Von Willebrand disease and von Willebrand factor: an old story, a new perspective

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Chapter 5

Acquired von Willebrand syndrome and response to desmopressin

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Dear Sir,

Acquired Von Willebrand Syndrome (AVWS) is a rare and probably underestimated bleeding disorder, characterized by late onset in individuals with no family or personal history of bleeding. Clinical symptoms of AVWS are not specific and include spontaneous muco-cutaneous bleeding, gastrointestinal haemorrhage and postsurgical bleeding.

Different pathological mechanisms were described in AVWS [1], based on the underlying disease associated with AVWS in most patients: 1) autoimmune clearance or VWF inhibition by the paraprotein in patients with monoclonal gammopathy of undetermined significance (MGUS) or lymphoproliferative disorders with monoclonal gammopathy; 2) increased direct clearance of VWF by the neoplastic cells in essential thrombocytemia and solid tumors such as Wilm's tumor; 3) increased clearance (in particular of the high molecular weight multimers) associated with abnormal shear stress in cardiovascular diseases, such as aortic stenosis, septal defects, use of left ventricular assist devices; 4) increased clearance or inhibition of VWF by autoantibodies in autoimmune diseases, such as systemic lupus erythematosus, Crohn's disease; 5) decreased synthesis of VWF in hypothyroidism.

Several therapeutic approaches can be used in patients affected by AVWS. Treating the underlying disease can eradicate the AVWS in patients affected by hypothyroidism, autoimmune diseases, cardiovascular diseases, lymphoproliferative and myeloproliferative diseases [1]. Nevertheless, these therapies can take some time before being efficacious. For the immediate treatment of bleeding events other strategies need to be used. In particular desmopressin (DDAVP) and FVIII/VWF concentrate increase FVIII and VWF levels immediately, but often only for a short period of time. The use of high dose intravenous immunoglobulins (1g/kg for 2 days or 0.5g/kg for 5 days) can be successfully used in patients with IgG monoclonal gammopathy, enabling to reach normal levels of FVIII and VWF after 3-4 days and lasting for 4-6 weeks [2]. Recently the successful use of thalidomide and lenalidomide was reported in four patients affected by AVWS and severe bleeding [3-5].

The aim of our study was to describe the biochemical and clinical response to DDAVP in patients affected by AVWS.

All patients affected by AVWS who underwent a DDAVP-test followed at our centre between 1982 and February 2017 were included (case series).

FVIII:C and VWF:RCo levels were measured before DDAVP infusion, after 1 hour and 4 hours. Response to DDAVP was defined as: complete (both FVIII:C and VWF:RCo 50 IU/dL or higher); partial (FVIII:C or VWF:RCo lower than 50 IU/dL but increased at

least 3-fold) or absent. VWF: propeptide was measured with an ELISA, using the MW1939 antibody pair anti-human VWFpp (Sanquin, Amsterdam, The Netherlands). VWF: propeptide/antigen ratio was evaluated as a measure of VWF clearance.

Eighteen patients were included in the study (7 males and 11 females). Median age at diagnosis was 55 years (range 22-74). Underlying disorders were present in 17/18 patients: 11 monoclonal gammopathy of uncertain, 1 Waldenstrom's macroglobulinemia, 1 chronic lymphatic leukemia, 3 essential thrombocytemia, 1 inflammatory bowel disease. Blood group was 0 in 5 patients, non-0 in 10 and not available in 3.

Table 1 shows patients characteristics. Median values of FVIII:C were 28 IU/dl (range 9-73, n=18) at baseline, 143 IU/dl (range 18-234, n=18) after 1 hour and 78 IU/dl (range 14-163, n=13) after 4 hours. Median values of VWF:RCo were 9 IU/dl (range 5-68, n=18) at baseline, 62 IU/dl (range 5-205, n=18) after 1 hour and 37 IU/dl (range 5-129, n=12) after 4 hours. The median value of VWF: propeptide/antigen ratio was 4.3 (range 0.9-47, n=16, normal range <1.7). The response to DDAVP after 1 hour was complete in 13 patients (72%), partial in 2 (11%) and absent in 3 (17%). After 4 hours, the response was complete in 5 of 13 patients (38%), partial in 1 (8%) and absent in 7 (54%), data not available in 5 patients.

Even with the small number of patients, an analysis of factors influencing the response to DDAVP is presented in table 2. Three variables seem to influence the response to DDAVP: 1) VVW propeptide/antigen ratio, that is a surrogate marker for clearance (higher levels of VWF propeptide/antigen ratio are associated with a worse response, especially after 4 hours, as expected in case of increased clearance); 2) underlying disease: patients with MGUS (especially those with IgM MGUS) seem to have a worse response to DDAVP, especially after 4 hours; 3) baseline levels of FVIII and VWF are, as it could be expected, an important variable in the response to DDAVP.

DDAVP was used in 11 patients (61%) to prevent bleeding during minor surgery or to treat minor bleeding events, with some failures. Other therapeutic interventions were used in 10 patients (FVIII/VWF concentrate in 5 patients, high dosage immunoglobulins in 1 patient, both in 4 patients), since DDAVP is not useful in patients with very low FVIII and VWF levels at baseline. This is especially disappointing as these are the patients with frequent and spontaneous bleeding symptoms. Besides the use of DDAVP can be contraindicated in older patients with hypertension or coronary heart disease.

In the present single centre case-series one third of the patients with AVWS (38%) showed a complete and sustained response after DDAVP infusion (4 hours). DDAVP

was used in the majority of patients to prevent bleeding in minor surgeries or to treat minor bleeding events. Large multicenter studies are necessary to evaluate DDAVP efficacy in AVWS.

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Table 1. Patients characteristics, associated disorders and response to DDAVP

N°	Age	Sex	Associated disorder	FVIII:C (IU/dL) before and after DDAVP administration			VWF:RCo (IU/dL) before and after DDAVP administration			Post-1h answer	Post-4h answer	VWF:pp/ag ratio
				baseline	Post-1h	Post-4h	baseline	Post-1h	Post-4h			
1	44	F	MGUS (IgG λ)	10	29	14	<6	7	<6	no	no	NA
2	55	M	MGUS (IgG k)	9	73	17	<6	5		no	no	47
3	55	F	MGUS (IgG λ)	13	120	34	12	52	16	yes	no	8
4	44	F	MGUS (IgM k+IgG λ)	20	140		<6	41		partial		3.5
5	54	M	MGUS (IgM k)	37	153		11	50		yes		NA
6	66	F	MGUS (IgG k)	68	204	163	28	109	98	yes	yes	2.9
7	43	F	MGUS (IgG k)	41	184	84	20	103	46	yes	no	4.8
8	38	F	MGUS (IgG k)	11	144	35	<6	68	<6	yes	no	4.1
9	56	F	MGUS (IgG k)	13	18		<6	8		no		34
10	61	F	MGUS (IgG λ)	19	182	78	6	98	28	yes	partial	6.9
11	67	M	Waldestrom's macroglobulinemia	51	165	138	35	137	129	yes	yes	1.9
12	74	M	Chronic Lymphatic Leukaemia IgM k + IgM λ	38	74	59	<6	27	<6	yes	no	4.5
13	22	F	Essential Thrombocytemia + Ehler Danlos Syndrome	64	175		68	205		yes		1.51
14	54	F	Essential Thrombocytemia	49	234	105	38	120	96	yes	yes	1.3
15	42	M	Essential Thrombocytemia	32	126		16	56		yes		1.42
16	70	M	Inlammatory Bowel Disease	23	62	28	6	37	8	partial	no	17.3
17	47	M	none	18	142	108	5	134	108	yes	yes	6.2
18	70	F	MGUS (IgG λ)	73	196	145	49	110	89	yes	yes	0.9

Table 2. Response to DDAVP. Patients characteristics and response to DDAVP

		1 hour after DDAVP		4 hours after DDAVP	
		Complete or partial response to DDAVP		Complete or partial response to DDAVP	
		N	%	N	%
Sex	**Males**	7	86	5	40
	Females	11	82	7	57
Age	**<55 yrs**	9	89	5	40
	≥55 yrs	9	78	8	50
Blood group	**0**	5	100	4	50
	Non 0	10	70	8	38
Underlying disease*	**MGUS**	11	73	8	38
	ET	3	100	1	100
Baseline levels	**FVIII:C and/or VWF:RCo <25 IU/dL**	13	77	9	22
	FVIII:C and VWF:RCo ≥25 IU/dL	5	100	4	100
VWF:pp/ag ratio	**≤4.5**	9	100	6	67
	>4.5	7	71	6	33

*MGUS= monoclonal component of undetermined significance, ET= Essential Thrombocythemia