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Acquired von Willebrand syndrome in adult patients with congenital heart disease

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ABSTRACT

Objectives: Postoperative bleeding is common in patients with congenital heart disease (CHD). However, little is known about the role and prevalence of acquired von Willebrand syndrome (AVWS).
Methods: We evaluated the prevalence of AVWS in relation to underlying cardiac defects, operative procedures and the presence of Eisenmenger syndrome. The prothrombin time, aPTT, platelet function analysis (PFA-100), von Willebrand factor antigen (VWF:Ag), VWF activity, VWF collagen binding activity (VWF:CB), factor VIII activity and multimeric analysis were measured in addition to tests evaluating heart, liver and kidney functions.
Results: A total of 221 patients were screened and 192 patients were included in the study. The overall prevalence of AVWS was 20.8%. AVWS was identified across all of the cardiac defects, with the highest prevalence in the defects of great complexity (38.6% compared to 9.4% in patients with CHD of simple/moderate complexity, $p < 0.001$), Eisenmenger syndrome ($p < 0.001$) and more severe heart failure symptoms (NYHA III/IV vs. NYHA I, $p < 0.001$; NYHA III/IV vs. NYHA II, $p = 0.044$). A combination of multimeric analysis, VWF:CB to VWF:Ag ratio (sensitivity: 77.5%, specificity: 93.3%) and PFA-100 (PFA Col/Epi sens.: 77%, spec.: 52%; PFA Col/ADP sens.: 75%, spec.: 74.3%) were used to detect AVWS.
Conclusions: This study demonstrated that AVWS occurred in patients with various congenital cardiac defects, but the highest prevalence occurred in the patients with complex CHD and Eisenmenger syndrome. We, therefore, suggest preoperative screening for AVWS in all of the patients with CHD, particularly in the patients with CHD of greater complexity and suffering from Eisenmenger syndrome.

1. Introduction

von Willebrand factor (VWF) is a plasma glycoprotein that is required for normal haemostasis and is synthesised by endothelial cells and megakaryocytes [1]. VWF is characterised by its multimeric nature and large size, 15–20 million Da; the largest multimers are the most competent in maintaining haemostasis [2].

von Willebrand disease (VWD) is the most commonly inherited bleeding disorder, with an estimated prevalence of 1% of the population [3]. Unlike VWD, acquired von Willebrand syndrome (AVWS) is an underdiagnosed and underestimated haemorrhagic disorder that can occur with many different underlying diseases. In AVWS, laboratory findings are similar to those of congenital VWD (type 2A) [4]. Heyde was the first to describe gastrointestinal bleeding in the patients with acquired aortic valve stenosis [5]. Various articles have subsequently linked acquired heart disease to AVWS [6–8]. However, AVWS may also occur with congenital heart disease (CHD) [2,4], as initially described in children [9–11], but the prevalence of AVWS with CHD is completely unknown.

Congenital cardiac defects are frequent in the general population (≈8:1000) [12], representing the largest group among congenital anomalies including a great variety of heterogeneous lesions [13]. Most patients with CHD require several surgical procedures during their lifetime [14]. In adults, the reported incidence of bleeding complications associated with cardiac surgery for CHD that require surgical re-intervention was 10–16% [15–17].

Pathophysiologically, high shear stress induces VWF proteolysis by its cleaving protease ADAMTS-13 in AVWS, leading to a loss of VWF high molecular weight multimers (HMWMs) [18]. Another hypothesised mechanism is the adsorption of HMWM by activated platelets [19].

We hypothesised that surgical as well as non-surgical bleeding in the patients with CHD may be caused by AVWS. Therefore, we systematically evaluated the prevalence of AVWS in a large cohort of adults with different types of congenital cardiac defects such as ventricular septal defect (VSD), atrial septal defect (ASD), Tetralogy of Fallot (ToF), transposition of the great arteries (TGA), pulmonary atresia,

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double-chambered right ventricle, atrioventricular canal, double inlet left ventricle, singular ventricle and different types of valve defects.

2. Methods

2.1. Study design and population

The patients were recruited from the out-patient department for adults with CHD at Hannover Medical School. The study was approved by the local ethics committee, and written informed consent was obtained from each patient.

A total of 221 patients were consecutively screened. The patients under medication, which potentially influenced the coagulation tests performed in this study (e.g. aspirin, n = 18), as well as the patients in acute phase (elevated c-reactive protein (CRP) [cut-off: >3.0 mg/L], n = 11) were excluded. A subgroup of patients taking vitamin K antagonists (VKAs, n = 42) remained in the study because VKAs do not influence the results of the primary haemostasis tests performed in this study, specifically the VWF antigen, VWF activity and VWF multimeric analyses.

One hundred and ninety-two patients were enrolled (115 male and 77 female, between the ages of 21 and 72, median: 31, 25th–75th percentiles: 25.0–37.75); 29 patients (15.1%) suffered from arterial hypertension, and 156 patients (81.2%) had at least one operative procedure. Twenty-nine patients had an artificial heart valve (15.1%), and 15 patients (7.8%) had a biologic heart valve replacement. Thirteen patients suffered from aortic or subaortic valve stenosis (6.8%). Seventy patients (36.4%) had a patch, and 23 patients (11.9%) had a conduit. Twenty-one patients (10.9%) suffered from secondary pulmonary hypertension (Eisenmenger syndrome, ES), 14 patients (7.2%) had undergone a Fontan-procedure, 107 patients (55.2%) suffered from an intracardiac shunt, and 29 patients (15.1%) had a ToF or a ToF-like combination of lesions (the main patient diagnoses are listed in Table 1).

Prior bleeding episodes including spontaneous bleeding, intraoperative and postoperative bleeding as well as blood transfusions were evaluated by a standardised questionnaire. To differentiate between inherited bleeding disorders and AVWS, the bleeding episodes from first degree family members were registered.

2.2. Heart defect grouping

The heart defects were stratified according to complexity as proposed by the American College of Cardiology (32nd Bethesda Conference, 2001) by Warnes et al. [14]. This clinical classification differentiated lesions of simple, moderate and great complexity related to the morphological defect. The present study population consisted of 47 patients (24.5%) with simple, 70 patients (36.5%) with moderate and 75 patients (39%) with great complexity of CHD (Tables 1 and 2).

2.3. Blood samples

The prothrombin time (PT), activated thromboplastin time (aPTT), VWF antigen (VWF:Ag), VWF activity, VWF collagen binding assay (VWF:CB), factor VIII coagulant activity (FVIII:C), VWF multimeric analysis and CRP were assessed from blood samples containing 1:10 dilution of 0.106 M sodium citrate and centrifuged at 4000 rpm for 15 min. The blood containing the 1:10 dilution buffered with 0.129 M sodium citrate was obtained for the platelet function assay (PFA-100). For liver, kidney and heart functional assays (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γGT), cholinesterase (CHE), creatinine and N-terminal probrain natriuretic peptide (NT-proBNP)), serum was collected, and the investigations were performed in a routine laboratory at Hannover Medical School. For the full blood count and blood grouping, the blood containing potassium-EDTA was collected. Blood samples for all coagulation assays including VWF:Ag, VWF activity and PFA-100 were processed and further investigated within two hours after collection. Other parameters where either further investigated or stored at minus 20° at the Werlhof-Institute, Hannover. All of the blood samples were pre-analytically handled with care and transported in the same way.

2.4. Laboratory assays

Factor VIII activity (FVIII:C) was measured using a modified activated partial thromboplastin time (aPTT) and factor-VIII-deficient plasma (Instrumentation Laboratory Company, Lexington, USA). VWF:Ag and VWF activity testing was performed using a latex-immunoassay (Instrumentation Laboratory Company, Lexington, USA). The quantification of VWF activity was performed instead of quantification of VWF ristocetin cofactor activity (VWF:RCo). VWF activity values are highly comparable to VWF:RCo activity with good sensitivity and specificity for diagnosing VWD and AVWS [20,21]. To minimise dilution effects in the blood samples of the patients with ES and, therefore, inaccurate measurement of the coagulation factors, a haematocrit above 60% was used and the samples were citrate adjusted to obtain the correct ratio of plasma to anticoagulant [22].

VWF:CB and sodium dodecyl sulphate-agarose (SDS) discontinuous gel electrophoresis for VWF multimeric analysis was performed at the AescuLabor Hamburg, Germany, as previously described [23].

2.5. Platelet-function-analyser (PFA-100)

The PFA-100 closure time is a high shear stress system to test VWF-dependent platelet function simulating primary haemostasis after an injury to a small vessel. It is a sensitive screening parameter for VWD [3,24–26] and was performed using collagen/EPI and collagen/ADP cartridges (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany).

2.6. Clinical assessments

For diagnosing AVWS, clinical and laboratory findings were assessed. Because of limitations of the diagnostic criteria of the subcommittee on VWF of the ISTH [4,27] in patients with cardiac lesions and normal values of VWF:Ag [23] we based the diagnosis of AVWS on structural abnormalities of the VWF shown by multimeric analysis, including personal or familial bleeding [3].

NTpro-BNP [28], albumin and aspartate aminotransferase (AST) were used as surrogate markers of heart failure [29–31]. The NYHA classification of the patients was obtained from the medical file.

2.7. Statistical analysis

The data are presented as the mean with the standard deviation (SD), median with the 25th and 75th percentiles, or numbers and percentages. We used the Mann–Whitney U test and the χ^2-test to detect group differences between the patients with and without AVWS. The abilities of the VWF:CB to VWF:Ag ratio and PFA-100 to predict AVWS were measured by receiver operating characteristic (ROC) analysis. Multivariate logistic regression analysis was conducted to detect independent associations between AVWS and aortic or subaortic valve defects, NYHA class, complexity of the heart defect, intracardiac shunt, Eisenmenger syndrome and previous Fontan procedures.

A two-tailed probability ≤0.05 was considered significant. The normal value thresholds from our laboratory for each parameter were used as cut-off points. The statistical analyses were performed using SPSS software version 18.0.0 (IBM, USA).

3. Results

3.1. Haemostasis screens

Platelet count did not differ in patients with AVWS and those without (216 ± 99 G/L versus 239 ± 65 G/L, normal range (NR): 150–400 G/L) nor did PT (99.2 ± 18.2% versus 106.5 ± 19.9%, NR: 75–115%) in patients not on VKAs. Patients with aortic valve stenosis were not thrombocytopenic (mean: 247 ± 64 G/L, range: 141–337 G/L). PTT, however, was significantly longer in patients with AVWS (36.5 ± 11.7 s versus 31.8 ± 4.2 s; p = 0.044, NR: 25.1–36.5 s).

3.2. VWF function assays

There were no significant differences in the VWF:Ag, VWF activities and FVIII:C of the patients with AVWS and those without. The mean VWF:CB, however, was strongly impaired (83.6 ± 27.7 versus 100.6 ± 34.6%; p = 0.005, NR: 50–250%). The mean VWF:CB to VWF:Ag ratio was significantly lower in the patients with AVWS (0.7 ± 0.1 versus 0.9 ± 0.2; p < 0.001; sens.: 77.5%, spec.: 93.3%, NR: ≥0.8) (Table 3, Fig. 1).

The platelet function ascertained by the PFA-100 system was strongly prolonged in the patients with AVWS (222 ± 70 versus 170 ± 63 s (NR: 84–160 s) in the collagen–epinephrine cartridge (sensitivity: 77.8%, specificity: 53.3%) and 165 ± 67 versus 111 ± 44 s (NR: 68–121 s) in the collagen–ADP cartridge (sens.: 75.0%, spec.: 74.3%); both p < 0.001) (Fig. 2).

Multimeric analysis showed deficiency of HMWM of the VWF in the patients with AVWS (Fig. 3).

3.3. Prevalence of AVWS

A total of 40 patients (20.8%) presented with AVWS. There was no gender-specific difference (male: 21/115 (18.3%); female: 19/77 (24.7%), p = 0.36) nor any significant differences in age (median: 29.5 years, 25th–75th percentiles: 25.3–38.5 versus 31.0 years, 25.0–37.8) (Table 3).