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SSC OFFICIAL COMMUNICATION

Provisional criteria for the diagnosis of VWD type 1

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Type 1 von Willebrand disease (VWD), the most common form of this disease, is defined by quantitative deficiency of von Willebrand factor (VWF) and bleeding symptoms in a proband who also has family members with the same features. A major discrepancy between VWF antigen (VWF:Ag) and ristocetin cofactor activity (VWF:RCo), or a manifestly abnormal VWF multimer profile, points toward an abnormal VWF molecule and suggests a diagnosis of VWD type 2 rather than VWD type 1. Although simple in concept, this definition can be difficult to translate into operational steps to diagnose individual patients correctly. This difficulty is due to several factors that have been increasingly clarified during recent years. Type 1 VWD, although generally transmitted in a dominant way, is variably penetrant in different families and may be variably expressed in the same family. The VWF levels in affected patients and healthy controls overlap considerably and there is no strong relationship between plasma VWF levels and bleeding manifestations, apart from very severe cases. Furthermore, VWF levels are 25–30% lower in O blood group individuals, and blood group O is over-represented among VWD patients. Also, mucocutaneous bleeding symptoms are more common in the healthy population than is often recognized. All of these factors interfere with the evaluation of the three main criteria used to diagnose VWD: reduced VWF level, bleeding symptoms, and inheritance [1–3].

During 1995–1996, an *ad hoc* working party (Chair J. E. Sadler, Co-chair F. Rodeghiero) of the Subcommittee on VWF of SSC/ISTH proposed consensus criteria for the diagnosis of VWD type 1. They were formulated taking into consideration the opinion and the experience of the members of the working party (WP) through a structured questionnaire and ranking the preferred choices or criteria in response to several questions concerning bleeding symptoms, inheritance and laboratory investigations. The normal range of VWF was differentiated according to O and non-O blood groups. The problem of diagnosis in young children or in patients lacking a convincing personal or family bleeding history was recognized, and therefore a distinction was made between 'type 1 VWD' and 'possible type 1 VWD'. These criteria were approved at the 42nd Annual SSC Meeting held in Barcelona as provisional criteria, with the caveat that they should represent a starting point for further investigation and validation by appropriate clinical studies.

These criteria were never published and have not been easily available, although they have been used in several studies of VWD type 1 prevalence or diagnosis [4–6]. Multicenter studies using modifications of these provisional criteria are underway to better define markers for diagnosis and to clarify the association of bleeding symptoms with specific molecular defects at the VWF locus.

Each of these criteria and their combination needs to be evaluated with respect to sensitivity and specificity in order to produce clinically useful guidelines for the diagnosis and management of VWD type 1. Experience during the last 10 years indicates that most mild VWD cases could simply represent coincidental association of low VWF level with bleeding symptoms, even if all of the provisional criteria for diagnosing 'VWD type 1' are satisfied [1]. Well-controlled epidemiological criteria considering the combination of bleeding symptoms and reduced VWF values in more than one family member could produce a diagnosis of VWD in up to 1% of a screened population of school children [7]. As a matter of fact, only one of the 10 patients identified in this investigation has sought medical assistance for bleeding during the past 15 years, indicating that diagnosing very mild cases may not be helpful [8]. Clearly, we need different criteria in order to make clinically meaningful diagnoses. These diagnoses should benefit patients by improving the prevention or treatment of significant bleeding; they should not just label them with a congenital disorder that entails unmerited negative social and personal consequences [9].

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Despite the limitations discussed above, the provisional consensus criteria developed by the Subcommittee on VWF may provide a useful point of reference for studies of how to diagnose VWD type 1 or manage patients with low VWF levels. Therefore we have included them here (Appendix) in case they may be useful for such investigations.

Appendix

Bleeding symptoms

Significant mucocutaneous bleeding symptoms:

Nose bleeding, ≥2 episodes without a history of trauma not stopped by short compression of < 10 min, or ≥1 episode requiring blood transfusion.

Cutaneous hemorrhage and bruisability with minimal or no apparent trauma, as a presenting symptom or requiring medical treatment.

Prolonged bleeding from trivial wounds, lasting ≥15 min or recurring spontaneously during the 7 days after wounding.

Oral cavity bleeding that requires medical attention, such as gingival bleeding, or bleeding with tooth eruption or bites to lips and tongue.

Spontaneous gastrointestinal bleeding requiring medical attention, or resulting in acute or chronic anemia, unexplained by ulceration or portal hypertension.

Heavy, prolonged, or recurrent bleeding after tooth extraction or other oral surgery such as tonsillectomy and adenoidectomy, requiring medical attention.

Menorrhagia resulting in acute or chronic anemia, or requiring medical treatment, not associated with structural lesions of the uterus.

Bleeding from other skin or mucous membrane surfaces requiring medical treatment (e.g. eye, ear, respiratory tract, genitourinary tract other than uterus).

Criteria for bleeding symptoms A significant mucocutaneous bleeding history requires at least two symptoms in the absence of a blood transfusion history, or one symptom requiring treatment with blood transfusion, or one symptom recurring on at least three distinct occasions.

Criteria for family history A positive family history compatible with VWD type 1 requires that at least one first-degree relative, or at least two second-degree relatives, have a personal history of significant mucocutaneous bleeding and laboratory tests compatible with VWD type 1 (discussed below). When available, the use of VWF mutations or genetic markers linked to the VWF locus may permit the analysis of more remote relatives, and may allow asymptomatic relatives with low VWF levels to provide evidence for inheritance.

Laboratory tests in suspected VWD

Screening tests Complete blood count with differential and platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), VWF:RCo, VWF:Ag.

Screening or confirmatory tests Factor VIII level, ABO blood type.

Confirmatory tests Ristocetin-induced platelet agglutination (RIPA), VWF multimers.

Criteria for laboratory tests Laboratory test results are compatible with VWD type 1 if the levels of both VWF:RCo and VWF:Ag are > 2 SD below the population mean and ABO type adjusted mean on > 2 determinations. If the tests are performed, RIPA must not indicate abnormal sensitivity to low concentrations of ristocetin, and the plasma VWF multimer distribution must be normal.

Criteria for categories of VWD type 1

Type 1 VWD VWD type 1 is an inherited bleeding disorder due to quantitative deficiency of VWF. The diagnosis therefore is based upon criteria for symptoms, VWF deficiency, and inheritance, all of which must be satisfied. These include: significant mucocutaneous bleeding, laboratory tests compatible with VWD type 1, and either a positive family history for VWD type 1 or an appropriate VWF mutation.

Possible type 1 VWD Possible VWD type 1 includes persons with laboratory tests compatible with VWD type 1 and either significant mucocutaneous bleeding or a positive family history for VWD type 1.

To meet this definition, an asymptomatic person with low VWF must have a positive family history, which means that they must have at least two relatives with definite VWD type 1.

In many circumstances, symptomatic patients with either VWD type 1 or possible VWD type 1 will be treated identically. Such empiric treatment may also be appropriate for selected asymptomatic patients. The distinction between 'possible VWD type 1' and 'VWD type 1' will be useful for certain clinical studies and genetic studies. Alternative diagnoses should continue to be considered for patients with 'possible VWD'.

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