# Diagnosis and Management of von Willebrand Disease in a Single Institution of Argentina

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## ABSTRACT

Von Willebrand disease (VWD) is a bleeding disorder with variable clinical expression. In this article we describe types, clinical features, genetic testing when needed, genotype/phenotype relationships, and the response to desmopressin (DDAVP) testing, according to our experience. Our findings are possible type 1, 69.6%; type 1, 13.5%; severe type 1, 0.35%; type 3, 0.55%; type 2A, 9.5%; probable 2B, 0.6%; type 2M, 2.5%; and probable type 2N, 3.4%. The most frequent symptoms are ecchymoses-hematomas and epistaxis, and, in females >13 years also menorrhagia. In pregnant patients, assessment of laboratory parameters in months 7 and 8 is recommended to plan the need for prophylaxis at term. DDAVP merits to be considered as the first-choice therapy, including pregnant women and children, and no patient showed significant unwanted effects. Because this is a safe, effective, and affordable therapy, we hope to encourage clinicians, mainly pediatricians and obstetricians, to a wider use of DDAVP, especially in developing countries. We also report two patients with prophylactic treatment.

**KEYWORDS:** Von Willebrand disease, management strategy, genotype/phenotype relationships, DDAVP in women and children, prophylaxis in VWD

Historically, our institution established the von Willebrand disease (VWD) diagnosis criteria, laboratory assays, and treatment policy in Argentina, fostering learning, training, and reference status, with growing experience over the last 3 decades. The incidence of VWD in our region has been previously reported by Srivastava,[1] with remarkably >50% of the expected number of cases deriving from a single institution in 1998. In most patients, studies have the financial support of the government. Our country has now 41 million inhabitants, and in our institution we have 2367 records of VWD patients. Although the mean of parental consanguinity rate in normal births in Argentina reported was 0.29%, our group's experience has demonstrated only one case of recognized parental consanguinity in one 2-year-old girl with type 3 VWD.

## CRITERIA AND STRATEGY FOR DIAGNOSIS

The criteria we use to define VWD are purposely restrictive to avoid overdiagnosis and are essentially

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supported on a clinical basis. All the patients undergo a minimum of two laboratory studies. As usual in clinical practice, the most abnormal value for any given test is considered for the final analysis. The incomplete penetrance of the phenotype, like in type 1 VWD and the variable expression of bleeding symptoms within families[2] make further characterization more difficult. The diagnostic strategy followed in our institute is outlined in the following sections.

## Phenotypic Analysis

The following coagulation tests are performed: bleeding time (BT) using the Ivy method, prothrombin time (PT), platelet count, activated partial thromboplastin time (aPTT), factor VIII (FVIII), von Willebrand factor (VWF) antigen (VWF:Ag), VWF ristocetin cofactor (VWF:RCo), VWF collagen binding, VWF FVIII binding (VWF:FVIIIB), and mixing studies to evaluate the presence of inhibitors in patients with either a prolonged aPTT or VWF:RCo <10 IU/dL. The multimeric pattern of VWF is analyzed using sodium dodecyl sulfate 1% and 1.7% agarose gel electrophoresis. In all the cases, without considering ABO blood groups and the hormonal period in women, VWF:RCo is <50 IU/dL, with the exception of type 2N VWD. Ristocetin-induced platelet agglutination (RIPA) at 1.2 mg ristocetin per milliliter is the first RIPA test performed. Where RIPA 1.2 mg/mL is normal, testing is repeated using ristocetin 0.5 to 0.7 mg/mL; where RIPA 1.2 mg/mL is absent, testing is repeated using ristocetin at 1.5 and, if required, 2 mg/mL.[3] In selected cases, VWF propeptide-to-VWF:Ag ratios are determined to evaluate the clearance or survival of VWF. Laboratory investigation is offered to all available members of affected families. Although desmopressin (DDAVP) data are primarily used for potential therapy management, in selective cases DDAVP data may also be used to assist in diagnosis. Given the size of our country, in many cases we keep samples for genotyping, to avoid the expense of having patients return.

## Genotypic Analysis

Genetic testing for VWD is not performed routinely. Since 1998, we have performed genotypic studies in patients with suspected type 2N, using the conformational sensitive gel electrophoresis (CSGE) method as screening. We study exons 17 through 27. The exon that shows an abnormal pattern of bands in CSGE is then sequenced for further analysis, using the ABI PRISM 310. In our experience CSGE is not useful to screen the exon 22 due to its lack of sensitivity to detect patients with heterozygous single nucleotide polymorphism (SNP), yielding false negatives 40% of the time.[4] Given the high frequency of mutations located in the exon 28, we have developed the study of this exon to search for mutations responsible for 2A, 2M, and all the 2B phenotypes.

## Type 1 and Type 3 variants of von Willebrand Disease

It is easy to classify the types of individuals with very high bleeding tendency because almost all of them belong to type 2 and 3. Type 1 and possible type 1 are harder to recognize. Most subjects with low VWF (30 to 50 IU/dL) and mild bleeding symptoms may be considered as "low VWF" or "possible" type 1 VWD.[5] We believe that possible type 1 implies a risk for bleeding that acquires importance in challenging situations such as surgeries. In a previous report,[6] we stated that low levels of VWF:RCo and a personal bleeding history are crucial in the diagnosis and treatment of VWD. Our criteria for diagnosing type 1 versus type 3 VWD are possible type 1 VWF:RCo within 31 to 49 IU/dL, type 1 VWD with a VWF:RCo within 15 to 30 IU/dL, and severe type 1 with VWF:RCo within 5 to 15 IU/dL and with a poor response to DDAVP. In all these cases, VWF:RCo-to-VWF:Ag are >0.6. Type 3 are those patients with VWF <5 IU/dL, FVIII usually <10 IU/dL, and subsequently no response to DDAVP.

## Type 2 Variants of von Willebrand Disease

Type 2 VWD variants express an impaired VWF function related to a physiopathology deficiency. VWF:RCo-to-VWF:Ag is <0.6 in type 2A, 2B, and 2M, and >0.6 in type 2N. Type 2A and 2M variants are defined for those patients with low affinity of VWF for platelet GPIb, reduced or absent RIPA 1.2 mg/mL, reduced VWF:RCo, and normal or slightly reduced levels of VWF:Ag and FVIII. The multimeric pattern shows the absence of large and intermediate multimers of VWF in type 2A and normal multimers in type 2M. Type 2B variant is defined for those patients with a high affinity of VWF for platelet GPIb and enhanced RIPA at low doses, reduced VWF:RCo, and normal or slightly reduced levels of VWF:Ag and FVIII. Absence of large multimers of VWF is the characteristic multimeric pattern. The platelet count may range from low to normal.[7] In situations of stress, such as pregnancy or response to DDAVP, thrombocytopenia is accentuated. Type 2N variant, characterized by a markedly decreased binding affinity for FVIII, is suspected when FVIII is very low, the FVIII-to-VWF:Ag is <0.7 and VWF:FVIIIB-to-VWF:Ag <0.8. However, we refer to "probable 2N VWD" until we find a candidate mutation.

## Blood O Group and Female Hormones

Considering type 1 and possible type 1 VWD patients, we found slightly lower levels of VWF:Ag in those with

group O versus non-O. Like other authors,[8] we believe that patients with low VWF levels and bleeding symptoms should be considered to have a bleeding risk disorder, regardless of the ABO blood group they belong to. Approximately 73.5% of "type 1/possible type 1" VWD patients belong to blood group O, whereas the frequency of this group in the Argentinean population is 50.9%, similar to that observed in the other types of VWD (i.e., non–type 1 VWD and possible type 1 patients). Despite the improvement in both VWF and FVIII during pregnancy and the avoidance of oral contraceptives intake before laboratory testing and the DDAVP response test, we do not take into account the day of menses for blood extraction, given our belief that VWF levels do not vary significantly during the menstrual cycle.[9]

## Population Characteristics

A few of our patients (4.2%) had abnormal laboratory findings only, without either personal or familial bleeding manifestations. Most patients (72.2%) are >13 years of age at the time of diagnosis. The prevalence of females is 62.8%. Table 1 shows the incidence of symptoms in our patients. The laboratory data (according to the VWD variant) are summarized in Table 2.

We have 2367 registered patients with VWD. The distribution of the different types of VWD in our patients is possible type 1, 69.6%; type 1, 13.5%; severe type 1, 0.35%; type 3, 0.55%; type 2A, 9.5%; probable (until genetic confirmation) type 2B, 0.6%; type 2M, 2.5%; and probable 2N, 3.4%. Note that 1.5% of patients who do not fulfill any classification criteria are not included in this calculation. Although we have a significant number of patients, we cannot provide an accurate estimate of prevalence according to the base population in our region because this is a single-institution experience. Nevertheless, based on our case number (2367) and given the population of Argentina (~41 million), we can conservatively estimate an approximate VWD prevalence of 56.4 per million population.

In some VWD patients, we also found association with other disorders: 18 patients with obligatory carriers of hemophilia A; 26, mutations for hemophilia A; 18,

**Table 1 Description of the Clinical Symptoms and DDAVP Response in Our von Willebrand Disease Patient Cohort**

| | VWD Quantitative Variants | | | | Qualitative Variants | |
|---|---|---|---|---|---|---|
| | **Type 3** ***n*** **= 13** | **Severe Type 1** ***n*** **= 8** | **Type 1** ***n*** **= 319** | **Possible Type 1** ***n*** **= 1648** | **Types 2** ***n*** **= 299** | **Probable 2N** ***n*** **= 80** |
| **Percentage of patients** | 0.55 | 0.35 | 13.5 | 69.6 | 12.6 | 3.4 |
| | **Clinical Symptoms Expressed as Percentage of Patients** | | | | | |
| With bleeding symptoms | 96.9 | 100 | 85.5 | 88.7 | 91.2 | 95.0 |
| With transfusion | 50.0 | 12.5 | 11.5 | 9.2 | 31.7 | 32.5 |
| Epistaxis | 90.6 | 64.3 | 43.3 | 37.5 | 48.2 | 33.3 |
| Menorrhagia | 54.5 | 62.5 | 52.5 | 54.6 | 49.5 | 64.7 |
| Tooth extraction bleeding | 68.7 | 66.6 | 52.5 | 52.7 | 60.0 | 52.2 |
| Bleeding in surgery | 85.7 | 66.6 | 42.1 | 39.4 | 50.0 | 37.5 |
| Bleeding in partum | 66.6 | – | 32.9 | 31.4 | 47.6 | 25.0 |
| Hematomas | 73.3 | 56.2 | 53.6 | 50.6 | 55.0 | 60.3 |
| Gum bleeding | 43.3 | 50.0 | 25.5 | 27.1 | 26.5 | 17.8 |
| Hemarthrosis | 13.3 | 0.0 | 3.8 | 5.1 | 6.9 | 20.5 |
| Gastrointestinal bleeding | 23.3 | 0.0 | 3.2 | 2.1 | 5.2 | 4.1 |
| With other symptoms | 21.4 | 18.7 | 8.9 | 6.5 | 11.6 | 24.6 |
| >3 bleeding sites; median (range) | 3 (0–7) | 3 (1–6) | 2 (0–6) | 2 (0–7) | 2 (0–7) | 2 (0–5) |
| % females >3 | 68.7 | 50.0 | 50.8 | 44.2 | 50.7 | 42.8 |
| % males >3 | 56.2 | 50.0 | 28.5 | 21.9 | 39.4 | 46.1 |
| BS; median (range) | 5 (0–15) | 4 (1–8) | 3 (0–11) | 3 (0–11) | 3 (0–10) | 4 (0–7) |
| % females >5 | 62.5 | 37.5 | 24.1 | 22.0 | 33.3 | 33.3 |
| % males >3 | 75.0 | 66.6 | 44.7 | 44.3 | 59.8 | 80.7 |
| DDAVP response | | | | | | |
| % pts with adequate | 0.0 | 0.0 | 90 | 98.6 | 53.7 | 38.5 |
| inadequate | 0.0 | **100** | 8.2 | 1.3 | 38.9 | 38.5 |
| nonresponse | **100** | 0.0 | 1.8 | 0.0 | 7.4 | 23.0 |

Number and percentage of patients (pts) in each VWD variant.
Percentage of patients with clinical symptoms, according to the different variants.
VWD, von Willebrand disease; BS, bleeding score; DDAVP, desmopressin.

**Table 2 Laboratory Data of our von Willebrand Disease Patients Cohort**

| Laboratory Assays | VWD Quantitative Variants | | | | Qualitative Variants | |
|---|---|---|---|---|---|---|
| | Type 3 | Severe Type 1 | Type 1 | Possible Type 1 | Types 2 | Probable 2N |
| BT min $\bar{x}$ ± SD | 10.3 ± 3.1 | 6.4 ± 3.3 | 5.0 ± 2.6 | 5.2 ± 2.6 | 6.8 ± 3.3 | 4.6 ± 1.9 |
| pts with abnormal value | 100% | 50% | 49.5% | 48.5% | 67.5% | 28.1% |
| FVIII IU/dL $\bar{x}$ ± SD | 11.8 ± 6.3 | 32.1 ± 11.7 | 47 ± 21.7 | 50.9 ± 20.2 | 48 ± 27.1 | 22.8 ± 15.7 |
| pts with low value | 100% | 100% | 59.5% | 54.7% | 33% | 100% |
| VWF:Ag IU/dL $\bar{x}$ ± SD | 1.7 ± 1.9 | 6.2 ± 5 | 28.0 ± 8.6 | 43.9 ± 12.3 | 70 ± 40.7 | 85.7 ± 26.2 |
| VWF:RCo IU/dL $\bar{x}$ ± SD | 1 ± 0 | 3.5 ± 2 | 25 ± 5 | 41.5 ± 4.9 | 22 ± 17.1 | 78.8 ± 27.3 |
| VWF:RCo/VWF:Ag | NA | 0.89 ± 0.09 | 1.04 ± 0.38 | 0.98 ± 0.37 | 0.34 ± 0.21 | 0.93 ± 0.26 |
| FVIII/VWF:Ag | NA | NA | NA | NA | NA | 0.3 ± 0.19 |

BT, bleeding time; SD, standard deviation; pts, patients; FVIII, factor VIII; VWF:Ag, von Willebrand factor antigen; VWF:RCo, VWF ristocetin cofactor; $\bar{x}$, mean; NA, not applicable.

mutations for hemophilia B; 27, storage pool deficiency; 100, abnormal platelet release reaction; 6, Ehlers-Danlos syndrome; 4, Noonan's syndrome; and 2, Rendu-Osler-Weber disease. One patient had presented three episodes of severe bleeding at ovulation, requiring surgery twice, with the diagnosis of mild VWD and mild storage pool deficiency. Mild VWD associated with other thrombopathies or coagulopathies should be considered as a potentially severe bleeding disorder.[10]

### PATIENTS WITH TYPE 1 AND 3 VON WILLEBRAND DISEASE

Normal levels of FVIII are found in 45.2% of type 1 and possible type 1 variants. The lower the levels of VWF:RCo, the higher the percentage of patients with bleeding symptoms, especially epistaxis and bleeding in surgeries. Epistaxis is the most common bleeding symptom in type 3 and severe type 1 patients.

It is important to note that our patients with type 3 showed no response of VWF parameters and BT to DDAVP, whereas severe type 1 showed a poor response, with a minor increase of VWF, and a slight shortening of the BT that did not reach normal values (Table 1).

### PATIENTS WITH DIAGNOSIS OF TYPES 2A, 2M, AND 2B VON WILLEBRAND DISEASE

We found normal levels of FVIII in 33% of these variants, and bleeding symptoms in 91.2% of patients. We described two new mutations and reported them into the International Society on Thrombosis and Haematosis Scientific and Standardization Committee (ISTH-SSC) VWF database: E1549K, which was found in heterozygosity in six members of the same family, related to type 2M phenotype, and C1272F, found in a boy and his mother, with 2A phenotype. We have two patients with a laboratory pattern of 2B VWD, but we could not find any candidate mutation in exon 28 of the *VWF* gene. Thus specific determinations for diagnosing platelet type VWD should be completed and the candidate mutations further investigated.

### PATIENTS WITH PROBABLE TYPE 2N VON WILLEBRAND DISEASE

In this group, the frequency of males is higher ($p < 0.0001$). When we compared the incidence of clinical symptoms between patients with probable 2N and with possible type 1+probable 2N, this last group had a higher incidence of hemarthrosis ($p < 0.0001$), and received more transfusions (cryoprecipitates, FVIII concentrates). We have found R854Q in eight patients.[11] In one of these cases, we could study 22 members of the family (Table 3: P-1 proband), R854Q being found in heterozygosity in 5 of them, with a 22.7% familial penetrance. Of these patients 60% had clinical symptoms. R924Q was also found in heterozygosity in five patients[12]; one being double heterozygous for R924Q and R1205H.

## GENOTYPE/PHENOTYPE RELATIONSHIPS

Discrepancies between the VWD variants and the candidate mutations related to different phenotypes have been reported. We have found the R1315C mutation in four patients with 2M phenotype, which has been reported in the ISTH database in association with type 2M, type unclassified, type 1, and type 3. We also found the I1628T mutation in three members of one family, also associated with a 2M phenotype, and reported in the ISTH database as 2A and SNP. These data show a diagnostic problem to be taken into account during VWD classification[13] (Table 3).

**Table 3 Phenotypic and Genotypic Profiles in Our von Willebrand Disease Patients with Candidate Mutations**

| Patients | BT (min) | Platelet Count ($10^9$/L) | FVIII (IU/dL) | VWF:Ag (IU/dL) | VWF:RCo (IU/dL) | Multimeric Pattern | Mutation | | VWD Type |
|---|---|---|---|---|---|---|---|---|---|
| A-1 mother | 9 | 282 | 35 | 44 | ND | Absence of intermediate and HMWM | C1272F | Heterozygous | 2A |
| A-2 proband | >9 | 534 | 30 | 32 | ND | Absence of intermediate and HMWM | C1272F | Heterozygous | 2A |
| | 8 | 216 | 45 | 56 | 36 | Absence of HMWM | R1306W | Heterozygous | 2B |
| C | >9 | 150 | 56 | 47 | <10 | Absence of HMWM | R1308C | Heterozygous | 2B |
| D | >10 | 150 | 45 | 52 | 19 | Absence of HMWM | V1316M | Heterozygous | 2B |
| E | NT | 175 | 40 | 46 | 20 | Absence of HMWM | V1316M | Heterozygous | 2B |
| F | 6.5 | 840 | 35 | 10 | <10 | Normal | R1315C | Heterozygous | 2M |
| G | >9 | 456 | 25 | 15 | ND | Normal | R1315C | Heterozygous | |
| H-1 proband | 4.5 | 458 | 28 | 20 | <10 | Normal | R1315C | Heterozygous | |
| H-2 cousin | 7.5 | 754 | 30 | 21 | <10 | Normal | R1315C | Heterozygous | |
| I-1 | 4.5 | 304 | 130 | 112 | <10 | Normal | G1324S | Heterozygous | |
| J-1 proband | >9 | 653 | 40 | 49 | ND | Normal | I1628T, M740I | Double heterozygous | 1 + 2M |
| J-2 mother | NT | 450 | 90 | 80 | 61 | Normal | M740I | Heterozygous | 1 |
| J-3 father | >10 | 435 | 45 | 31 | ND | Normal | I1628T | Heterozygous | 2M |
| J-4 sister | 5.5 | 747 | 47 | 53 | ND | Normal | I1628T | Heterozygous | |
| K | 4.5 | 304 | 130 | 112 | <10 | Normal | G1324S | Heterozygous | 2M |
| L-1 proband | 8 | 450 | 20 | 15 | ND | | C1374 | Homozygous | 2M |
| L-2 sister | 5.5 | 282 | 70 | 34 | <10 | Normal | | Heterozygous | |
| L-3 son | 6.3 | 210 | 30 | 28 | <10 | | R1374C | Homozygous | |
| M-1 proband | 9 | 317 | 115 | 92 | ND | | E1549K | Heterozygous | 2M |
| M-2 sister | NT | 344 | 100 | 93 | 22 | | | Heterozygous | |
| M-3 grand mother | >15 | 450 | 45 | 85 | <10 | | | Heterozygous | |
| M-4 cousin | 5 | 524 | 45 | 61 | <10 | | | Heterozygous | |
| M-4 cousin | 8.5 | 258 | 90 | 91 | <10 | | | Heterozygous | |
| M-5 aunt | 6 | 283 | 50 | 45 | ND | | | Heterozygous | |
| M-6 uncle | | | | | | | | | |
| N-1 proband | 4 | 566 | 31 | 13 | <10 | 50% of ultra-large multimers | R1205H, R924Q | Double heterozygous | Vicenza + 2N |
| N-2 mother | 3.5 | 430 | 40 | 75 | 66 | Normal | R924Q | Heterozygous | 2N |
| O-1 proband | 3.3 | 420 | 7 | 82 | 90 | NA | R854Q | Heterozygous | 2N |
| O-2 aunt | NT | 530 | 33 | 45 | 42 | NA | | | |
| P-1 proband | NT | 439 | 70 (pregnant) | 95 | 82 | NA | | Heterozygous | |
| P-2 grandmother | Not available for laboratory assays | | | | | | | Heterozygous | |
| P-3 son | Not available for laboratory assays | | | | | | | Heterozygous | |
| P-3 brother | Not available for laboratory assays | | | | | | | | |
| P-4 brother | Not available for laboratory assays | | | | | | | Heterozygous | |
| Q | NT | 661 | 47 | 96 | 110 | NA | | Heterozygous | |
| R-1 proband | 8 | 450 | 20 | 103 | 93 | NA | R924Q | Heterozygous | 2N |
| R-2 son | 6 | 507 | 50 | 97 | 74 | NA | | | |
| S | NT | 395 | 50 | 110 | 87 | NA | | Heterozygous | |

BT, bleeding time; FVIII, factor VIII; VWF:Ag, von Willebrand factor antigen; VWF:RCo, VWF ristocetin cofactor; VWD, von Willebrand disease; ND, nondetectable; HMWM, high molecular weight multimer; NA, not applicable; NT, not tested.

## MAJOR BLEEDING RELATED TO SURGERIES

VWD is rarely associated with spontaneous bleeding in the most common forms but may result in a severe hemorrhage after a hemostatic challenge such as trauma or surgery. In a selected group of patients with type 1, possible type 1, and type 2 VWD, with surgical events before diagnosis, the frequency of major bleeding related to surgery was evaluated.

Laboratory tests, bleeding score, number of bleeding sites, and positive family history did not prove to be effective as risk markers of major bleeding. A total of 17.5% of the surgeries in type 1 and possible type 1 VWD patients and 50% in type 2 had major bleeding. Patients with possible type 1 VWD had a similar frequency of major bleeding related to surgeries as those of type 1 (32.6% of type 1 and 24.8% of possible type 1), whereas 54.9% of type 2 patients presented major bleeding. In type 1 and possible type 1, bleeding after tooth extraction was the most frequent clinical symptom; in type 2 it was postpartum bleeding. Both findings could define risk factors of major bleeding. Cesarean delivery and adenotonsillectomy are the surgeries with the highest frequency of major bleeding.[14,15]

## TREATMENT STRATEGY

Intravenous DDAVP is our choice of treatment in patients responsive to DDAVP, and coagulation factor concentrates is our choice in nonresponsive or in cases with a contraindication to DDAVP. Sometimes DDAVP is used without response testing. Subcutaneous infusion is as efficient as intravenous administration.

### Biologic Response to DDAVP

DDAVP response was evaluated in 567 patients >18 years of age. DDAVP was infused intravenously over a period of 20 minutes, at a dose of 0.3 μg/kg body weight, in saline solution. Blood samples were obtained for platelet count, PT, aPTT, FVIII, VWF:Ag, VWF:RCo, and euglobulin clot lysis time before and after 1, 2, and 24 hours of DDAVP infusion. BT is also performed. In the case of accelerated fibrinolytic response, the dose of DDAVP is reduced to 0.2 μg/kg body weight, for further treatments. The response is adequate when there is an increase of plasma FVIII and VWF:RCo of threefold over baseline, and both levels reach values of at least 50 IU/dL, 1 and 2 hours after the DDAVP infusion. The response is inadequate if neither FVIII nor VWF reach the plasmatic levels required for hemostasis (>50 IU/dL). No response means that all the parameters remain abnormal or FVIII does not reach the plasmatic levels required for hemostasis in cases of the probable type 2N variant. Responses to DDAVP according to the different variants are shown in Table 1.

## VON WILLEBRAND DISEASE IN SPECIAL POPULATIONS

### Women

Women are exposed to the additional hemostatic challenges of menstruation and childbirth. The most frequent symptoms in women are mucocutaneous bleeds (81%) and menorrhagia (79%), which can be confirmed by a pictorial bleeding assessment chart. In relation to pregnancy, >20% of the patients reported bleeding after delivery. We have studied 285 healthy nonbleeding women (mean age: 25.1 years): 184 in antepartum period, 64 during puerperium, and 37 nonpregnant.[16] We recorded an increase in FVIII and VWF. We found that VWF:Ag was significantly increased from the sixth week of pregnancy onward. The VWF level dropped significantly from 7 days after delivery, in contrast to the immediate decrease described by Noller et al.[17]

### DDAVP during Pregnancy

Women with VWD have a higher incidence of primary and secondary postpartum hemorrhage,[5] more likely to occur when FVIII levels are <50 IU/dL during month 7 or 8 of pregnancy.[18] The literature is scarce on the use of DDAVP during pregnancy.[19] We therefore reviewed the antenatal use of DDAVP in 54 women (1990 to 2005).[20] Ten women had type 1 and 44 had possible type 1 VWD. These women reported nose and gum bleeding and easy bruising (55.5%), menorrhagia (53.7%), postpartum bleeding history (38.7%), and postsurgery bleeding (27.8%). The response to DDAVP was tested before pregnancy in 63% of the women, all with a good response. We reevaluated laboratory parameters in months 7 and 8 to evaluate if prophylaxis at term was necessary or not.

There have been several concerns regarding the use of DDAVP antepartum: the chance of maternal and neonatal hyponatremia, and the oxytocin-like effects on uterine muscle. The individual hemostatic response to pregnancy is variable, and childbirth carries a higher risk of postpartum bleeding in several patients. At the end of the first trimester, between 10 and 12 weeks, three women received DDAVP for five procedures without adverse effects. Their newborns were in good health and appropriate weight. We also prescribed DDAVP in 30 vaginal and 45 cesarean deliveries. In 48 cases, DDAVP was infused before the epidural catheter placement for analgesia and no local complication was observed. The effective hemostasis was obtained with a single dose of DDAVP at the time of delivery, avoiding fluid retention. No adverse effects were observed in mothers or newborns. Thus we believe DDAVP should be considered as the first choice of therapy, even in pregnant women.

## DDAVP in Children

The diagnosis and management of mild and moderate VWD in pediatrics is challenging and requires a high index of suspicion. In accordance with the National Heart, Lung and Blood Institute guidelines on VWD,[5] we reported that, like us, many pediatric hematologists do not use DDAVP in children <2 years of age.

We therefore analyzed retrospectively[21] our cohort of 221 children (137 females) comprising 27 type 1 and 194 possible type 1, to identify patient characteristics related to biological and clinical response to DDAVP. The most frequent bleeding symptoms in children were epistaxis (61.5%), easy bruising/hematoma (58.4%), gum bleeding (27.2%), and bleeding after tooth extraction (13.6%) and after surgery (13.2%). In girls, the prevalence of menorrhagia was 51.8%. Other infrequent symptoms were bleeding from gastrointestinal and urinary tracts, teething, and umbilical stump bleeding.

Children with type 1 were younger than those with possible type 1. Girls were diagnosed more frequently as possible type 1 and older than boys at diagnosis. Hyponatremia and volume overload due to the antidiuretic effects of DDAVP are relatively rare but frequent in patients receiving repeated infusions and with poor fluid restriction. We apply strict fluid restriction. Only one dose of DDAVP was given, which proved effective and safe for children with VWD, and we have seen no major complications. The DDAVP infusion test was performed in 214 of 221 children, and >90% of the patients showed a good response. We found no relationship between response to DDAVP and age or gender. We modified the DDAVP testing only for children <20 kg of weight, performing the baseline and post 90-minute evaluation. Accordingly, we believe that the DDAVP infusion test should be performed in all children >2 years of age with low VWF levels and a bleeding history, particularly in those with VWF <30 IU/dL, who are at a higher risk of no adequate response. Type 1 patients had a risk of DDAVP test failure threefold higher than those with possible type 1. Clinical response to DDAVP, prescribed both for treatment and for prophylaxis, was evaluated 87 times in 68 children with no major adverse events or bleeding and proved effective with one single dose of DDAVP in almost all patients.

When all the patients were analyzed, including children ($n = 783$; mean age: 25.7 years; range: 2 to 66 years) we found that patients with FVIII and VWF:RCo <30 IU/dL were at risk of DDAVP failure. Children <10 years of age showed nonresponse more frequently than older patients (16.9% versus 4.9%; $p < 0.001$). No patient showed significant unwanted effects. Therefore, we could define three markers related to the DDAVP responsiveness: age, FVIII, and VWF:RCo levels. In the DDAVP failure, the age could also reflect a severity of the illness in this younger population. Because this is a safe, effective, and affordable therapy, we hope to encourage all pediatricians to a wider use of DDAVP, especially in children from developing countries.[22]

## Long-Term Prophylaxis in von Willebrand Disease

Prophylaxis has been successfully used in hemophilia for many years, but because bleeding in VWD is usually mild, the need for prophylaxis has been less well recognized, and only in the last years have reports on prophylaxis begun to appear.[23] Patients with type 3 VWD and some severe type 2 and type 1 VWD with joint bleeding, epistaxis, menorrhagia, and oral and gastrointestinal bleeding may benefit from prophylaxis when bleeding is frequent and leads to the need for blood transfusions and hospital admission.

We started a prophylaxis protocol in two type 3 VWD patients. In one of them, an 8-year-old boy, the reason was recurrent hemarthrosis. Haemate-P was administered twice a week for 3 years, with clear reduction in the appearance of joint bleeding. Only once did he present with profuse nose bleeding, and Haemate-P was infused daily for 4 days. The other patient was diagnosed VWD type 3 when he was 7 months old due to recurrent and life-threatening epistaxis that required a blood transfusion on three occasions before diagnosis. He showed evidence of an inhibitor to VWF:RCo in the first determination. Prophylaxis with Haemate-P twice a week was begun, but the response was not satisfactory, although it was recognized that the infusions were not performed regularly. Nose bleeding recurred, the nasal mucosa was severely damaged after several tamponades, and even though platelet concentrates were added to Haemate-P, the response was poor. Prophylaxis was switched to three times a week. The inhibitory effect detected initially increased. The patient finally died at 22 months of age due to hypovolemic shock without response to cryoprecipitates, Haemate-P, platelets, or recombinant factor VIIa. In this case, a rare inhibitory effect might have been responsible for the failure of the prophylaxis. A few additional patients could have been eligible for a prophylactic scheme in the past, and this approach will probably be used more frequently in the future. We should consider searching for inhibitory activity in all patients with undetectable levels of VWF:RCo and very low levels of factor VIII.

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