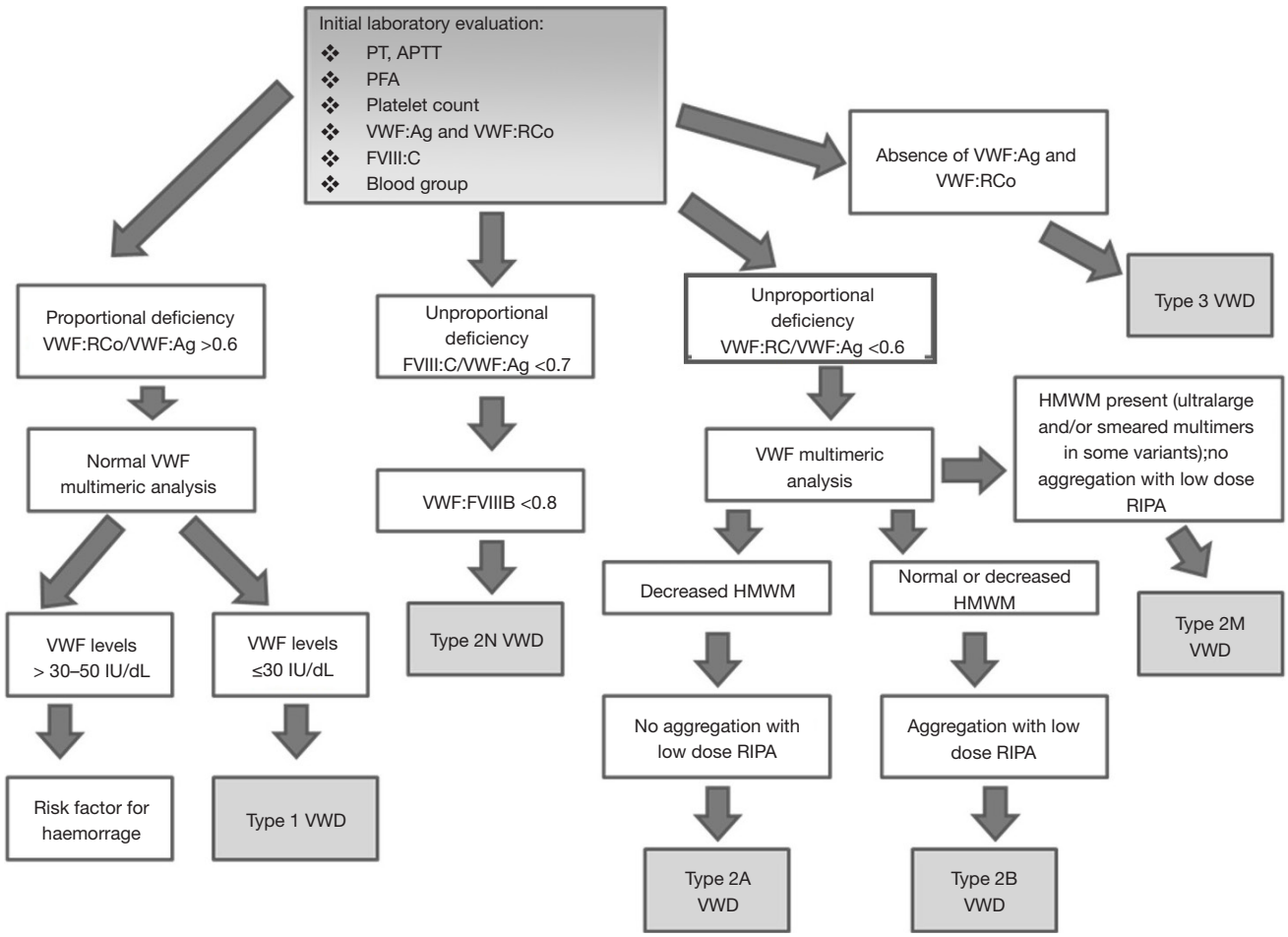

Figure 2 Suggested diagnostic algorithm in von Willebrand disease (VWD). The flow chart for the diagnostic process is indicated. PT, prothrombin time; APTT, activated partial thromboplastin time; PFA, PFA100 platelet function analyzer for evaluation of the occlusion time; VWF, von Willebrand factor; VWD, von Willebrand disease; RIPA, Ristocetin induced platelet agglutination; FVIII:C, factor VIII procoagulant activity; VWF:RCo, ristocetin cofactor activity; VWF:Ag, VWF antigen; VWF:FVIIIB, VWF binding to FVIII; HMWM, high molecular weight VWF multimers.

is recommended: (I) to maintain adequate dental hygiene; (II) to facilitate local hemostasis (compression suture after tooth extraction etc.) to prevent and restrain minor bleeding during surgical procedures; (III) to prevent and warn of the risk posed by the use of drugs that affect platelet function, such as antiplatelet and anti-inflammatory drugs (except COX-2 inhibitors). In the case of fever or pain, paracetamol or metamizole can be used; (IV) to avoid strenuous exercise and intramuscular injections; and (V) to administer vaccines subcutaneously. An immunization program against hepatitis viruses A and B must be followed and prove that adequate levels of immunity have been attained. Although no consensus exists, it is necessary to periodically check the levels of antibodies to such viruses, except in patients subjected to treatments that induce a state of immunodeficiency (for example, anti-CD20).

Therapeutic resources

Desmopressin acetate (DDAVP)

Typically, DDAVP induces elevated levels of FVIII and VWF 3–5 times above baseline levels. Its effectiveness varies depending on the subtype of VWD. Approximately 75–80% of VWD patients respond to DDAVP. In Spain, it is marketed for intravenous use (Minurin®, Ferring) or high concentration—150 g—as an intranasal spray (Octostim®

Table 3 Practical approach for molecular study in VWD

Type of VWD	SANGER			NGS	MLPA
	Initial analysis	Next exons to be analyzed	Additional analysis		
1	All exons	Promoter	–	Whenever possible	–
2A	28	11–15, 52	–	Whenever possible	In case of suspicion of deletions or duplications
2B	28	None	*Gp1b*	Whenever possible	–
2M	28	29–32, 52	–	Whenever possible	–
2A/2M	28	11–15, 29-32, 52	–	Whenever possible	–
2N	18-20	17, 24–25, 27	*F8* exons 1–26, Intron 1 and 22 inversions	Whenever possible	–
3	All exons	Promoter	–	Whenever possible	In case of suspicion of deletions or duplications

It may be useful in cases with genotype/phenotype discrepancy. NGS, next-generation sequencing; MLPA, multiplex ligation-dependent probe amplification. *F8*, Gen of VIII; *Gp1b*, Glycoprotein 1b platelet gene.

nasal spray, Ferring).

It is advisable to evaluate the response to DDAVP in baseline conditions, preferably in patients with activity levels above 10 IU/dL of VWF:RCo and above 20 IU/dL of FVIII:C. It is necessary to analyze the response by measuring levels of VWF preferably at baseline, at 1 h (peak) and at least 4 h (clearance). Even though the response is predictably poor in patients with lower levels, it may be useful to conduct this assessment (34).

Dosages and methods of administration and other aspects related to DDAVP use, such as tachyphylaxis and adverse effects, have been described elsewhere (15-20).

Indications

DDAVP is the treatment of choice in most VWD type 1 patients, except in patients lacking platelet VWF or when the FVIII:C is below 5% and in cases with *VWF* mutations associated to an increased clearance of the VWF (such as Vicenza VWD and others), which have an initial response but also a marked clearance in plasma. In types 2A and 2M, the response is poor or absent, although it may be useful in some minor hemorrhages or surgeries. In type 2B, although it may aggravate thrombocytopenia, some cases of successful treatment have been reported; but in general, it is not recommended for this subtype. In type 2N, response depends on the type of mutation. In the homozygous form caused by the p.Arg816Trp mutation, it is often ineffective. In some mutations, such as p.Arg854Gln, whose affinity disorder to FVIII is milder, it may be clinically useful.

Criteria of response to DDAVP in VWD

The response to DDAVP is subdivided into full response, partial response or no response:

- Full response: increase of values of VWF:RCo and FVIII to a level of 50 IU/dL or higher. Patients with values of VWF:RCo and/or FVIII of about 50 IU/dL or higher at baseline are considered as full responders if they reach a level of 100 IU/dL or higher in both parameters.
- Partial response: increase of VWF:RCo or FVIII lower than 50 IU/dL but at least 3 times above baseline values.
- No response: when the above criteria are not met.

Contraindications

DDAVP should not be used in cases of psychogenic and common polydipsia, heart failure and other conditions requiring treatment with diuretics, unstable angina and decompensated heart failure, and in type 2B VWD.

Anti-fibrinolytic agents

Synthetic anti-fibrinolytic agents

They are mainly useful as adjuvants. especially useful in bleeding from mucous membranes: epistaxis, gingival bleeding, menorrhagia and other bleeding (35). The most commonly used in Spain is tranexamic acid marketed under the name of Amchafibrin® (AMCHA). It is often used in mucocutaneous bleeding before and after dental surgery

Table 4 FVIII/VWF concentrates available in Spain and VWF concentrates

Concentrate	Company	Purification	Viral inactivation	SA*	VWF:RCo/Ag (ratio)	VWF:RCo/FVIII (ratio)
FVIII/VWF						
Fandhi	Grifols	Heparin affinity chromatography	S/D* + dry heat (80°, 72 h)	~40[a]	0.47±0.1	1.04±0.1
Haemate P	CSL Behring	Multiple precipitation	Pasteurization (60°, 10 h)	75[a], 38[b]	0.59±0.1	2.45±0.3
Wilate	Octapharma	Ionic echange + size exclusión chromatography	S/D* + dry heat (100°, 2 h)	>100[b], ≥53[c]	0.47	1.1
VWF						
Wilfact	LFB	Ionic echange + affinity chromatography	S/D* + 35 nm; NF, dry heat (80°, 72 h)	111±11[a]	0.95	50
Vonvendi* (VWF recombinant)	Shire	Ionic exchange chromatography	S/D*	116±7	1.09±0.26	(no FVIII)

*, licensed by the FDA; not yet available in Spain. [a], IU of VWF/mg; [b], IU of FVIII/mg of protein, before albumin addition; [c], IU of VWF:RCo/mg protein. VWF, von Willebrand factor; S/D, solvent/detergent; SA, specific activity; NF, nanofiltration.

and menorrhagia. Used in combination with DDAVP, it may be useful in mucosal bleeding. It is contraindicated in hematuria because it facilitates the formation of fibrin clots in the lumen of the ureters and may cause urinary tract obstruction. AMCHA should be used cautiously in patients with thrombotic risk factors. They should not be used if there is significant renal impairment or if the patient has a history of seizures.

Hormonal treatment

Oral contraceptives are often used in women with VWD; a risk-benefit assessment should always be performed. They reduce endometrial proliferation which is why they may be useful in menorrhagia. Although they discreetly increase circulating levels of VWF, this might not be the only element responsible for their hemostatic function, although their mechanism of action is unknown so far. They are useful in the treatment of menorrhagia in mild to moderate VWD. Oral contraceptives should be prescribed under the supervision of a specialist in obstetrics/gynecology.

Haemostatic factor concentrates

Treatment of bleeding through replacement of the deficient protein is a widely used therapeutic modality (15-24,31,32,36). Administration of fresh frozen plasma (FFP), except in some situations, has been abandoned because of its inability to achieve high and sustained plasma levels without causing volume overload. Plasma VWF concentrates are the treatment of choice when DDAVP is not effective or contraindicated and they are effective in all subtypes of VWD.

Cryoprecipitate

The use of cryoprecipitate is not currently recommended in Spain.

VWF and factor VIII concentrates available in Spain

These are shown in *Table 4* (2,30).

Plasma or recombinant purified FVIII concentrates do not contain VWF and are, therefore, not useful as the sole treatment of VWD. There are clear differences between the concentrates available, which are marked by the degree of product purity, methods of viral inactivation and the extent of functional preservation of VWF (assessed as the VWF:RCo/VWF:Ag and VWF:CB/VWF:Ag ratios, as well as the multimeric analysis of VWF content). Their ratio of VWF to FVIII is important (measured as the FVIII:C/VWF) with respect to a potential secondary elevation of FVIII after their repeated administration.

Table 5 shows details of treatment and prophylaxis of bleeding or in surgery in patients with VWD when treatment with DDAVP is ineffective or contraindicated. In contrast to patients with hemophilia, regular replacement therapy (prophylaxis) to prevent bleeding is not commonly used in those with VWD, even though its benefit has been described in several case series (37-39), although with not yet well-established regimes.

There is currently a single recombinant VWF product,

Table 5 Suggested indications for replacement therapy in VWD with FVIII/VWF concentrates

Sort /type of episode	Recommended hemostatic levels of FVIII and VWF levels	Dosage**	Duration
Spontaneous or post-traumatic severe bleeding	>50 IU/dL	50 IU/kg/24 h of VWF	Until bleeding stops (~7–10 days)
Spontaneous or post-traumatic mild to moderate bleeding	>30 IU/dL	20–40 IU/kg/24 h	Until bleeding stops (~1–3 days)
Major surgery* (consider antithrombotic prophylaxis)	80–100 IU/dL	50 IU VWF/kg/12 h	First 24 h
	80–100 IU/dL	50 IU VWF/kg/24 h	1–3 days
	50 IU/dL	30 IU VWF/kg/24 h	Until complete healing (~7–10 days)
Minor surgery	>30 IU/dL	30–60 IU/kg/24 h or 48 h	Until complete healing (~1–5 days)
Dental extractions	–	Single dose 20–40 IU/kg	–
Delivery and puerperium	>50 IU/dL	50 IU/kg/24 h	3–5 days
Repeated severe bleeding (GI, hemarthrosis, epistaxis in children)	Consider prophylaxis, avoid levels of FVIII >150 IU/dL	20–40 IU/kg × 3 times/week	–
Elective surgery and prophylaxis: (consider VWF concentrate devoid of VIII)	–	Surgery: first dose (FVIII + VWF); next doses (only VWF); FVIII and VWF monitoring; prophylaxis (only VWF)	–
Type 3 VWD with alloantibodies	–	High dosage of FVIII by continuous infusion, rFVIIa	Avoid VWF concentrates to avoid anaphylactic reactions

Measure plasma levels of FVIII:C (and VWF:RCo) every 12 h on the day of surgery, then ever 24 h. *, it depends on the type of surgery; **, dosage should be based on VWF:RCo content whenever possible. Dosages are indicated for patients with FVIII:C and/or VWF plasma levels <10 IU/dL. FVIII, factor VIII; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor level; VWD, von Willebrand disease; GI, gastrointestinal.

characterized by the absence of the theoretical risk of pathogen transmission and by homogeneity of content in VWF and high molecular weight multimers (HMWM) has recently completed successful clinical trials (40,41). It seems very promising but is not yet licensed in Spain. Although no specific indications on its clinical use are so far available, with further safety and efficacy data, the recombinant product may be preferable to the plasma-derived concentrates, particularly in terms of preventing viral transmission, especially in newborns with type 3 VWD, avoiding a lifelong plasma exposure. Also, it may be preferable in the obstetrics setting and in cases of major surgeries, where accumulation of endogenous and exogenous FVIII can potentially predispose to thrombosis. The apparent extended half-life may also make its use attractive in the prophylaxis setting (42).

The plasma derived high-purity VWF concentrate with low amounts of FVIII as well as the recombinant VWF concentrate require a co-administration of a priming dose of FVIII, when prompt hemostasis is required in patients with baseline FVIII:C levels lower than 30 IU/dL.

Pharmacovigilance

It is very important that patients have a record of each dose of VWF/FVIII concentrate and the name and product lot number to keep track of the batches used for pharmacovigilance purposes and to relate them with any side effects in association with their use.

Pharmacokinetic studies

These are useful to properly administer replacement therapy as the optimal dose and duration, especially for surgical prophylaxis, have not been fully established in clinical trials. Most guidelines recommend replacement therapy of FVIII

in IU or in VWF per kg of body weight; however, since concentrations of FVIII and VWF in available preparations are not equivalent, calculating the dose in relation to VWF units is advised. It is important to know the ratio of FVIII and VWF in concentrates in order to optimize efficiency and reduce thrombotic risk.

If excessive FVIII:C plasma levels are observed, dose reduction, lengthening the dosage interval or using a VWF product with a low level of FVIII should be considered.

Other haemostatic concentrates

In addition to VWF/FVIII concentrates for the treatment of VWD, two other concentrates can be used in special situations: platelet concentrates and active recombinant FVII concentrate (2).

Platelet concentrates

Platelets contain 10–15% of total blood VWF. In some patients, even after correcting the levels of VWF and FVIII, bleeding does not stop and the closure time of the platelet function analyser (PFA-100®) is still very long. In these cases, usually involving type 3 or low platelet VWD, and if the bleeding is severe, transfusion of platelet concentrates at doses of 1 IU/10 kg of body weight or 1 IU of apheresis may be indicated. It should be emphasized that these concentrates are not inactivated and patients run a potential risk of alloimmunisation (2).

Recombinant activated factor VII concentrate (rFVIIa)

This has been used occasionally and effectively in the special situations of type 3 VWD with alloantibodies (2).

Topical haemostatic drugs

There are various adjuvants for the treatment of bleeding episodes, mainly in surgical interventions. They are effective in different clinical scenarios, including dentistry and surgery. Fibrin adhesives are hemostatic drugs derived from human plasma for topical application that increase concentrations of fibrinogen and thrombin at the bleeding site. Besides being useful for the control of localized or diffuse bleeding, they promote wound healing by fibroblast proliferation on fibrin plugs. In general, commercial products contain various amounts of fibrinogen, fibronectin, factor XIII, plasminogen, thrombin and calcium, and they are subjected to viral inactivation processes. Besides the risk of viral transmission, typical of any plasma-derived product, other adverse effects, such as hypotension and anaphylactic reactions to compounds with bovine thrombin and even secondary thromboembolic events after accidental intravenous injection, have been reported.

Experience with these products for topical use is broad, but their therapeutic effectiveness has not been proven clearly and objectively and the level of scientific evidence on their effectiveness is limited.

A suggested practical flow-chart for VWD therapy is shown in *Table 6*.

Key points/conclusions

(I) The diagnosis of VWD is for a life time, and it is advisable to make it the most precise possible in order to prescribe the most suitable therapy.

(II) Pharmacological resources should be used in VWD as the first line of therapy in patients with an adequate response.

(III) Those patients in whom a test infusion with DDAVP is not able to achieve clinically useful FVIII and/or VWF levels are candidates for replacement therapy.

(IV) Some controversy has been raised on the utility of pharmacokinetic studies with FVIII/VWF concentrates before their use in therapy. Although further studies will be needed, it seems advisable to carry out pharmacokinetic studies.

(V) The treatment of VWD in women should be multidisciplinary with the participation of an obstetrician and a gynecologist.

(VI) In the case of suspicion of anti-VWF alloantibody development it is mandatory to confirm the presence to avoid anaphylactic reactions after VWF concentrate administration.

(VII) In contrast to patients with hemophilia, regular replacement therapy (prophylaxis) to prevent bleeding is not commonly used in those with VWD, even though its benefit has been described in several case series. It should be considered for severe and repeated hemorrhages (hemarthrosis, gastrointestinal bleeding and epistaxis in children) with no response to conventional therapy.

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Table 6 Suggested practical flow-chart for von Willebrand disease (VWD) therapy

Tranexamic acid
Consider the use of tranexamic acid for the treatment or prevention of bleeding in mild cases or as an adjunctive therapy in more severe cases
Tranexamic acid should be considered to lessen bleeding during the late post-partum period
Desmopressin acetate (DDAVP)
A test infusion is recommended, especially in patients with von Willebrand factor (VWF) <30 IU/dL, measuring FVIII:C, VWF:Ag and VWF:RCo levels at 1 h (peak) and at least 4 h (clearance). Ideal candidates for treatment are those with levels post-infusion >50 IU/dL
Exclude patients with heightened RIPA and type 3 VWD
Cover bleeding episodes and minor surgical or invasive procedures with DDAVP
Evaluate a possible tachyphylaxis by measuring VWF/FVIII levels after repeated treatments with DDAVP
Avoid the use of DDAVP in children <2 years and in elderly patients with arteriosclerosis or cardiovascular disease. Limit fluid intake (<1 L) in adults for 24 h after DDAVP
Pregnant VWD women responsive to DDAVP can be safely treated (0.3 μg/kg for 3–4 days) at the time of parturition after umbilical section if FVIII or VWF is not >50 IU/dL to avoid excessive bleeding. DDAVP may also be used during the first trimester for invasive procedures
Replacement therapy
FVIII/VWF concentrates represent the treatment of choice for those VWD patients in whom DDAVP is either ineffective or contraindicated. They may be additionally used when prolonged hemostatic coverage is required since sustained clinically useful levels (>50 IU/dL) are difficult to maintain with DDAVP alone
The plasma derived high-purity VWF concentrate with low amounts of FVIII as well as the recombinant VWF concentrate may be preferable in some settings. However, they are not yet licensed in Spain. They require a co-administration of a priming dose of FVIII, when prompt hemostasis is required in patients with baseline FVIII:C levels lower than 30 IU/dL

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Footnote

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