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HIGHLIGHT

by Jordan A. Shavit, MD, PhD*

The Bleeding Edge of Symptom Assessment

(Commentary on Sidonio et al., page 736)

One of the most vexing problems for a pediatric hematologist is the appropriate investigation of mild bleeding symptoms. Bruising and epistaxis are typical features of childhood yet frequent reasons for referral, and are often difficult to quantify and precisely categorize as either normal or suspicious. There are a significant number of individuals in the general population who report non-specific bleeding symptoms [1], and this certainly applies to parental accounts. While coagulation cascade defects are relatively simple to identify by laboratory evaluation, testing of von Willebrand factor (VWF) antigen and activity levels are notoriously variable from examination to examination, even in the same individual. There is also a large overlap in VWF levels between individuals with von Willebrand disease (VWD) and the normal human population [2,3]. Consequently it has been estimated that there is a 0.4% prevalence of false-positive type 1 VWD [1]. Indeed prevalence estimates in children decreased from 1% to 0.1% when prescreening was done with a validated bleeding questionnaire [4]. Therefore it is critical to avoid testing unless there is significant symptomatology, yet the criteria for proceeding to laboratory analysis are not always clear.

Classically, diagnosis of VWD requires three components, laboratory testing consistent with the disorder, bleeding symptoms, and a family history, although often only one of the latter two is present upon initial consultation. Since a conservative estimate is that roughly 25% of healthy controls have non-specific bleeding symptoms [1], indiscriminate testing will continue to produce false-positive results. Furthermore, the laboratory definition of VWD has been revised by an NHLBI expert consensus panel [5]. Definitive VWD is now primarily distinguished by a ristocetin cofactor activity of less than 30%, while 30–50% is classified as "low VWF." Many clinicians currently treat these patients with low VWF in the same manner as mild VWD, as the precise bleeding risks for this group are not known at this time. However, due to the variability of VWF testing, many initially low VWF individuals are truly normal and subsequently test in the normal range on repeated examinations. Therefore, it would preferable if those individuals could be eliminated prior to testing in order to avoid the associated stresses and costs of misdiagnosis, as well as the accompanying iatrogenic risks when labeled with a bleeding disorder.

Given these issues, development of validated quantitative or qualitative bleeding criteria has been a significant aim in the hemostasis community for some time, and many studies have been performed over the years for VWD (reviewed in Ref. 5). The primary methodology has been questionnaires, such as the Vicenza Bleeding Score and MCMDM-1VWD (Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD) [6,7]. However, these were primarily based on adult patients, and a Pediatric Bleeding Questionnaire has been developed more recently [8,9].

In this issue of *Pediatric Blood & Cancer*, Sidonio et al. describe a large retrospective evaluation of approximately 300 pediatric patients over a 5-year period that measured the prevalence of VWD and disorders of platelet function, as well as determined if qualitative bleeding symptoms predicted these diagnoses. The patients were referred by primary physicians or surgeons, and the criteria were a subset from the Vicenza Bleeding Score [7], including cutaneous and mucocutaneous bleeding, surgical bleeding, and family history. The authors produced four logistic regression models, both single and multiple variable, with the goal of correlating bleeding symptoms with low VWF, VWD, and/or a platelet function disorder. None of the odds ratios were statistically significant, and a subgroup analysis of adolescents with menorrhagia was similarly non-prognostic.

In their discussion, the authors highlight that this is one of the largest pediatric cohorts to be evaluated in this manner. However, they acknowledge the limitations of their study, including its retrospective use of a database that was not designed for this analysis, pointing to the need for a prospective trial. This call has recently been answered. Using the modified Vicenza Pediatric Bleeding Questionnaire [9], a prospective study of approximately 100 children at an academic children's hospital has been performed [10]. The findings were similarly disappointing with the exception of a high negative predictive value for exclusion of type 1 VWD. The primary limitation in that study was lack of standardization of the laboratory evaluation.

At this time additional prospective, standardized studies are required if a useful predictive system is to be validated. The unanswered question remains whether a pediatric bleeding questionnaire is attainable that will allow clinicians to reliably exclude most unaffected children from the vagaries of VWF and platelet laboratory evaluations. This is critical in order to avoid unnecessary diagnoses and interventions in otherwise healthy subjects. Sidonio et al. suggest the need for a more systematic and quantitative scoring system than employed in their study. However, this will have to be balanced against the time commitment required

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for the evaluation of bleeding scores, and whether they are dependent on skilled clinical support staff. The most efficient system will be one that can be performed with minimal cost and/or time, either through the primary physician, or by a home questionnaire or website administered remotely under the auspices of a coagulation disorders program. With increasing demands on the time of busy clinicians, there is the risk of defaulting to automatic laboratory testing or referral with inadequate screening. There is also a tendency to test patients who have traveled long distances to referral centers, even if symptoms seem to be minor. Despite these limitations, we must continue our attempts to develop focused screening strategies. While the interventions for minor bleeding disorders are relatively safe, there are still iatrogenic risks, such as hyponatremia secondary to vasopressin, or infusion of untreated human blood products in remote centers where factor concentrates are unavailable. Patients with hemorrhagic disorders are counseled to avoid collision sports and some parents may balk at other less risky but healthy activities. If there is a 0.4% prevalence of false-positive VWD, the rates of true and false-positive VWD cases may be equivalent. Therefore, in the absence of appropriate symptomatic screening we will continue to mislabel a large number of patients and put them at unnecessary risk.

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