Acquired Von Willebrand Syndrome: Mechanisms and response to treatment

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Introduction

Acquired Von Willebrand Syndrome (AVWS) is a rare and potentially life threatening bleeding disorder. It is often linked with other systemic diseases such as paraprotein associated lymhoproliferative diseases and malignancy.

The pathophysiological mechanisms are heterogeneous, they include reduced survival of VWF, loss of HMWM and specific inhibition of the VWF-platelet binding interaction. The response to treatment is likely to be determined by the relative contribution of these factors as well as the underlying pathology.

Material and Methods

We performed a retrospective data analysis of patients diagnosed with AVWS between 2008 and 2015 in three Haemophilia Comprehensive Care Centres in London. They were Imperial College NHS Trust, Guys and St Thomas' NHS Foundation Hospitals and St George's NHS Foundation Hospital. Patients were identified through the laboratory and the clinical database of the hospital. Data collected included bleeding characteristics, baseline demographics and the therapeutic agents used to control bleeding during haemostatic challenges.

Results

- 11 patients (median (IQR) age 65(56-75) years) were identified (Table 1).
- 7 patients had an IgG or IgM paraprotein , 2 had prostate cancer, 1 with CLL (no paraprotein) and 1 with cardiac disease.
- Four of the patients had a type 2 VWD pattern with VWF:RCo/VWF:Ag <0.6.(Patient 2,4,8,10)
- In 8/10 patients treated with VWF concentrate, the VWF:RCo was elevated into the normal range.
- 2 patient failed to respond to VWF concentrate (Patient 5,7). Both of the patients had paraproteins.
- In all cases the VWF:RCo recovery was reduced below expected and the infused concentrate showed accelerated clearance with estimated half-life <5 hours.
- In the 3/4 patients with reduce function/antigen ratios who received VWF concentrate, there was a significant increase in this ratio post infusion.(Patient 1, 4,10)
- One patient (Patient 7) was treated successfully with IVIG alone. (Figure 1)

Baseline Demographics (Table 1)

Sex No	Age	Cause	Bleeding Site	PP (g/L)	Baseline levels (iu/ml)		
					VWF:Ag (iu/ml) NR 0.45 – 1.5	VWF:RCo (iu/ml) NR 0.45 – 1.5	FVIII:C (iu/ml) NR 0.45 – 1.5
M 1	75	MGUS	No	IgM Kappa 24	0.21	0.29	0.11
M 2	79	Prostate CA	Joint bleed	nil	0.24	0.05	0.25
M 3	67	Cardiac Disease	Sucutaneous and Gastrointestinal	Nil	0.37	0.38	0.88
M 4	66	MGUS	Intracranial	IgG Kappa 1	0.12	0.05	0.09
M 5	53	CIDP	Mucosal	IgG Kappa 3	0.08	0.09	0.09
M 6	50	CLL Stage A	Subcutaneous	Nil	0.14	0.12	0.11
M 7	80	MGUS	Gastrotintestinal	IgM kappa 3 and IgG Lambda	0.14	0.13	0.15
F 8	60	MGUS	Gastrointestinal	IgG Lambda 5	0.24	0.11	0.31
F 9	64	Waldenstrom's macroglobinaemia	No	IgM Kappa 20	0.35	0.27	0.82
M 10	77	Prostate CA	Subcutaneous	Nil	0.2	0.07	0.22
M 11	55	MGUS	Subcutaneous and Gastrointestinal	IgG Kappa 2	0.28	0.19	0.54

Haemostatic Challenges

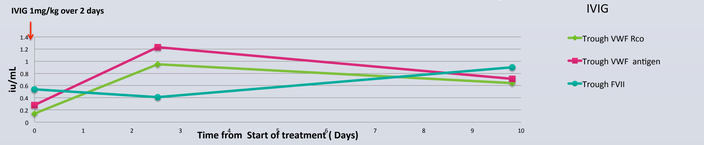
Table 2: Haemostatic challenges and therapeutic agents used to control bleeding

Sex No	Haemostatic challenge	Management of procedure						
		Loading dose VWF concentrate: RCo iu/kg, FVIII iu/kg	VWF:RCo (iu/ml) Pre Tx Post Tx	Actual/ Expected VVWF:RCo	FVIII:C iu/ml Pre Tx Post Tx	Actual/ Expected FVIII:C	RCo/Ag ratio	
							Pre Tx	Post Tx
M 1	Surgical excision Nasal Polyp	Wilate 80iu/kg 80iu/kg	0.12 1.34	0.78	0.2 0.84	0.85	0.8	1.08
M 2	Insertion Gold Bead treatment (for Prostate CA)	Wilate 38u/kg 38iu/kg	0.17 0.71	0.76	0.35 0.78	0.7	0.48	0.7
	Coronary artery angiography	Wilate 38iu/kg	0.06 0.6	0.73	0.2 0.7	0.76	0.4	0.5
M 3	Epistaxis	Haemate P 55 iu/kg	0.29 1.05	0.75	0.6 0.9	0.84	0.8	0.78
	Cataract removal	Haemate P 35iu/kg 15iu/kg	0.42 0.69	0.61	8 1.34	0.79	0.6	0.57
M 4	Intracranial bleed	Haemate P 147iu/kg 42iu/kg + IVIG	0.27 0.92	0.3	0.56 1.31	0.72	0.29	0.42
M 5	Bone marrow aspirate	Haemate P 100iu/kg	<0.1 <0.1	0.05	0.1 0.13	0.14	<0.5	0.5
M 6	Open hernia repair	Haemate P 166iu/kg 70iu/kg	0.12 1.34	0.4	0.17 1.16	0.73	0.63	0.52
	Lung lobectomy	Haemate P 166iu/kg 70iu/kg	0.14 1.61	0.46	0.15 1.04	0.67	0.87	0.65
M 7	Recurrent GI bleed	Haemate P 21iu/kg 13iu/kg +IVIG 1g/Kg	0.13 0.1	0.38	0.15 0.1	0.2	0.9	0.7
F 8	Recurrent GI bleed	IVIG 1g/kg every 3 weeks	0.12 1.9		0.31 1.98		0.5	1.5
F 9	Bone marrow aspirate and trephine biopsy	Haemate P 92iu/kg 40iu/kg	0.12 0.54	0.27	0.41 0.93	0.77	0.8	0.4
M 10	Subcutaneous bleed	Haemate P 60iu/kg 25iu/kg	0.04 0.85	0.67	0.26 0.96	1.26	0.2	0.6
M 11	Excision of rectal polyp	Haemate P 102 iu/kg 42 units + IVIG	0.33 1.64	0.7	0.87 1.59	0.54	0.6	0.6

Immunoglobulin therapy

Patient 8: 64 year old female with MGUS, rheumatoid arthritis and Sjogren's disease. Her IgG paraprotein was 12g/L. She presented with recurrent GI bleeding due to angiodysplasia. Haemostatic control was achieved with 3 weekly IVIG transfusion. Figure 1 below shows an increase in VWF antigen and VWF activity with IVIG treatment with a sustained response 10 days post treatment.

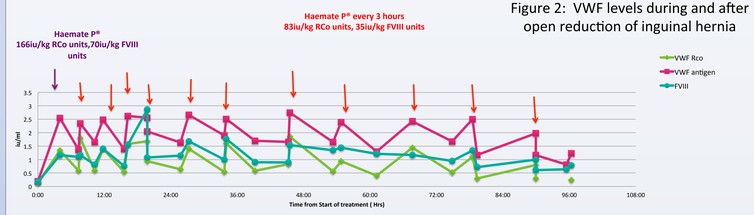
Figure 1: VWF levels post treatment with IVIG



Von Willebrand Concentrate

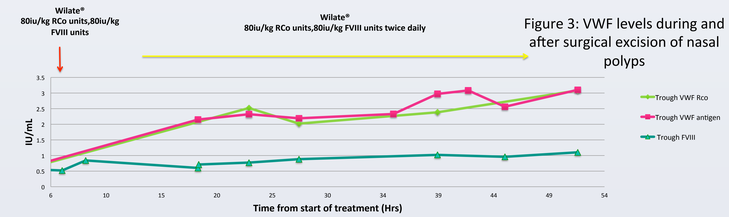
Patient 6: 52 year old gentleman with a background of CLL and no detectable paraprotein. He underwent open inguinal hernia repair (2011). Haemostatic control was achieved the use of frequent (3hrly) dosing of von Willebrand concentrate. VWF:RCo recovery was reduced below expected and the infused concentrate showed accelerated clearance with estimated half-life <5 hours. (Figure 2)

Figure 2: VWF levels during and after open reduction of inguinal hernia



Patient 1 : 74 year with IgM MGUS (PP24g/L) underwent surgical excision of nasal polyps (24g/L) Haemostasis was achieved with high doses of VWF concentrate (Wilate®). Despite repeated high doses of VWF concentrate, the FVIII level remained around 1 iu/mL. (Figure 3)

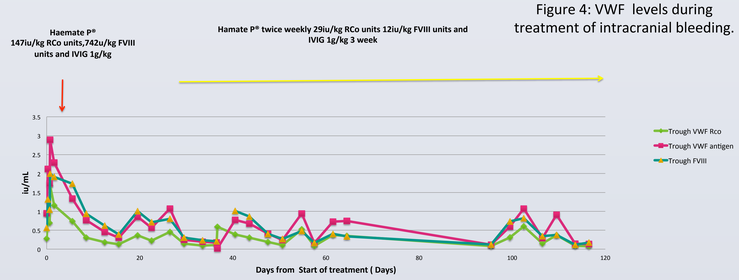
Figure 3: VWF levels during and after surgical excision of nasal polyps



Von Willebrand Concentrate and Immunoglobulin

Patient 4: 73 year old gentleman IgG MGUS. He developed intracranial haemorrhage as a result of AVWD. Haemostasis was maintained with twice weekly VWF concentrate and IVIG. (Figure 4)

Figure 4: VWF levels during treatment of intracranial bleeding.



Conclusion

- Reduced VWF survival is a recognised mechanism causing AVWS and was present in all 11 cases.
- Our data suggest that loss of HMWM and specific inhibition of VWF-platelet binding may also contribute and affect response to treatment.
- Replacement therapy was frequently successful but required high doses in some cases.
- Response was difficult to predict and requires close monitoring with dose adjustment.
- The reduced recovery of VWF:RCo makes it particularly important that the concentrate has a high function to antigen ratio.

Conflict of Interest:

PLL has no conflict of interest. SKA has received Speakers fees and served on the advisory board for Octapharma and CSL Behring, CMM has received research grant funding award, speaker fees and served on advisory board for CSL Behring and received speaker fees for Octapharma, MAL has received travel grant, speakers fees and served on the advisory board of Octapharma and CSL Behring.