Treatment of acquired von Willebrand syndrome in childhood

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A 3-1/2-year-old male with no personal or family history of bleeding disorders presented with abdominal distension, epistaxis, and anemia (hemoglobin 8.2 g/dL). A magnetic resonance imaging scan of the abdomen demonstrated a mass arising from the left kidney. Preoperative laboratory studies revealed a prolonged activated partial thromboplastin time of 49.2 seconds, a normal prothrombin time of 12.4 seconds, and a platelet count of 230 000/μL. Further testing revealed factor VIII (FVIII) activity of 16%, factor IX (FIX) activity of 74%, von Willebrand factor (VWF) activity of 12%, VWF antigen activity of 31%, and decreased high-molecular-weight VWF multimers consistent with acquired von Willebrand syndrome (AVWS). What is the best treatment for this child? (*Blood*. 2013; 122(12):2019-2022)

Introduction

To review the current best evidence regarding treatment of acquired von Willebrand syndrome (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 (IVIgs), steroids, von Willebrand factor (VWF) concentrates, or treatment of the underlying disorder. We performed a comprehensive review of the published literature indexed on the OVID Medline database by 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 hits) 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 thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, 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 related only 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.[1]

Hereditary low VWF activity with bleeding symptoms has an estimated prevalence of 1% in the population; 1 person in 10 000 may be diagnosed with VWD.[2] In contrast, AVWS is a rare acquired disorder with a prevalence estimated to be 0.04%,[3] although this may be an underestimate.[4] 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).[5,6] Common etiologies in adults, such as lymphoproliferative disorders and myeloproliferative diseases,[7] are uncommon in children[8] while AVWS associated with cardiovascular disease is common in both adults and children. In contrast, neoplasia (Wilms tumor), hypothyroidism, and autoimmunity 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).[9] 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 scheduled 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 VIII (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 autoantibodies

There have been several reports of AVWS in children with SLE or children who later went on to develop SLE.[9-12] 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 1-deamino-8-D-arginine

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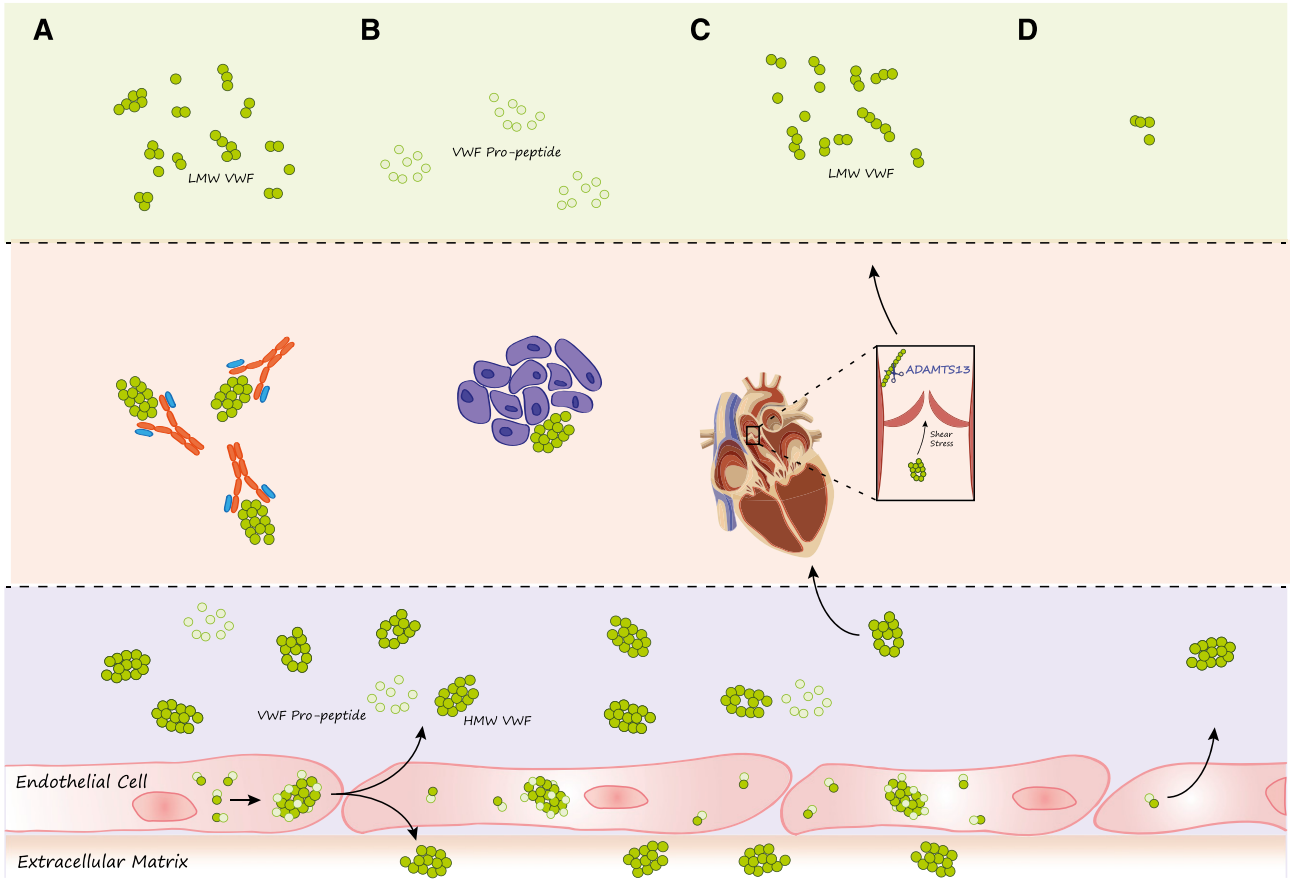

Figure 1. Pathophysiology of AVWS. (A) Increased clearance of VWF or inhibition of VWF activity as seen in disorders such as systemic lupus erythematosis or myeloproliferative disorders resulting in decreased circulating VWF antigen and decreased VWF activity. (B) Adsorption of VWF (particularly high-molecular-weight [HMW] 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 HMW multimers resulting in decreased levels of circulating VWF and decreased HMW multimers. (D) Decreased production of VWF as is seen hypothyroidism and possibly valproic acid treatment. LMW, low molecular weight.

vasopressin (DDAVP), factor infusion, and immunosuppressive regimens. The offending antibodies may target functional or nonfunctional 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.[13] IVIg has also been used effectively in patients with autoantibody-mediated AVWS.[8]

Treatment of AVWS caused by adsorption to malignancy

AVWS has been reported in association with multiple malignancies, including lymphomas, osteosarcoma, and primitive neuroectodermal tumor. Wilms tumor is the malignancy most commonly association with AVWS, with a prevalence of 8% in newly diagnosed Wilms tumor patients.[14] 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.[15-17] 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 because 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.[14] IVIg has also been used as a treatment of AVWS in Wilms tumor with success in 2 of 2 reported cases.[8] 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.[18-21] Inhibitory antibodies to VWF are not seen in AVWS caused by hypothyroidism.[22,23] Low levels of VWF may be a common finding in pediatric patients with hypothyroidism but often with minimal or no symptoms.[24] 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.[25]

Table 1. Evidence-based recommendations for treating AVWS

Underlying disorder	Pathophysiology	Causal treatment	Additional treatment options
Autoantibodies	Antibody-mediated increased clearance of VWF or inhibition of VWF function.	Steroids, cyclophosphamide, immunosuppressive therapy.	DDAVP, VWF concentrates, IVIg (2c).
Malignancy	Adsorbtion of VWF to tumor cells, particularly high-molecular-weight multimers.	Appropriate treatment of underlying cancer (resection, chemotherapy, radiation).	DDAVP, VWF concentrates (2c).
Hypothyroidism	Decreased production of VWF.	Thyroid hormone replacement.	DDAVP, VWF concentrates (2c).
Cardiovascular disease	Increased shear stress leading to activation of VWF and exposure of cleavage sites and reduction of high-molecular-weight multimers.	Repair of underlying heart lesion.	DDAVP, VWF concentrates (2c).
Valproic acid	Decreased production of VWF	Discontinuation of valproic acid	VWF concentrates (2c)

1c, strong recommendation, low- or very-low-quality evidence; 2c, weak recommendation, low- or very-low-quality evidence.

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,[26,27] pulmonary stenosis,[28] patent ductus arteriosus,[29] and ventricular and atrial septal defects[27] 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.[30] High shear stress results in availability of ADAMTS13 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.[31] 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. In a double-blind, placebo-controlled trial, DDAVP was shown to reduce bleeding in adults undergoing aortic valve replacement for aortic stenosis,[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.[33] AVWS, thrombocytopenia, and other coagulation abnormalities have been frequently associated with valproic acid therapy, with AVWS incidence as high as 20% to 67%.[34-38] However, larger, more recent studies have suggested the incidence may be much lower.[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 use VWF concentrates only, because DDAVP may increase the risk of seizures in these patients.[38]

Conclusion

For the 3-1/2-year-old patient described in our vignette, the likely diagnosis is AVWS caused by adsorption of VWF to a Wilms tumor, although an underlying VWD 2A cannot be excluded on the basis of 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. The following list of evidence-based recommendations is further explained in Table 1:

1. Patients with conditions 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 μg/kg over 30 minutes once or twice daily, and VWF concentrates should be administered at doses of 30 to 100 VWF:RCo [VWF: ristocetin cofactor] units/kg and titrated on the basis of 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 because it may precipitate seizures (2c).

Authorship

Contribution: M.U.C. conceived of the article topic, searched, reviewed, and summarized available literature, and wrote the manuscript; T.E.W. conceived of the article topic, searched, reviewed, and summarized available literature, and edited the manuscript; and A.B.F. reviewed, edited, and added expert content to the manuscript.

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References

1. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl): 53S-70S.
2. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood.* 1987;69(2): 454-459.
3. Kumar S, Pruthi RK, Nichols WL. Acquired von Willebrand's syndrome: a single institution experience. *Am J Hematol.* 2003;72(4):243-247.
4. Federici AB. Acquired von Willebrand syndrome: is it an extremely rare disorder or do we see only the tip of the iceberg?J Thromb Haemost. 2008; 6(4):565-568.
5. Sucker C, Michiels JJ, Zotz RB. Causes, etiology and diagnosis of acquired von Willebrand disease: a prospective diagnostic workup to establish the most effective therapeutic strategies. *Acta Haematol.* 2009;121(2-3):177-182.
6. Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood.* 2011;117(25):6777-6785.
7. Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. *Blood.* 1998;92(8):2707-2711.
8. Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemost.* 2000; 84(2):345-349.
9. Simone JV, Cornet JA, Abildgaard CF. Acquired von Willebrand's syndrome in systemic lupus erythematosus. *Blood.* 1968;31(6):806-812.
10. Igarashi N, Miura M, Kato E, et al. Acquired von Willebrand's syndrome with lupus-like serology. *Am J Pediatr Hematol Oncol.* 1989;11(1):32-35.
11. Niiya M, Niiya K, Takazawa Y, et al. Acquired type 3-like von Willebrand syndrome preceded full-blown systemic lupus erythematosus. *Blood Coagul Fibrinolysis.* 2002;13(4):361-365.
12. Soff GA, Green D. Autoantibody to von Willebrand factor in systemic lupus erythematosus. *J Lab Clin Med.* 1993;121(3):424-430.
13. Mohri H, Motomura S, Kanamori H, et al. Clinical significance of inhibitors in acquired von Willebrand syndrome. *Blood.* 1998;91(10): 3623-3629.
14. Coppes MJ, Zandvoort SW, Sparling CR, Poon AO, Weitzman S, Blanchette VS. Acquired von Willebrand disease in Wilms' tumor patients. *J Clin Oncol.* 1992;10(3):422-427.
15. Scott JP, Montgomery RR, Tubergen DG, Hays T. Acquired von Willebrand's disease in association with Wilm's tumor: regression following treatment. *Blood.* 1981;58(4):665-669.
16. Noronha PA, Hruby MA, Maurer HS. Acquired von Willebrand disease in a patient with Wilms tumor. *J Pediatr.* 1979;95(6):997-999.
17. Will A. Paediatric acquired von Willebrand syndrome. *Haemophilia.* 2006;12(3):287-288.
18. Michiels JJ, Schroyens W, Berneman Z, van der Planken M. Acquired von Willebrand syndrome type 1 in hypothyroidism: reversal after treatment with thyroxine. *Clin Appl Thromb Hemost.* 2001; 7(2):113-115.
19. Federici AB. Acquired von Willebrand syndrome associated with hypothyroidism: a mild bleeding disorder to be further investigated. *Semin Thromb Hemost.* 2011;37(1):35-40.
20. Manfredi E, van Zaane B, Gerdes VE, Brandjes DP, Squizzato A. Hypothyroidism and acquired von Willebrand's syndrome: a systematic review. *Haemophilia.* 2008;14(3):423-433.
21. Galli-Tsinopoulou A, Stylianou C, Papaioannou G, Nousia-Arvanitakis S. Acquired von Willebrand's syndrome resulting from untreated hypothyroidism in two prepubertal girls. *Haemophilia.* 2006;12(6): 687-689.
22. Dalton RG, Dewar MS, Savidge GF, et al. Hypothyroidism as a cause of acquired von Willebrand's disease. *Lancet.* 1987;1(8540): 1007-1009.
23. Takahashi H, Yamada M, Shibata A. Acquired von Willebrand's disease in hypothyroidism. *Thromb Haemost.* 1987;58(4):1095.
24. Olukman O, Sahin U, Kavakli T, Kavakli K. Investigation of acquired von Willebrand Syndrome in children with hypothyroidism: reversal after treatment with thyroxine. *J Pediatr Endocrinol Metab.* 2010;23(9):967-974.
25. Franchini M, Veneri D, Lippi G. Analysis of thyroid hormone status in 131 consecutive individuals with low von Willebrand factor levels. *Thromb Haemost.* 2005;93(2):392-393.
26. Casonato A, Sponga S, Pontara E, et al. von Willebrand factor abnormalities in aortic valve stenosis: Pathophysiology and impact on bleeding. *Thromb Haemost.* 2011;106(1):58-66.
27. Gill JC, Wilson AD, Endres-Brooks J, Montgomery RR. Loss of the largest von Willebrand factor multimers from the plasma of patients with congenital cardiac defects. *Blood.* 1986;67(3):758-761.
28. Wiegand G, Hofbeck M, Zenker M, Budde U, Rauch R. Bleeding diathesis in Noonan syndrome: Is acquired von Willebrand syndrome the clue? *Thromb Res.* 2012;130(5):e251-e254.
29. Rauch R, Budde U, Koch A, Girisch M, Hofbeck M. Acquired von Willebrand syndrome in children with patent ductus arteriosus. *Heart.* 2002;88(1): 87-88.
30. Miera O, Potapov EV, Redlin M, et al. First experiences with the HeartWare ventricular assist system in children. *Ann Thorac Surg.* 2011;91(4): 1256-1260.
31. Onimoe G, Grooms L, Perdue K, Ruymann F. Acquired von Willebrand Syndrome in congenital heart disease: does it promote an increased bleeding risk? *Br J Haematol.* 2011;155(5): 622-624.
32. Steinlechner B, Zeidler P, Base E, et al. Patients with severe aortic valve stenosis and impaired platelet function benefit from preoperative desmopressin infusion. *Ann Thorac Surg.* 2011; 91(5):1420-1426.
33. Michiels JJ, Budde U, van der Planken M, van Vliet HH, Schroyens W, Berneman Z. Acquired von Willebrand syndromes: clinical features, aetiology, pathophysiology, classification and management. *Best Pract Res Clin Haematol.* 2001;14(2):401-436.
34. Koenig S, Gerstner T, Keller A, Teich M, Longin E, Dempfle CE. High incidence of vaproate-induced coagulation disorders in children receiving valproic acid: a prospective study. *Blood Coagul Fibrinolysis.* 2008;19(5):375-382.
35. Serdaroglu G, Tutuncuoglu S, Kavakli K, Tekgul H. Coagulation abnormalities and acquired von Willebrand's disease type 1 in children receiving valproic acid. *J Child Neurol.* 2002;17(1):41-43.
36. Acharya S, Bussel JB. Hematologic toxicity of sodium valproate. *J Pediatr Hematol Oncol.* 2000; 22(1):62-65.
37. Kreuz W, Linde R, Funk M, et al. Induction of von Willebrand disease type I by valproic acid. *Lancet.* 1990;335(8701):1350-1351.
38. Kreuz W, Linde R, Funk M, et al. Valproate therapy induces von Willebrand disease type I. *Epilepsia.* 1992;33(1):178-184.
39. Eberl W, Budde U, Bentele K, et al. Acquired von Willebrand syndrome as side effect of valproic acid therapy in children is rare. *Hamostaseologie.* 2009;29(2):137-142.