Treatment of acquired von Willebrand Syndrome in Childhood

Blood Evidenced Based Focused Review

Michael U. Callaghan¹, Trisha E. Wong²,³,⁴ and Augusto B. Federici⁵

¹ Wayne State University and Children's Hospital of Michigan, Detroit, MI; ² Department of Pediatric Hematology/Oncology, Seattle Children's Hospital, Seattle, WA; ³Department of Pediatrics, University of Washington, Seattle, WA; ⁴Puget Sound Blood Center, Seattle, WA; ⁵Division of Hematology and Transfusion Medicine, L. Sacco University Hospital, Department of Clinical Sciences & Community Health, Universita' degli Studi di Milano, Milano, Italy
A 3½-year-old male with no personal or family history of bleeding disorders presented with abdominal distension, epistaxis and anemia (hemoglobin 8.2 g/dl). An MRI of the abdomen demonstrated a mass arising from the left kidney. Pre-operative laboratory studies revealed a prolonged activated partial thromboplastin time (aPTT) of 49.2 sec and a normal prothrombin time (PT) of 12.4 sec and a platelet count of 230,000/μL. Further testing revealed a factor VIII (FVIII) activity of 16%, FIX of 74%, von Willebrand factor (VWF) activity of 12%, VWF antigen of 31%, and decreased high molecular weight VWF multimers consistent with acquired von Willebrand Syndrome (AVWS). What is the best treatment for this child?

Introduction

To review the current best evidence regarding treatment of AVWS, we first addressed the question of whether AVWS is associated with increased risk of bleeding and next, whether bleeding is effectively treated with intravenous immunoglobulins (IVIg), steroids, VWF concentrates, or treatment of the underlying disorder. We performed a comprehensive review of the published literature indexed on the OVID Medline database using the following search terms: ("von"[All Fields] AND "willebrand"[All Fields] AND "disease"[All Fields] 14,823 hits) OR ("von"[All Fields] AND "willebrand"[All Fields]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms] 611,360)) AND keyword "acquired" [All Fields] 576 hits)). We reviewed the titles, abstracts and full text versions of these 576 hits to determine which articles provided evidence related to AVWS in childhood. Many were excluded for the following reasons: 42 articles because they dealt exclusively with problems of platelet or vascular function, 188 because they dealt only with congenital hemophilia or inherited von Willebrand disease (VWD), 115 because they dealt with TTP/HUS, 41 because they were concerned about hypercoagulable states, 87 because they dealt with other factor deficiencies, 21 because they dealt with problems of pregnancy, 55 because they contained evidence only related to adults, and 11 because they had no information relating to AVWS. We identified 24 articles from this search that provide evidence related to AVWS in childhood. From the references of these articles we identified 18 additional articles. The evidence is summarized and graded according to published guidelines.

Hereditary low VWF activity with bleeding symptoms has an estimated prevalence of 1% in the population and 1 person in 10,000 may be diagnosed with VWD. In contrast, AVWS is a rare acquired disorder with a prevalence estimated to be 0.04%, although this may be an underestimate. The pathophysiology of AVWS is heterogeneous and includes antibody mediated destruction, decreased production, adsorption of VWF to tumor or destruction from sheer stress. (Figure 1) Common etiologies in adults, such as lymphoproliferative disorders and myeloproliferative diseases, are uncommon in children while AVWS associated with cardiovascular disease is common in both adults and children. In contrast, neoplasia (Wilms' Tumor), hypothyroidism, and auto-immunity are more often associated with AVWS in children. Interestingly, the first reported case of AVWS was in a 13 year old boy with systemic lupus erythematosus (SLE). AVWS should be considered in children with bleeding and AVWS-associated disorders and should also be considered in asymptomatic children with AVWS-associated disorders who are schedule to undergo a procedure. Although, AVWS is uncommon it can complicate management of the underlying disorders and there is limited evidence for the management of bleeding symptoms in children with AVWS. We recommend that children with an underlying diagnosis associated with AVWS have VWF antigen, ristocetin cofactor activity, factor FVIII activity and VWF multimer analyses performed in the setting of bleeding symptoms or situations that present a high-risk of bleeding such as surgical interventions. While abnormalities identified by this testing could represent underlying congenital VWD, the correction of these abnormalities upon treatment of the AVWS-associated disorder strongly suggests a diagnosis of AVWS.
Treatment of AVWS caused by auto-antibodies

There have been several reports of AVWS in children with SLE or children who later went on to develop SLE. Because the onset of full-blown SLE may lag behind the diagnosis of VWF defects, this should be considered in children diagnosed with VWD in the absence of a clear family history. Patients with AVWS associated with SLE have been successfully treated with DDAVP, factor infusion and immunosuppressive regimens. The offending antibodies may target functional or non-functional epitopes of circulating VWF and result in production of VWF-immune complexes that are rapidly cleared by the reticuloendothelial system, resulting in shortened VWF half-life. It is recommended that prior to prophylaxis for high-risk situations, pharmacokinetics of DDAVP or infused VWF be evaluated since patients with inhibitory antibodies detectable in plasma mixing studies may have poor responses to DDAVP. IVIg has also been used effectively in patients with auto-antibody-mediated AVWS.

Treatment of AVWS caused by adsorption to malignancy

AVWS has been reported in association with multiple malignancies, including lymphomas, osteosarcoma, and primitive neuroectodermal tumor (PNET). Wilms’ Tumor is the malignancy most commonly associated with AVWS, with a prevalence of 8% in newly diagnosed Wilms’ tumor patients. In these malignancies, VWF is adsorbed to tumor tissue and thereby sequestered from the circulation. Because these patients often require resection of the tumor, treatment is frequently required to prevent surgical bleeding. Although based on a very small number of treated patients, published reports describe use of DDAVP and replacement of VWF. However, the half-life of VWF is decreased as the infused factor also adsorbs to the tumor. It is recommended that a DDAVP trial be performed prior to therapeutic use to determine the patient’s response. IVIg has also been used as a treatment for AVWS in Wilms’ Tumor with success in 2 of 2 reported cases. Removal and/or treatment of the underlying cancer results in remission of AVWS.

Treatment of AVWS caused by hypothyroidism

Hypothyroidism appears to cause decreases in production of VWF and causes a mild mucocutaneous bleeding phenotype. Inhibitory antibodies to VWF are not seen in AVWS caused by hypothyroidism. Low levels of VWF may be a common finding in pediatric patients with hypothyroidism but often with minimal or no symptoms. AVWS seen in children with hypothyroidism resolves with replacement of thyroxine. However, prophylactic DDAVP should be considered prior to thyroid biopsy or other surgery in these patients prior to correction of the thyroid hormone deficiency. A study of 131 patients diagnosed with VWD who were subsequently screened for hypothyroidism identified 8 patients in whom VWF levels normalized after thyroid hormone replacement.

Treatment of AVWS caused by a cardiovascular disease

The best-studied cause of AVWS in childhood is increased shear stress from congenital heart lesions. Aortic stenosis, pulmonary stenosis, patent ductus arteriosus, ventricular and atrial septal defects have all been associated with AVWS. Recently, with the increasing use of ventricular assist devices in children there have been cases of AVWS related to high shearing caused by these mechanical devices. High-shear stress results in availability of ADAMTS-13 cleavage sites and reduction of high-molecular weight multimers as is seen in some patients with congenital VWD 2A. Patients with congenital heart disease associated AVWS are at increased risk of significant perioperative bleeding and intracranial hemorrhage which could possibly be exacerbated with concomitant aspirin use. Correction of the underlying heart lesion usually results in remission of AVWS. DDAVP and replacement of VWF...
may reduce bleeding symptoms in children with high-shear stress lesions and reduced levels of high-molecular weight multimers. DDAVP has been shown in a double-blind placebo controlled trial to reduce bleeding in adults undergoing aortic valve replacement for aortic stenosis\textsuperscript{32}, although only a small subset of these patients had proven AVWS. Further the risk of DDAVP-induced fluid overload and hyponatremia in the setting of these major surgeries should always be considered.

**Treatment of Drug induced AVWS**

AVWS has been reported rarely with the use of griseofulvin, ciprofloxacin, tetracycline, thrombolytic agents and hydroxyethyl starch\textsuperscript{33}. AVWS, thrombocytopenia and other coagulation abnormalities have been frequently associated with valproic acid therapy, with AVWS incidence as high as 20-67\%\textsuperscript{34-38}. However, larger more recent studies have suggested the incidence may be much lower\textsuperscript{39}. While increased proteolysis has been implicated as a cause of AVWS with ciprofloxacin, the mechanism for AVWS caused by valproic acid has remained elusive. It has been recommended that perioperative management or treatment of bleeding complications in AVWS associated with valproic acid therapy should employ VWF concentrates only as DDAVP may increase the risk of seizures in these patients\textsuperscript{38}.

**Conclusion**

For our 3 years old patient described in the vignette the likely diagnosis is AVWS caused by adsorption of VWF to a Wilms’ tumor, although an underlying VWD 2A cannot be excluded based on the vignette. Appropriate therapy would include measurement of response to VWF replacement therapy prior to surgery and infused VWF concentrates perioperatively to normalize VWF levels. Resection and therapy for the underlying Wilms’ tumor should result in remission of this patient’s AVWS.

**Evidence-Based Recommendations** (Table 1)

1. Patients with condition associated with AVWS should be evaluated for AVWS prior to surgical interventions (1c).

2. When possible the AVWS associated disorder should be corrected (2c).

3. In AVWS caused by shear stress from a heart lesion DDAVP reduces surgical blood loss (2c).

4. Duration of response to DDAVP or VWF concentrate should be evaluated prior to prophylaxis for high-risk procedures, generally DDAVP should be administered at starting doses of 0.3 \( \mu \text{g/kg} \) over 30 minutes once or twice daily and VWF concentrates at doses of 30-100 VWF:RCo units/kg and titrated based on individual patient response (1c).

5. IVIg may be used as an ancillary treatment in AVWS mediated by immune destruction of VWF (2c).

6. Valproic Acid therapy related AVWS should be treated with VWF concentrates and DDAVP should be avoided as it may precipitate seizures (2c).
Authorship
MUC conceived of the article topic, searched and reviewed and summarized available literature and wrote this manuscript. TEW conceived of the article topic, searched and reviewed and summarized available literature and edited this manuscript. ABF reviewed, edited and added expert content to this manuscript.

Conflict of Interest Disclosure
The authors have no conflicts of interest to declare.
References


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<td>Cardiovascular Disease</td>
<td>Increased shear stress leading to activation of VWF and exposure of cleavage sites and reduction of high molecular weight multimers.</td>
<td>Repair of underlying heart lesion.</td>
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Figure Legend

Figure 1. Pathophysiology of AVWS (A) Increased clearance of VWF or inhibition of VWF activity as seen in disorders such as systemic lupus erythematosus or myeloproliferative disorders resulting in decreased circulating VWF antigen and decreased VWF activity (B) Adsorption of VWF (particularly high-molecular weight multimers) to tumor cells as is seen in Wilms' tumor or other malignancies resulting in decreased circulating VWF (C) Increased shear stress resulting in access of VWF cleavage sites and clearance of high molecular weight multimers resulting in decreased levels of circulating VWF and decreased high molecular weight multimers. (D) Decreased production of VWF as is seen hypothyroidism and possibly valproic acid treatment.
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