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Acquired von Willebrand disease due to severe pulmonary valve stenosis: A relevant cause of bleeding in children with Noonan syndrome ?

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Noonan syndrome (NS) is a congenital disorder characterized by dysmorphic facies, short stature and congenital heart defects. Various haemostatic disorders have been described, however, not all were related to a relevant bleeding diathesis, present in up to 65% of patients. Several subgroups of NS patients - especially those with PTPN11 mutation - are associated with pulmonary stenosis. It is known, that heart defects with a large blood flow through a restrictive opening are prone to shear stress related destruction of the VWF, resulting in acquired von Willebrand disease (aVWD). Our aim was to find out whether the pulmonary stenosis is responsible for the bleeding tendency in some of the NS patients.
We investigated the haemostatic system in 15 children with genetically proven NS (14 with PTPN 11, one with SOS1 mutation, responsible for 50% and 10-15% of NS gene mutations, respectively). All of them were asked for signs and symptoms of bleeding, and all underwent a full echocardiographic study.
Platelet count, global coagulation parameters, fibrinogen and antithrombin were normal in all patients. None of the patients had a relevant reduction of a coagulation factor activity. Five patients showed a pulmonary stenosis with systolic gradients >60 mmHg. In three of them a deficiency of the high molecular weight multimers (HMWM) and a pathologic collagen-binding capacity was detected, suggesting aVWD. 9/15 (60%) of patients - two with a deficiency of HMWM - indicated a relevant bleeding diathesis and complained about easy bruising, 3/15 reporting spontaneous gum bleeding.

The mechanism responsible for the destruction of the HMWM in other heart defects could also explain bleeding in some of the NS patients: A high velocity jet across the (here: pulmonary) stenosis appears to cause chronic shear-induced platelet-VWF interaction and clearance. It was first described in aortic stenosis by Warkentin in 1992.
Our discovery of an aVWD in 3/15 children with NS suggests a considerable prevalence of this disorder at least in patients with clinically relevant pulmonary stenosis. This is of importance as in most of them cardiac catheterization or open heart surgery have to be performed and might be compromised by the bleeding tendency.