Acquired von Willebrand Syndrome in Children

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Abstract

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder caused by various underlying diseases or conditions and should be distinguished from the inherited type of von Willebrand disease. AVWS is associated with underlying diseases such as cardiovascular, autoimmune, malignant, proliferative disorders, or with mechanical circulatory support (MCS). AVWS was first reported in 1968 and most case reports describe AVWS in adults. However, AVWS can appear in pediatric patients occasionally as well. Because bleeding complications are rare in everyday life, AVWS may be underdiagnosed in pediatric patients. Therefore, the diagnosis should be suspected in a pediatric patient who is known for one of these underlying diseases or conditions and who presents with an onset of bleeding symptoms, especially before the child will undergo an invasive procedure. Here, we present an overview of the diagnostic analyses regarding AVWS and of the underlying diseases or conditions in which AVWS should be considered. Importantly, the patient's history should be investigated for bleeding symptoms (mucocutaneous or postoperative bleeding). As no single routine coagulation test can reliably confirm or exclude AVWS, the diagnosis may be challenging. Laboratory investigations should include analysis of von Willebrand factor (VWF):antigen, VWF:collagen-binding capacity, VWF:activity, and VWF multimeric analyses. For treatment, tranexamic acid, 1-desamino-8-D-arginine vasopressin, and VWF-containing concentrate can be used. AVWS disappears after the underlying disease has been successfully treated or the MCS has been explanted.

Keywords

- acquired von Willebrand syndrome
- extracorporeal membrane oxygenation
- congenital heart defects
- bleeding

Introduction

Acquired von Willebrand syndrome (AVWS) is a rare acquired bleeding disorder characterized by clinical symptoms and laboratory findings similar to those seen in inherited von Willebrand disease (VWD). In contrast to AVWS, congenital VWD results from mutations in the von Willebrand factor (VWF) gene.[1]

Patients with AVWS can present with bleeding symptoms such as epistaxis, gastrointestinal, and surgical hemorrhage. Under conditions of major trauma or surgery, AVWS becomes relevant and can be the reason for extensive bleeding. Life-threatening intracranial bleedings, even though rare, may also occur.[2]

AVWS comprises hemorrhagic disorders in which the VWF is either qualitatively or quantitatively abnormal. The major finding of AVWS is the loss of high-molecular-weight (HMW) multimers of VWF which can be shear stress induced and ultimately leads to impaired function of VWF (qualitative defect). The loss of HMW multimers of VWF results in diminished capability of VWF to interact with collagen and/or with platelets which is identifiable by decreased values for VWF: collagen-binding capacity (VWF:CB) and/or VWF ristocetin cofactor (VWF:RCo), respectively. Therefore, the ratio of VWF:CB to the VWF:antigen (VWF:CB/VWF:Ag) and the ratio of VWF:RCo to the VWF:antigen (VWF:RCo/VWF:Ag) are decreased.[3] The VWF:RCo assay measures the binding of VWF to glycoprotein Ib receptors of fixed platelets. In addition, VWF

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activity (VWF:GPIbR) which investigates binding of VWF to recombinant GPIb is also reduced. Therefore, in patients with AVWS, the ratio of VWF activity (VWF:GPIbR) to VWF:antigen (VWF:GPIbR/VWF:Ag) is decreased as well. Diagnostic criteria of AVWS are displayed in (►Textbox 1).

Diagnostic criteria of AVWS

- Multimeric analysis: loss of HMW multimers of VWF
- ↓ VWF:collagen-binding capacity
- ↓ VWF:ristocetin cofactor
- ↓ VWF:activity (VWF:GPIbR)
- ↓ Ratio of VWF:CB/VWF:Ag
- ↓ Ratio of VWF:RCo/VWF:Ag
- ↓ Ratio of VWF:GPIbR/VWF:Ag

Textbox 1

In case of bleeding symptoms, several pharmacologic treatment options such as tranexamic acid, desmopressin, VWF-containing factor VIII concentrate, VWF concentrate, and/or recombinant factor VIIa are available[2,4] (►Textbox 2).

Therapeutic options of children with AVWS

- Tranexamic acid
- Desmopressin
- VWF- containing factor VIII concentrate
- VWF concentrate
- Recombinant factor VIIa

Textbox 2

Usually, AVWS occurs in middle-aged and elderly patients. Although literature concerning AVWS in children is rare, AVWS has been described in pediatric patients, often in those with congenital heart disease and during mechanical circulatory support (MCS),[5] but also in children with other medical conditions. Probably, AVWS is underdiagnosed in the younger age groups and the diagnosis may be delayed or missed. The various causes of AVWS are summarized in (►Textbox 3). AVWS can be reversible in most cases if the underlying condition can be cured (►Textbox 4).

Causes of AVWS

- Consumption: congenital heart defects, mechanical circulatory support
- Immunological: lymphoproliferative or myeloproliferative disorders, systemic lupus erythematosus, hypothyroidism
- Drug-induced: valproic acid, ciprofloxacin

Textbox 3

Prognosis of AVWS

AVWS is completely reversible

- After surgical repair in case of CHD
- After device explantation in case of MCS
- After successful treatment of the underlying disease (e.g., CML, SLE)

Textbox 4

Methods

A narrative review, including all published data from Medline and PubMed database regarding AVWS in children, was conducted.

AVWS in Children with Congenital Heart Disease

In children with congenital heart defects (CHD), AVWS is mostly associated with septal defects (ventricular septal defects, atrial septal defects, or combined atrioventricular septal defects) and patent ductus arteriosus (PDA). Some patients with AVWS suffer from aortic or pulmonary stenosis (►Table 1).

In children with CHD, flow dynamics are altered and predispose to areas of stasis, and/or higher shear stress with platelet activation.[6] Shear stress in circulation can also lead to decrease or loss of VWF HMW multimers and thus can lead to AVWS. Most probably, AVWS is relatively common in children with CHD and completely resolves shortly after surgical or interventional repair.[7] Bleeding history of some of the children with CHD show mild bleeding symptoms. Even if clinical symptoms are missing during everyday life, AVWS can be the reason for extensive bleeding under conditions of major trauma or surgery. Cardiac surgery of the newborn and infant with complex congenital CHD is associated with a high rate of intraoperative bleeding complications.[8]

In some children with persistent PDA, deficiency of HMW multimers of VWF has been reported. Following interventional PDA occlusion, the VWF HMW multimers normalized shortly after the intervention in all patients, confirming the acquired nature of the disorder.[9]

In addition, the frequency and relationship of AVWS in children with aortic and pulmonary stenosis were investigated by Binnetoğlu et al.[10] AVWS was found to be associated with stenotic obstructive cardiac diseases. Therefore, laboratory analyses should comprise comprehensive analysis of VWF parameters in these patients besides whole blood count, prothrombin time, and activated partial thromboplastin time.

AVWS in Children with Mechanical Circulatory Support

In critically ill children with advanced heart or respiratory failure, MCS, such as ventricular assist device (VAD) or extracorporeal circulatory life support (ECLS), and extracorporeal membrane oxygenation (ECMO) have extended survival and improved quality of life.[6,11] However, bleeding

Table 1 AVWS in children with CHD or MCS

Cause of AVWS	Pathophysiology	Additional findings/information	Clinical symptoms	Prognosis
CHD/Vessel defect: • Ventricular septal defects • Atrial septal defects • Atrioventricular septal defects • Patent ductus arteriosus • Aortic or pulmonary stenosis	Turbulent forces within the abnormal cardiac anatomy ⇒ enhanced shear rates and stress ⇒ mechanical degradation of VWF	Risk factor for intravascular bleeding and/or intravascular thrombosis	Mild bleeding problems in daily life; extensive bleeding may occur under conditions of major trauma or surgery	AVWS resolves completely after surgical/interventional repair
MCS: • Ventricular assist device • Extracorporeal circulatory life support • Extracorporeal membrane oxygenation	Interactions between blood components and foreign surfaces, changes in hemodynamics and rheology ⇒ pathological flow condition, elevated shear stress ⇒ mechanical degradation of VWF ⇒ impaired interaction between VWF and collagen and platelets	AVWS developed in all children within 24 h, 2/3 of patients experienced bleeding complications, no thromboembolic event after MCS termination	Mucocutaneous bleeding symptoms, thoracic and mediastinal bleeding (primarily located in the surgical wound area)	AVWS is reversible, VWF parameters normalized within 24 h after weaning

Abbreviations: AVWS, acquired von Willebrand syndrome; CHD, congenital heart defect; MCS, mechanical circulatory support; VWF, von Willebrand factor.

and/or thrombotic complications remain a major cause of morbidity and mortality in children with MCS. Complex interactions between blood components and the foreign surfaces and changes in hemodynamics and rheology may lead to AVWS with life-threatening bleeding episodes rather than thromboembolic events (►Table 1). In addition, reduced platelet aggregation and increased platelet activation in children during VAD or ECMO support may contribute to the imbalance of the hemostatic system.[11,12]

Consistent with data from studies in adult patients, a study cohort of 30 children with MCS (ECLS, $n = 13$; ECMO, $n = 5$; and VAD, $n = 12$) showed that all children developed AVWS which was usually diagnosed during the very early postoperative course.[11] Laboratory analyses detected a loss of HMW VWF multimers (►Fig. 1), decreased VWF:CB/VWF:Ag ratios, and reduced VWF:CB levels. Therefore, analyzing clinical and biochemical data plays a major role in diagnosing AVWS which may be the main cause of bleeding in these patients. Bleeding complications such as thoracic and mediastinal bleeding (primarily located in the surgical wound area) were observed in all three groups, requiring surgical revision in addition to conservative therapy in some children. AVWS can develop within few hours after implanting VAD or starting ECMO or ECLS support. Interestingly, AVWS in this cohort was always reversible within 3 to 24 hours after device explantation or cessation of ECMO/ECLS support which is consistent with data from studies on adult patients. Interestingly, the patients in this cohort did not show any thromboembolic event after MCS termination, despite upregulation of VWF:Ag. This phenomenon may be due to the decrease of the VWF:CB and the reduced VWF:CB /VWF:AG ratios.

The severity of bleeding tendency among patients during MCS can vary and a direct association with patients' ages, bleeding location, and overall outcome cannot always be identified.[11] Therefore, comprehensive clinical and biochemical phenotyping is essential to perform a risk-stratification of patients during MCS workup. It has been discussed, whether very low VWF:CB and VWF:activity levels, respectively, and very low VWF:CB/VWF:Ag and VWF:Act/VWF:Ag ratios may hint to a more severe form of AVWS. Interestingly, AVWS seems to be more pronounced in patients with ECLS/ECMO compared with patients on VAD support.[11,13] Accordingly, patients on ECLS/ECMO required more red blood cell and platelet transfusions.

The therapy for bleeding in those patients remains difficult. During ECLS/ECMO or VAD support, patients were anticoagulated with unfractionated heparin.[11] For long-term therapy, patients with left VAD are switched to low-molecular-weight heparin or phenprocoumon (vitamin K antagonist). In case of life-threatening bleeding, substitution of VWF-containing factor VIII concentrates or VWF concentrates may be considered.

AVWS in Children with Other Underlying Diseases

Lymphoproliferative, Myeloproliferative Disorders, Other Neoplasms, and Autoimmune Diseases

AVWS can be associated with further underlying diseases such as lymphoproliferative disorders, myeloproliferative

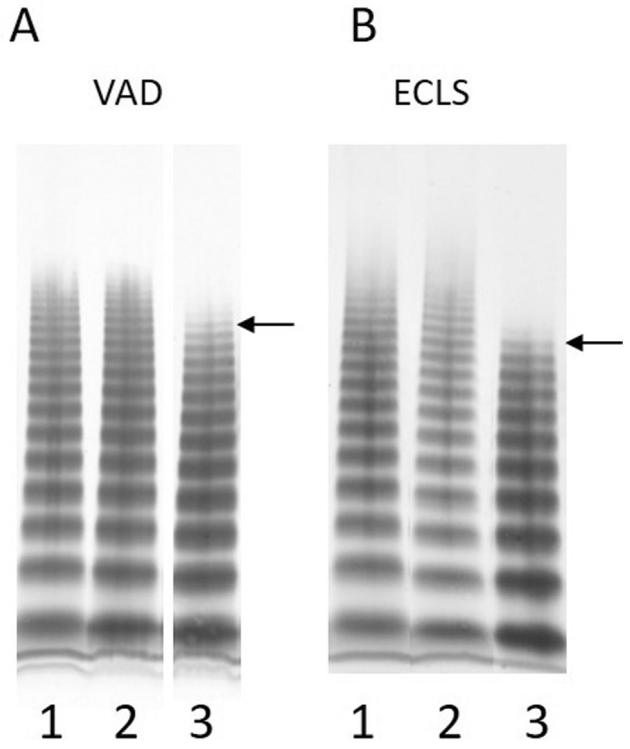

Fig. 1 Sodium dodecyl sulfate (SDS)-agarose gel electrophoresis of von Willebrand factor multimers, visualized by enzyme immunostaining after capillary transfer onto polyvinylidene difluoride membranes. Multimeric analysis was performed by SDS-agarose gel electrophoresis in 1.0% of SDS-agarose gels: (**A**) (1) Standard Human Plasma (SHP), (2) before VAD, and (3) under VAD support. (**B**) (1) SHP, (2) before ECLS, and (3) under ECLS support. ECLS, extracorporeal circulatory life support; VAD, ventricular assist device.

disorders, other neoplasms, and autoimmune diseases[14] (►**Table 2**). In rare cases, AVWS is also associated with hypothyroidism, uremia, and certain drugs such as valproic acid and ciprofloxacin.[5] In younger patients, AVWS is also associated with renal tumors, glycogen storage disease type 1a (GSD-1a), or systemic lupus erythematosus (SLE).[15] The pathophysiology of AVWS in children and adolescents is related to the underlying diagnosis.

Some case reports described that children with acute lymphoblastic leukemia or chronic myeloid leukemia (CML) had developed an AVWS-associated bleeding phenotype.[16,17] At diagnosis of CML, patients may present with elevated platelet counts. High cell counts may result in thrombosis and/or secondarily in bleeding complications. Interestingly, patients with pediatric CML frequently exhibit high platelet counts not resulting in thrombosis because binding of VWF multimers to platelets can result in loss of large VWF multimers ultimately leading to AVWS.

Children with myeloproliferative disorders such as essential thrombocythemia and polycythemia vera can also develop AVWS due to the high platelet counts and changes regarding rheology and shear stress.[18,19]

AVWS in patients with SLE is caused by autoantibodies directed against the circulating VWF/FVIII (factor VIII) complex.[20,21] Binding of autoantibodies leads to large immune complexes which are rapidly cleared by the reticuloendothelial system causing a deficiency of both VWF and FVIII. AVWS in SLE can be cured by the treatment of the underlying autoimmune disease with corticosteroids or immunosuppression.

AVWS associated with hypothyroidism is rare in children and mostly diagnosed during the peripubertal period in the context of Hashimoto's thyroiditis.[22] The AVWS associated with hypothyroidism differs from the other forms of AVWS: there is a reduction regarding the synthesis and release of VWF that is not associated with a reduced half-life because of either autoantibodies or secondary structural changes regarding the VWF multimers.[23]

AVWS has been described in some pediatric patients with Wilms' tumor and with embryonal adenomas of the kidney.[24,25] There is no evidence of autoantibodies against VWF or adsorption of VWF onto tumor cells. It is being discussed that abnormal vasculature and high blood flow through the tumor vessels could produce conditions of high shear stress with physical disruption of VWF multimers. High levels of hyaluronic acid secreted by some Wilms' tumors may also contribute to the abnormal VWF parameters.[15] Accordingly, the coagulopathy disappears after successful chemotherapy or resection of the tumor.

Glycogen Storage Disease Type 1a

AVWS can also be associated with GSD-1a, usually presenting with easy bruising and troublesome epistaxis in late infancy or early childhood.[15,26]

Pulmonary Arterial Hypertension

Recently, a causative relationship between idiopathic pulmonary arterial hypertension and AVWS was hypothesized.[27] Interestingly, VWF multimer distribution patterns seem to be normal in all pediatric patients, while most patients demonstrated low-normal VWF parameters. Lung transplantation led to postsurgical normalization of hemostatic abnormalities.

Epstein–Barr Virus

Bleeding symptoms in children have been also described following Epstein–Barr virus (EBV) infection. However, causative relation of bleeding to prior EBV infection remains uncertain. A 6-year-old girl developed petechiae and bruising 2 weeks after an EBV infection.[28] She had a prolonged bleeding time, reduced values for FVIII activity, VWF:Ag, and VWF:RCo and loss of VWF HMW multimers. AVWS resolved after 2 weeks and did not reoccur.

Anticonvulsive Medication

Patients with epilepsy, treated with valproic acid, may present with a variety of coagulation defects: thrombocytopenia, platelet dysfunction, hypofibrinogenemia, reduced vitamin K–dependent factors, factor XIII deficiency, and AVWS.[29] The cause of AVWS in patients taking valproic acid is unknown. Therefore, in children taking anticonvulsive drugs and who present with bleeding symptoms, AVWS should be investigated.

Table 2 Clinical picture of AVWS in children with various underlying diseases or taking certain drugs

Cause of AVWS	Pathophysiology	Additional findings/information	Clinical symptoms	Prognosis
Lympho-myeloproliferative disorders				
CML	Elevated platelet counts => loss of VWF high-molecular-weight multimers	Splenomegaly, pronounced leucocytosis, thrombocytosis	mild bleeding signs, rarely thrombosis	AVWS resolved after successful initiation of CML treatment
ET		Increased risk for bleeding or thrombotic events, splenomegaly, elevated numbers of mature megakaryocytes	bleeding episodes (epistaxis, prolonged menstrual bleeding), visual impairment, palmar and plantar stabbing pain	reduction of the platelet count led to normalization of the VWF ratio
PV	Loss of VWF high-molecular-weight multimers	Increased risk for bleeding or thrombotic events		After successful therapy (i.e., stem cell transplantation) normalization of parameters
Autoimmune diseases				
SLE	Autoantibodies directed against the circulating VWF/FVIII complex		mucocutaneous bleeding symptoms, prolonged bleeding after dental extraction	AVWS can be cured by treatment of the underlying autoimmune disease with corticosteroids or immunosuppression
Other diseases				
Hypothyroidism	Reduced/defective synthesis of VWF	Possibility of bleeding	Rectal bleeding, anemia	Normalization of coagulation parameters after restoration of euthyroidism
Wilms' tumor (nephroblastoma)	Unknown	High serum levels of hyaluronic acid	Mild mucocutaneous bleeding symptoms	Abnormalities of coagulation resolved after chemotherapy and extirpation of the neoplasm
GSD-1a	Unknown		Easy bruising, epistaxis	
IPAH	Increased shear stress throughout the pulmonary vasculature	Normal distribution pattern of VWF high-molecular-weight multimers	Mild to moderate bleeding symptoms	Normalization of the hemostatic defects following lung transplantation
Uremia	Proteolytic degradation of VWF	Increased risk for bleeding and/or thrombotic events		
Drugs				
Valproic acid	Unknown	No relationship between valproate dosage or duration of therapy and the incidence of AVWS	Spontaneous bleeding unclear Extensive bleeding may occur under conditions of major trauma or surgery	

Abbreviations: AVWS, acquired von Willebrand syndrome; CML, chronic myeloid leukemia; ET, essential thrombocythemia; GSD-1a, glycogen storage disease type 1a; IPAH, idiopathic pulmonary arterial hypertension; PV, polycythemia vera; SLE, systemic lupus erythematosus; VWF, von Willebrand factor.

Conclusion

AVWS is a common, but still often unrecognized disorder in pediatric patients with MCS, CHD, or further underlying diseases. The pathophysiology and management of acute bleeding episodes depends on the primary underlying disease. VWF abnormalities in AVWS are a result of increased shear stress followed by proteolysis of VWF in case of MCS or CHD, VWF adsorption to surfaces of transformed cells or platelets, or antibody-mediated clearance as well as functional interference. Clinically, AVWS can aggravate bleeding tendencies in these children, especially if hepatic insufficiency, temporary thrombocytopenia, and severe inflammation occur. Therefore, VWF parameters should be investigated in children with MCS or CHD and in case of nonsurgical bleeding. Since the bleeding event may be triggered by several causes, a score incorporating several parameters (i.e., pronounced hemolysis, infections or reduced ratios of VWF:RCo/VWF:Ag, VWF:GPIbR/VWF:Ag, or VWF:CB/VWF:Ag) may help identify patients with an increased risk for bleeding complications.[11]

In summary, the diagnosis of AVWS should be suspected, if a pediatric patient presents with an onset of bleeding symptoms and suffers from one of the diseases or conditions mentioned earlier. The cause of the bleeding symptoms should be further investigated especially before the child undergoes an invasive procedure.

Conflict of Interest

The authors declare that they have no conflict of interest.

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