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ORIGINAL ARTICLE

PT-VWD posing diagnostic and therapeutic challenges – small case series

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Abstract

Despite the increased worldwide awareness, over the last decade, of the platelet-type von Willebrand Disease (PT-VWD), many uncertainties remain around this rare platelet bleeding disorder. This report aims to correctly identify and study the phenotype of new patients and highlights the diagnostic and therapeutic challenges this disease remains to pose. We describe four PT-VWD cases confirmed by genetic analysis in which either the diagnosis and/or the treatment posed challenge. We provide the details of the clinical presentation, laboratory analysis, and the treatment and the responses in each case. We show that in addition to type 2B VWD, PT-VWD can be misdiagnosed as idiopathic thrombocytopenic purpura, neonatal alloimmune thrombocytopenia, and unexplained gestational thrombocytopenia. The disease can be diagnosed as early as 1 year of age and with phenotypically normal parents. Bleeding in some patients can be managed successfully using Humate P and DDAVP combined with tranexamic acid with no significant thrombocytopenia. We provide for the first time an evidence of an efficient response to rFVIIa in PT-VWD. Anaphylactic reaction to VWF preparations may be related to PT-VWD and the development of HLA antibodies is not uncommon. Progressive thrombocytopenia with normal VWF levels can be seen with PT-VWD and the platelet count was normalized at 2.5 weeks postpartum in one case. We conclude that these studies represent a record of clinical observations/interventions that help improve diagnoses/management of PT-VWD, highlight the variations in age and clinical presentations, laboratory diagnostic approaches, the importance of genetic testing for accurate diagnosis and consideration of therapeutic alternatives.

Keywords

DDAVP, large platelets, platelet aggregation, PT-VWD, thrombocytopenia, Type 2B VWD

History

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Introduction

The diagnosis and treatment of PT-VWD: current knowledge

Platelet-type von Willebrand disease (PT-VWD) is a rare autosomal-dominant bleeding disorder caused by a gain-of-function mutation in the platelet *GP1BA gene* coding for the platelet surface glycoprotein Iba (GPIbα), the receptor for the adhesive glycoprotein von Willebrand factor (VWF).

PT-VWD is typically characterized by a mild-to-moderate bleeding phenotype but can be life-threatening in stressful conditions such as surgery, pregnancy, and childbirth [1]. The laboratory features will reflect the pathophysiology of this disease: inappropriate or enhanced agglutination to low-dose ristocetin, decreased VWF levels, partial loss [2] or absence of the high molecular weight multimers of VWF, and varying degrees of thrombocytopenia. Unlike type 2B VWD where the defect is a gain-of-function mutation in the *VWF gene*, PT-VWD exhibits this gain-of-function defect in the platelet *GP1BA gene*. Compared to type 2B VWD (~5% of all VWD types), PT-VWD is more rare, commonly undiagnosed, and often misdiagnosed. The percentage of misdiagnosis among type 2B VWD is 15% based on an international prospective/retrospective study [3].

There is a critical need to appropriately diagnose PT-VWD as this has important therapeutic implications. PT-VWD from type 2B VWD can be distinguished with a carefully assessed RIPA-based plasma/platelet-mixing studies which are based on the fact that (washed) PT-VWD platelets (but not type 2B platelets) aggregate in normal plasma with a low concentration of ristocetin and that (washed) normal platelets aggregate in the presence of type 2B (but not PT-VWD) plasma at similarly low concentrations of ristocetin [4]. The limited access to confirmatory genetic analysis and the need for trained professionals to perform and interpret aggregation and platelet-mixing assays particularly with the low platelet count in some patients may result in misdiagnoses in the majority of patients. In fact, apart from only a few instances where a primary PT-VWD diagnosis was made, most cases have been misdiagnosed as either type 2B VWD or ITP [4].

The treatment of PT-VWD can be challenging [5]. Ideally, platelet concentrates are sufficient to secure hemostasis in various bleeding conditions; preferably HLA-matched platelets. The

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administration of VWF concentrate in a low dosage to increase the hemostatic activity – without causing thrombocytopenia – would be useful. A level of VWF:RCo = 40–47 IU/mL has been reported [6]. Desmopressin (DDAVP) is generally contraindicated in PT-VWD because the release of large VWF multimers from endothelial cells and worsen thrombocytopenia [6]. Although so far not supported by clinical evidence, theoretically, recombinant-activated FVII could be of benefit for the treatment of refractory life-threatening bleeding [5].

In this report, we present four PT-VWD cases in which either the diagnosis and/or the treatment has posed a challenge. While these case studies cannot provide specific guidance for the diagnosis and management of successive patients, they are a record of clinical observations and interventions that improve our understanding of PT-VWD. Importantly, the cases emphasize the variable age and clinical presentation of PT-VWD, the diagnostic difficulties and variations among the different laboratories, the importance of genetic testing, and the lack of a common approach to treatment.

Case 1 presentation – Hematological Research Institute, National Academy of Medicine, Buenos Aires, Argentina

A male patient diagnosed with idiopathic thrombocytopenic purpura (ITP) was referred to this center at age of 13 for reevaluation because of ongoing bleeding symptoms despite splenectomy and also thrombocytopenia that was not sufficient to explain these symptoms.

Detailed history revealed that this patient initially presented on day 45 of life with epistaxis, purpura, and thrombocytopenia and was diagnosed with ITP. Between 1 and 4 years of age, he was admitted to the hospital for several reasons, pneumonia and surgery for inguinal hernia complicated by severe bleeding and symptomatic anemia. Bleeding episodes were successfully treated with intravenous gamma-globulin (IVIg) and corticosteroids, but the interpretation was *difficult* due to the frequent association with platelet transfusion. At 12 years of age, laparoscopic splenectomy was performed which was complicated by massive intraperitoneal bleeding, requiring multiple platelet transfusions, cryoprecipitate, fresh frozen plasma, IVIg, and corticosteroids. Bone marrow aspiration had been performed in four different occasions, based on persistent bleeds and the failure to respond to IVIg therapy and to corticosteroids and showed only an increased number of megakaryocytes.

This patient was born from a cesarean section of twin pregnancy due to placenta previa. The patient has two sisters: one, symptomatic with menorrhagia incapacitating work activity and a history of hemorrhagic follicular cyst, while the other had no bleeding symptoms. The patient has three brothers: the twin who died at 45 days of age with apparent diagnosis of leukemia, another symptomatic with almost daily episodes of epistaxis, which requires tamponades, and a third healthy one. The father showed bleeding symptoms related to spontaneous trauma and surgery. The mother had poor obstetric history with seven pregnancies: two miscarriages (12 and 20 weeks), five cesarean sections: the first one for hypertension at 35 weeks; three cesarean section at term, and the last one was the twin pregnancy complicated by severe bleeding necessitating a hysterectomy.

Upon reevaluation, laboratory findings (Table I; Figure 1A) led to an initial diagnosis of type 2B VWD but platelet-mixing studies documented PT-VWD (Figure 1B–D). Platelet aggregation studies showed reduced aggregation to low-dose ADP (2.5 μM) and normal-to-high dose (5 μM). There was also reduced aggregation in response to low-dose collagen (1 μg/mL) and normal-to-high dose (8 μg/mL) (Figure 1E). A mepacrine uptake assay by flow cytometry was normal, indicating that the platelet dense granule content was not affected. Blood smear showed very large platelets with clear signs of activation and pseudopods (Figure 1F). The patient has received VWF concentrate; Humate-P and DDAVP in some episodes in combination with tranexamic acid but there was no response; epistaxis persisted, even accompanied by hematocrit drop (from 40% to 28%) and thrombocytopenia (20×10^9/L). We attempted to try rFVII twice since and surprisingly the bleeding stopped after 2 h, with a single dose of 5 μg in each episode.

Case 2 – Hemophilia Treatment Center, North Shore long Island Jewish Health System, Cohen Children's Medical Center of New York – USA

A full-term Hispanic boy was born via uncomplicated vaginal delivery. Circumcision at the time of birth was complicated by prolonged bleeding. He did not have easy bruising, umbilical cord bleeding, bleeding after heel stick, or other signs of mucocutaneous bleeding. The patient exhibited thrombocytopenia but otherwise normal blood picture and basic coagulation profile. Parents were tested for platelet antigen 5a (HPA5a): mother was negative and father was positive; hence, a diagnosis of neonatal alloimmune thrombocytopenia (NAIT) was made. He received IVIg twice and one platelet transfusion with resolution of bleeding and improvement in platelet count. In the following months, he was seen as an outpatient and his platelet count ranged from 70 to 160×10^9/L with no signs of bleeding.

At 8 months of age, he developed a large 3 ×10 cm left frontal, temporal, and parietal cephalohematoma after a fall from his crib. There was no evidence of intracranial bleed or skull fracture on CT scan of the brain. The peripheral blood smear showed platelet clumping and large granular platelets. These features were all consistent with VWD type 2B. However, genetic analysis showed no mutations in exon 28 of *VWF gene* thus the genetic sequence of *GP1BA gene*, revealing a mutation diagnostic of PT-VWD. Laboratory findings including genetic analysis are shown in Table I. The patient received Humate P at 30 U/kg twice a day for 3 days and the same dose once a day × 1 day with significant reduction in size of hematoma with no reduction in platelet count. Further infusions were deferred due to lack of venous access. Both clinically asymptomatic parents had normal VWD panels including VWF multimer and RIPA test.

Case 3 – National Centre for Hereditary Coagulation Disorders, St. James's Hospital, Dublin, Ireland

A female patient was referred to our center for investigation of an alternative cause to "gestational thrombocytopenia" from previous two pregnancies. She had no past medical history of note and was not taking any medications. She had lifelong easy bruising, epistaxis, and menorrhagia since menarche. Dental extraction at 16 years of age was complicated by persistent bleeding which required suturing. The two pregnancies prior to her diagnosis were both complicated by progressive thrombocytopenia from a normal baseline platelet count. Her first delivery was an emergency lower section C-section (LSCS) for fetal distress. At that time, she received a platelet transfusion due to a platelet count of 15×10^9/L and heavy vaginal bleeding. The second delivery was an elective, uncomplicated LSCS at 39 weeks gestation with a platelet count of 69×10^9/L. Secondary postpartum hemorrhage occurred in both deliveries but did not necessitate transfusion.

Baseline laboratory investigations and initial platelet-mixing studies to assess for type 2B VWD and/or PT-VWD were inconclusive but later genetic testing confirmed a mutation in the *GP1BA gene* (Table I).

Table I. Clinical and laboratory phenotype of the four described cases.

	Case 1 13 years	Case 2 8 months	Case 3 30 years	Case 4 20 years
Gender	Male	Male	Female	Female
Age of presentation Bleeding symptoms	45 days Epistaxis, purpura, postsurgical bleeding Reevaluation at 13 years	Birth Bleeding at circumcision, cephalohematoma Reevaluation at 8 months	Menarche Lifelong bleeding, bruising, epistaxis and menorrhagia Reevaluation during pregnancy	5 years Lifelong bleeding, bruising, epistaxis Reevaluation at 20 years
Misdiagnosis	Idiopathic thrombocytopenia, purpura	Neonatal alloimmune thrombocytopenia	VWD type 2B, gestational thrombocytopenia	VWD Type 2B, gestational thrombocytopenia

Laboratory data	**At diagnosis**	**At diagnosis**	**At diagnosis**	**Pregnancy stage**			
				Baseline	**2nd trimester**	**3rd trimester**	**Postpartum**
Platelet ($\times 10^9$/L)	95	61	135	156	81	51	183
Factor VIII (IU/mL)	1.00	0.94	0.78	ND	0.87	1.66	0.87
VWF:Ag (IU/mL)	1.29	0.88	0.69	0.57	0.71	1.52	1.03
VWF:RCo (IU/mL)	0.28	0.34	0.22	0.86	0.52	1.08	0.61
VWF:CB (IU/mL)	0.70	ND	ND	ND			
RCo/Ag ratio	0.22	0.39	0.32	1.15	0.73	0.71	0.59
CB/Ag ratio	0.54	ND	ND	ND			
VWF: HMW Multimers	Partial loss	Absent	Absent	Normal when performed during pregnancy			
Low-dose RIPA	Enhanced Decreasing concentration (0.7,0.6, 0.5, 0.4, etc.) to reach the minimum concentration that shows response (in this case was 0.3 Figure 1A). RIPA is considered positive when aggregation is >20%	Enhanced Reference range for standard dose RIPA (1.0 mg/mL) is 50–150% and for low dose (0.63) is 0%. Patient's aggregation was 64%	Enhanced Reference range for low-dose RIPA (0.5 mg/mL) is 0. Patient's aggregation was 40%	Enhanced Reference range for standard dose RIPA (1.5 mg/ml) is 50–150% and for low dose (0.5) is 0%. RIPA is considered positive when any aggregation is observed. Patient's aggregation was 80%			
Platelet aggregation	Reduced to ADP (2.5 μM) Normal to ADP (5 μM) Reduced to collagen (1 μg/mL) Normal to collagen (8 μg/mL)	Normal to ADP (4,10, 20 μM) Normal to collagen (0.2, 0.1 g/L) Normal to epinephrine (100 μM) Normal to arachidonic acid (0.5 g/L)	Normal to ADP (2 μM) Normal to collagen (0.2 g/L) Normal to epinephrine (10 μM)	Normal to ADP (4,10, 20 μM) Normal to collagen (0.2, 0.1 g/L) Normal to epinephrine (100 μM) Normal to arachidonic acid (0.5 g/L)			
HLA antibodies	ND	ND	Uncommon HLA type HLA class I IgG	HLA class I, II IgG			
Genetic analysis *GP1BA gene*	p.Met255Val	p.Met255Val	p.Gly249Val	p.Gly249Val			

Treatment	**Treatment**	**Clinical response**	**Treatment**	**Clinical response**	**Treatment**	**Clinical response**	**Treatment**	**Clinical response**
	VWF concentrate (Humate-P)	Poor response	VWF concentrate (Humate-P)	Good response	VWF concentrate (Fandhi)	Anaphylactic reaction	HLA-matched apheresis platelets	Good response
	DDAVP combined with Tranexamic acid	Poor response	Tranexamic acid	Good response	DDAVP	Good response re: VWF:RCo but no improvement in PFA-100 closure times		
	HLA-matched platelets, cryoprecipitate, steroids, IVIg	Good response			DDAVP combined with Tranexamic acid	Good response		
	Recombinant FVIIa	Good response			HLA-matched platelets	Difficult due to HLA antibodies		

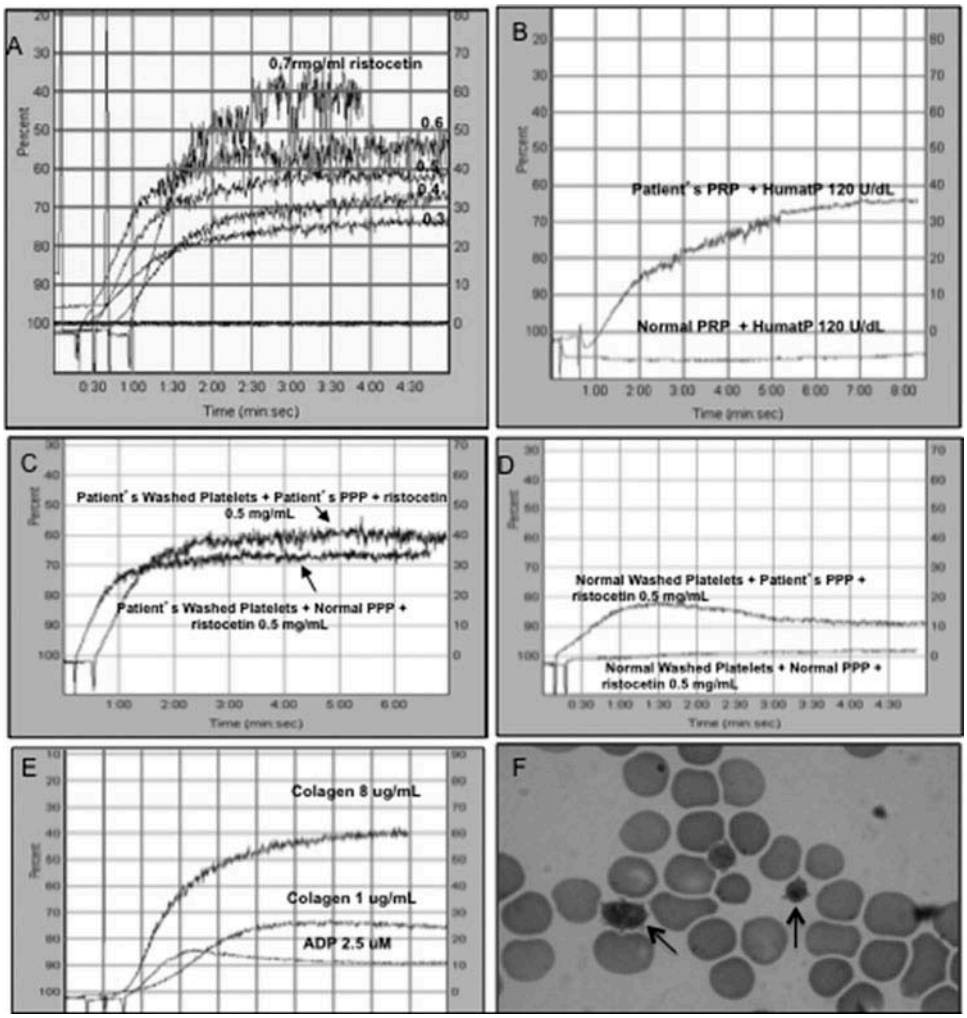

Figure 1. Diagnostic work up for PT-VWD. (A) RIPA at different concentrations of ristocetin 0.7, 0.6, 0.5, 0.4 mg/mL. (B–D) Platelet-mixing studies. (E) Platelet aggregations in response to ADP and collagen. (F) Blood smear showing very large platelets (indicated by black arrowheads) with evidence of activation.

Obtaining compatible HLA-matched platelets proved difficult due to an uncommon HLA type as well as detectable HLA Class I IgG antibodies. An initial trial of a VWF containing concentrate (Fandhi, Grifols®) resulted in an anaphylactic reaction. DDAVP induced a partial response with mild thrombocytopenia as shown in Table II. Platelet and VWF levels were monitored in two subsequent pregnancies. VWF levels normalized but platelets decreased to a nadir of 55 in the 3rd trimester. Elective cesarean sections were performed at 39/40 weeks of gestations in both cases with platelets on standby and no excess bleeding.

Table II. The use and response to DDAVP in PT-VWD in case 3. Results of two trials are provided.

	VWF:RCo (IU/mL)	Platelet count ($\times 10^9$/L)
	DDAVP trial 1	
Baseline	0.2	135
DDAVP +1 h	1.3	107
DDAVP +5 h	0.96	91
	DDAVP trial 2	
Baseline	0.22	198
DDAVP +1 h	0.7	161
DDAVP +2 h	0.5	158
DDAVP +4 h	0.41	154

Intravenous DDAVP (0.3 μg/kg) and tranexamic acid have been used successfully for three dental extractions on two separate occasions with the development of mild thrombocytopenia. Although her VWF:RCo improved with the administration of DDAVP, there was no improvement in her PFA-100 closure times at 1 h (Coll/Epi > 250 s; normal range 85–165 s, Coll/ADP > 250 s; normal range 71–118 s). She also received IV DDAVP after a minor head injury and although her platelet count was reduced, it remained within the normal range. No hemorrhagic complications occurred with DDAVP use for both the extractions or management of head injury.

Case 4 presentation: Division of Hematology and Hematologic Malignancies, University of Calgary, Canada

A female patient presented to medical attention at the age of 5 with easy bruising, epistaxis, and a family history of VWD. The patient's father had been diagnosed with type 2B VWD. The patient's VWF studies also confirmed the same diagnosis but the patient was lost to follow-up until the age 20 at which time she reported menorrhagia, treated with an oral contraceptive pill but no other new bleeding symptoms. On reevaluation, the genetic analysis failed to demonstrate a mutation within exon 28 of the VWF gene; therefore, the diagnosis was questioned and platelet *GP1BA gene* sequencing reveled a PT-VWD mutation. The father's diagnosis has since been reevaluated and he is affected by the same PT-VWD as the index case.

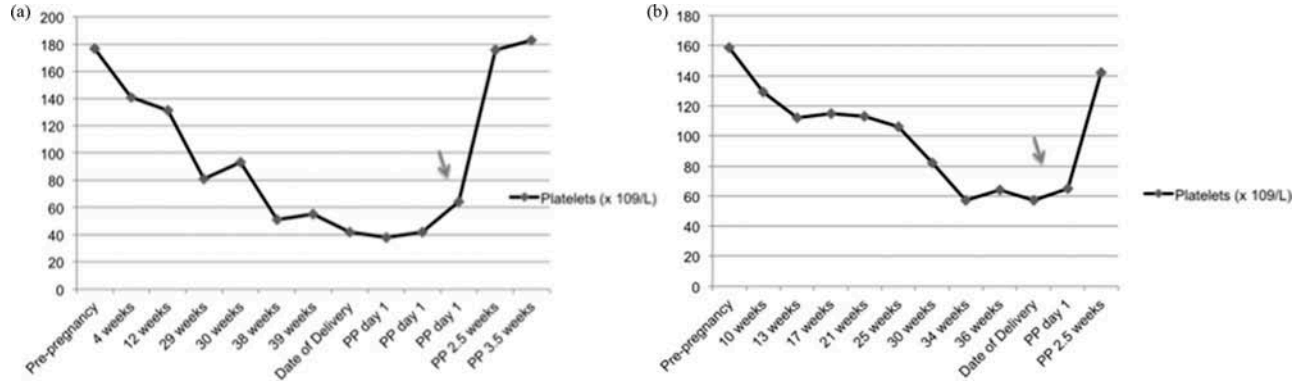

Figure 2. (a) Platelet counts are shown throughout pregnancy and in the postpartum period. The date of delivery occurred in the 39th week of gestation. On postpartum day 1, the patient had several complete blood counts performed as she was bleeding excessively from a 3rd degree tear. She received a unit of pooled platelets (gray arrow) with an incremental increase in platelet count from 42 to 64. PP: postpartum. (b) Platelet counts are shown throughout pregnancy and in the postpartum period. The date of delivery occurred in the 38th week of gestation. The patient received a prophylactic unit of HLA-matched apheresis platelets (gray arrow) between the date of delivery and postpartum day 1 and had an incremental increase in platelet count from 57 to 65. PP: postpartum.

The patient had two pregnancies. During her first pregnancy, VWF parameters in the second and third trimesters were within normal range (Table I). Her pregnancy was complicated by thrombocytopenia to a nadir of 38 × 10^9/mm^3 on postpartum day 1 (Figure 2a), excessive bleeding from a 3rd degree tear, and delayed postpartum hemorrhage for 6 weeks. Her hemoglobin decreased in the peripartum period from 143 to 87 g/L. She received a single unit of apheresis platelets on postpartum day 1 with an incremental rise in platelet count from 42 to 64 × 10^9/L.

At 2.5 weeks postpartum, her platelet count had normalized (176 × 10^9/L). VWF studies were repeated at 3.5 weeks postpartum (Table I). Platelet aggregation studies were normal to ADP, epinephrine, collagen, and arachidonic (Table I).

During her second pregnancy and in anticipation of further platelet transfusions, platelet antibody testing was performed. No antibodies were detected against platelet antigens HPA-1a or b, 3a or b, 4a, 5a or b, GPIb/IX, but HLA class I and II antibodies present. HLA-matched apheresis platelets were made available for expected date of delivery. Again, this pregnancy was complicated by thrombocytopenia to a nadir of 57 × 10^9/L on the date of delivery (Figure 2b). She was prophylactically transfused immediately postpartum with a single HLA-matched unit of platelet. No bleeding complications occurred, despite requiring an episiotomy. Her hemoglobin decreased from 136 to 110 g/L postpartum.

Discussion

The four cases described in this report highlight several important challenges in the diagnosis and management of PT-VWD.

There is a considerable variation in the clinical presentations and age at which patients presented. This variation has led to misdiagnoses in some instances. PT-VWD is known to present with mild-to-moderate mucocutaneous bleeding. Both cases 1 and 2 presented with closely similar bleeding phenotype early in life but two different misdiagnoses were established. While misdiagnosis of PT-VWD has been previously reported [3], the multiple frequent transfusions to stop bleeding in case 1 appear to have masked the correct diagnosis for over 12 years. It is important to note that when meticulously performed, platelet-mixing studies (Figure 1) facilitate a correct diagnosis of the disease. This was previously documented [4]. Case 3 and case 4 were only correctly diagnosed after revaluation and/or referral during pregnancy where gestational thrombocytopenia was the alarming sign.

In both type 2B VWD and PT-VWD, VWF levels can be difficult to interpret in light of variables such as age, stress, and pregnancy. Age and ABO have recently proven to have an interrelated effect on VWF/FVIII levels [7]. Bleeding phenotype in PT-VWD in association with pregnancy has been described through only a small case series. Patients become increasingly thrombocytopenic throughout the pregnancy, which adds technical difficulty to the performance of RIPA and would require platelet transfusion [8,9]. This was also observed in our cases 3 and 4. The poor obstetric history in case 1 is interesting but there is no evidence of the impact of carrying an affected baby in an unaffected mother on the poor outcome of the twin pregnancy. However, the role of normal blood platelets in reconstruction of the maternal spiral artery has been documented [10].

ITP but not NAIT has been reported as a misdiagnosis for PT-VWD [3]. It is worth noting that the incidence of NAIT caused by antibodies against platelet GPIbα or antigens other than platelet membrane glycoprotein GPIIßIIIα has been reported and the reported incidence of the anti-GPIbα-mediated NAIT is far lower than in ITP [11]. This indicates that perhaps the diagnosis of PT-VWD needs to be considered when ITP or NAIT are suspected.

The laboratory approaches to diagnosis of PT-VWD also vary among the different centers and can lead to miss/under diagnosis. The examination of peripheral blood smears in case 1 showed very large platelets which exhibited clear signs of activation including pseudopods. While this relatively simple assessment can aid the diagnosis, it is not a routine examination in all centers. Similarly, MPV is not commonly reported in patients with thrombocytopenia. While most centers would include VWF: Ag, VWF: RCo and FVIII:C, platelet count and VWF multimers, and RIPA in the diagnosis and subtyping of VWD and PT-VWD, the VWF: CB assay is not routinely performed by all centers.

Although the discrepancy between the results of VWF:RCo and VWF:CB in case 1 cannot be fully explained, both the VWF:RCo/Ag and VWF:CB/Ag ratios indicated partial loss of HMW multimers. The VWF:CB has been used by some groups to subtype patients with VWD and it was reported that the VWF: RCo/Ag and CB/Ag ratio generally perform better that VWF: RCo [12]. Variability in preparations of collagen and other technical aspects limits the interpretation of the results [12,13]. The use of international cross-referenced plasma samples, such that was used in case 1, can help standardize the results across laboratories. More systematic studies in VWD as well as in PT-

VWD patients are needed to identify the role of VWF: CB in the diagnosis.

Platelet aggregation in response to different agonists has not been comprehensively studied in patients with PT-VWD. In all four cases but one, aggregation was normal. However, there seems to be variations among centers in the type or dose of the platelet agonists routinely used. While it is possible that the defective aggregation in case 1 is due to co-inherited platelet defect, it might also be indicative of thrombocytopathy in PT-VWD. The response to rFVIIa treatment, while other measures failed in case 1, may support this. Thrombocytopathy in PT-VWD is the subject of another ongoing study using the PT-VWD mouse model by our group [14].

Heterogeneity exists in different PT-VWD even among the same family. The absence of a bleeding phenotype in both parents in case 3 is worth attention. *De novo* mutations have been described in VWD. While linkage analysis can help trace mutations, it may not always be feasible [15]. The detection of uncommon HLA type as well as HLA Class I IgG antibodies in case 3 alerts us to the value of HLA-matched transfusion. Where platelet refractoriness has already developed, acid treatment of platelets has been shown to remove the majority of Class I HLA complexes and may be an alternative to HLA-matched platelets [16].

Management of PT-VWD can be challenging. While platelet transfusion theoretically constitutes the ideal treatment, case 3 responded well to Humate-P without a significant reduction in platelet count and without a need for platelet transfusion. DDAVP, which enhances the release of endothelial VWF and worsen bleeding condition in PT-VWD, has improved the clinical condition in case 3. The effect was augmented by combination with tranexamic acid. Additionally, anaphylactic reaction to a VWF containing concentrate (with a VWF:RCo/FVIII:C approximately 1:1) was observed in case 3. Such reaction has been reported previously in Hemophilia A [17,18] but not in PT-VWD. The rFVIIa provided positive response in case 1 when other measures failed. These observations indicate the importance of considering alterative treatment and perhaps individualization of therapy at times, in PT-VWD.

Conclusion and final remarks

Awareness/clinical suspicion of PT-VWD is important not only when 2B VWD is suspected but also when alloimmune thrombocytopenia or ITP or gestational thrombocytopenia are considered. The disease needs to be considered in the neonatal period and young patients even with a lack of family history. Platelet-mixing studies are sufficient to diagnose the disease, if appropriately performed, and DNA remains a golden standard in confirming the diagnosis. While genetic analysis has had limitations over the past decade, the recently emerged next-generation sequencing (NGS) is likely to bring a future alternative to overcome these limitations. This technique has proven success in the diagnosis of many platelet function defects including PT-VWD [19,20].

While platelet transfusion is an ideal treatment, the risk of platelet refractoriness due to the development of HLA alloantibodies and the difficulty of obtaining HLA-matched platelets call for alternatives. VWF containing concentrates with higher VWF:FVIII ratio should not be excluded as a treatment option. DDAVP appears to be also effective in some cases and rFVIIa is effective in cases where other measures fail. However, regular monitoring using VWF:RCo and platelet count is important along with these types of therapy. In pregnancy, close monitoring of VWF levels and platelet count can help avoid unnecessary transfusions and ensure better management.

Finally, physicians worldwide are encouraged to continue to contribute to the international PT-VWD registry www.pt-vwd.org and share their knowledge and expertise by participating in the ISTH PT-VWD study conducted under the auspices of the ISTH-SSC for Platelet Physiology: "Prospective evaluation of bleeding phenotype in PT-VWD to support evidence based diagnosis and management" by filling this survey http://www.surveygizmo.com/s3/1808256/PT-VWD. We hope that these studies would advance our understanding of such a rare but significant bleeding disorder and would enable to develop a standard and appropriate management for many undiagnosed patients worldwide.

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Declaration of interest

The authors report no declarations of interest.

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