SCIENTIFIC LETTER

Acquired von Willebrand syndrome in children with patent ductus arteriosus

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Since acquired von Willebrand syndrome (AVWS) was first described in 1968, approximately 270 cases have been reported in the literature. In 12% of these cases AVWS was secondary to cardiovascular disorders.[1] Only two of these reports dealt with children.[2 3] Gill and colleagues reported on 12 patients with non-cyanotic heart defects (atrial and ventricular septal defects, aortic stenosis) and abnormal von Willebrand factor (VWF) subunits.[2] Four out of five patients with ventricular septal defect who underwent repeat examination following surgical repair showed normalisation of the multimeric pattern.

We recently described the first case of AVWS in an infant with persistently patent ductus arteriosus (PDA).[3] To study the frequency of this association and its aetiology, we examined 12 children (eight girls, four boys, median age 3.4 years) who were consecutively admitted for interventional occlusion of a moderate size PDA.

METHODS

We prospectively evaluated clinical and echocardiographic data, global coagulation tests, quantitative and qualitative VWF assays: antigen (VWF:Ag), collagen binding capacity (VWF:CB), and analysis of the multimeric pattern.

RESULTS

Pre-interventional activity of factor VIII:C, international normalised ratio, fibrinogen, D-dimer (n = 11), and platelet counts were normal in each child (data not shown). Strikingly, four patients (33%) were deficient in high molecular weight multimers, similar to von Willebrand disease type 2 (group 1). These patients were younger and had clearly lower VWF:Ag, VWF:CB, and VWF:CB/Ag ratios than the remaining eight children with normal multimeric pattern (group 2) (table 1). Activated partial thromboplastin time (aPTT) was prolonged (57 seconds) in only one patient of group 1 and none of group 2. There was no difference in bleeding history between the two groups. All of the group 1 patients had a loud systolic or systolic–diastolic heart murmur with or without thrill (grade III or IV, table 1), whereas in group 2 four patients had only medium intensity murmurs (grade II). Cardiac catheterisation revealed higher left to right shunting across the PDA in group 1 (table 1). Six months after interventional PDA occlusion (Amplatzer occluder) high molecular weight multimers had normalised in all patients with pathologic VWF, confirming the acquired nature of the disorder. In these children, median values of VWF:Ag increased from 67 to 94 U/l (p = 0.10, paired *t* test), VWF:CB from 45 to 90 U/l (p = 0.01), and VWF:CB/Ag from 0.68 to 0.85 (p = 0.02).

DISCUSSION

The loss of the largest multimers in cardiovascular patients could be explained by various pathogenetic mechanisms.[4] Conceivably, high shear rates across the ductus might lead to adsorption of high molecular weight multimers on to the surface of activated platelets, which would then be cleared or temporarily sequestered from the circulation.[4 5] This hypothesis is compatible with our findings, as the patients deficient in large multimers tended to have a higher left to right shunting across the PDA. Alternatively, proteolytic enzymes could be liberated following coagulation activation with increased cleavage of large multimers into smaller fragments.[2] However, we and others found no indication for enhanced in vivo proteolysis as subunit fragments were normal.[5]

In summary, this is the first systematic investigation of the association between AVWS and PDA. The detection of AVWS in four out of 12 children with relevant PDA suggests that this abnormality is not rare, taking into account a 5–10% frequency of PDA among congenital cardiac defects. Larger studies are necessary to confirm these findings and to study their clinical relevance. In particular, it might be useful to investigate the incidence of haemorrhage in children with congenital cardiac disorders and abnormal hemodynamics associated with high shear rates. As aPTT and bleeding time are often found to be normal, it seems adequate to perform a

Abbreviations: Ag, antigen; aPTT, activated partial thromboplastin time; AVWS, acquired von Willebrand syndrome; CB, collagen binding capacity; PDA, patent ductus arteriosus; VWF, von Willebrand factor

Table 1 Comparison of pre-interventional values between patients with normal and abnormal multimer pattern. Normal ranges were established at authors' institutions

	n	Age (years)	Heart murmur II°/III°/IV°	Qp/Qs	Platelets (×10³/μl)	aPTT (s)	VWF:Ag (U/l)	VWF:CB (U/l)	VWF:CB/ VWF:Ag
Normal multimers	8	5.6 (1.2–18.7)	4/2/2	1.34 (1.00–1.69)	283 (213–416)	37 (34–40)	96 (71–121)	91 (65–136)	0.95 (0.79–1.32)
Acquired VWD	4	2.1 (0.8–6.9)	–/2/2	1.47 (1.40–2.24)	306 (176–356)	36 (35–57)	67 (57–95)	45 (43–48)	0.68 (0.47–0.77)
Normal range					150–400	29–50	50–160	50–160	0.8–4
p Value		0.23	–	0.15	0.87	0.61	0.06	0.007	0.007

Values are median (range).
aPPT, activated partial thromboplastin time; Qp/Qs, flow ratio of the pulmonary and systemic circulations, determined at cardiac catheterisation; VWF:Ag, von Willebrand antigen; VWF:CB, von Willebrand collagen binding capacity.

pre-interventional screening for AVWS in these children, following the recommendations of the subcommittee on VWF of the International Society on Thrombosis and Haemostasis.[1]

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IMAGES IN CARDIOLOGY

Crossed pulmonary arteries, ventricular septal defect, and chromosome 22q11 deletion

A 2 month old was referred for ventricular septal defect closure. Echocardiography demonstrated malposed (crossed) pulmonary arteries and a large subarterial ventricular septal defect. Magnetic resonance imaging confirmed the anatomy. Transverse images (panels A, B, and C) show the crossing pulmonary arterial relationships in a superior to inferior progression. A portion of the large ventricular septal defect is seen in panel D. Panel E demonstrates the abnormal "stacking" of the left pulmonary artery superior to the right in the frontal plane. (LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery; Ao, aorta; SVC, superior vena cava; RV, right ventricle; LV, left ventricle; LA, left atrium; RA, right atrium.)

Given the association of this uncommon malformation with deletion of chromosome region 22q11, a fluorescent in situ hybridisation (FISH) assay was performed. This was positive for haplo-insufficiency in the region. The infant underwent uneventful surgical correction.

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