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## Von Willebrand's disease – is a new classification system required?

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A B S T R A C T

The first attempts to break down von Willebrand's disease (VWD) into subclasses date back to the mid 1980s, predominantly based on knowledge achieved through the disseminated use of the new multimeric methods that gave way to various subclass phenotypes of VWD. In 1993–4, the VWF Subcommittee of ISTH endorsed and published a revised and simplified classification system attempting to focus more on pathophysiology and clinical characteristics in VWD, rather than merely protein phenotypic subsets. During the last 4–6 months discussions have taken place amongst members of a working group hosted by the Scientific and Standardization von Willebrand subcommittee in order to evaluate whether there is a need for revision of the present classification guideline. A major aspect in this work is the clinical approach. It is well known that the availability of laboratory tools for use in diagnosis of VWD varies considerably from center to center and therefore a new recommendation are required presenting with common diagnostic denominators for use in the VWD diagnosis. Further, concerns have been raised around the use of a VWD diagnosis in those patients who present with milder changes in level or function of plasma VWF. Highlights from the e-mail based working group discussions will be presented for further debate in the scenario of the present Nordic symposium on von Willebrand's disease.

Key words: von Willebrands disease, von Willebrand factor, VWF, VWD

Since the first description by Erik von Willebrand, numerous published studies have disclosed the highly heterogeneous nature of Von Willebrand's disease (VWD).

Based primarily on the mode of inheritance, Ingram<sup>1</sup> proposed the earliest classification system. With the appearance of electrophoretic methods for study of the von Willebrand factor (VWF) multimers<sup>2</sup> as well as improved methods for quantitation of VWF, new principles for classification were based on these methodologies. Although not formally approved at that time, VWD was divided into three major classes denoted type I (reduced protein with no structural abnormality), type II (structural or functional abnormality in VWF), and III (extremely reduced levels of VWF and a severe bleeding phenotype). Initially, two major type II subclass variants were described, type IIA and type IIB.<sup>3</sup> Subsequently, several distinct type II subclasses were reported, based on the multimeric VWF sub band composition pattern as assessed by high resolution gel electrophoretic techniques. Simultaneously, type I subclasses were also detailed to display a

mixture of quantitative as well as qualitative VWF defects.

### The 1994 Classification System

With the intention to more closely harmonize the biochemical subclass phenotypes with the clinical pathophysiology of VWD, a proposal was forwarded and endorsed by the von Willebrand Factor Scientific and Standardization Subcommittee of the International Society on Thrombosis and Haemostasis in 1993–4.<sup>4</sup> The fundamental principles of the 1994 classification system are listed in Table 1. Type 1 hold quantitative defects with a *normal* range of multimers, while type 2 subclasses comprise qualitative defects with or without structural deformities in VWF multimers and/or loss of HMW multimers. The major type 2 forms are 2A and 2B, which mirror the original type IIA and IIB subclasses, respectively, but each group will also contain subclass variants previously allocated to other major subgroups. Many variant

forms previously designated subtype II were now transferred to the type 2A subclass. Type 2B was enlarged to include all forms showing increased sensitivity to ristocetin induced interaction with platelets independent of the multimeric pattern. The common hallmark here is the result of the ristocetin induced direct platelet agglutination test as performed on patient's own platelets (RIPA) revealing an increased responsiveness to low concentrations of ristocetin, such as 0.4 µg/mL.

Type 2M, representing a new entity, is characterized by a normal range of multimers with a decreased level of VWF:RCo activity in comparison with the VWF:Ag level. In type 2N, the major finding is a low level of factor VIII due to the presence of mutations in regions encoding VWF epitopes that bind factor VIII, while the amount of VWF and its ristocetin cofactor function is normal in most of individuals. Hence, type 2N comprise all forms with decreased affinity to factor VIII, independent of the multimeric VWF composition.

### Experiences with the 1994 classification scheme

With ten years use of the 1994 classification system, its performance has been debated. Particular problems and some of arguments often put forward are summarized here.

#### Type 2M

When establishing a type 2M diagnosis, evidence must be provided that the entire range of HMW multimers is present. In order to ensure this, a low-resolution multimeric sizing gel technique should be utilised (preferably a gel concentration < 1.2%) to avoid erroneous classification of a patient who in the true sense suffers from a type 2A disorder. Only few laboratories use multiple concentrations of agarose gels providing low-, intermediate-, as well as high resolution characteristics for VWF multimeric size determination and sub band dissection, and a type 2M diagnosis may thus cause technical difficulties in many places. Indeed, recent findings of the MCMDM-VWF-1 study carried out by a group of European Centers have revealed that many patients originally assigned with a type 1 diagnosis in fact suffer from a subtype 2 disorder. This diagnostic dilemma was originally proposed by Lethagen *et al.* in 1997.<sup>5</sup> Moreover, cases have been identified with a reduced collagen interaction unrelated to loss of HMW multimers, prompting considerations around a separate type 2M subtype entity with that particular characteristic.<sup>6</sup>

**Table 1. Recommended classification of von Willebrand's disease, as proposed by the von Willebrand Factor Scientific Subcommittee of ISTH.<sup>12</sup>**

Major Class	Subgroup	General characteristics of VWF
1		Quantitative deficiency of VWF
2	common	Qualitative deficiency of VWF
2	A	Loss of high-molecular forms of VWF multimers plus reduced VWF-platelet interaction
2	B	Increased interaction (sensitivity) towards platelet glycoprotein Ib
2	M	Qualitative deficiency of VWF dependent reactivity with no loss of high-molecular weight forms of VWF
2	N	Qualitative defects in VWF binding of factor VIII
3		Complete deficiency of VWF

#### Mild type 1 VWD variants

There is general consensus that a patient with a level of VWF:Ag at 5–25% of normal and a similarly reduced level of VWF:RCo, plus a full range of normal multimers can be assigned a diagnosis of VWD type 1. With reference to the discussion around type 2M, the type 1 diagnosis is based on observations providing assurance that there is no loss of HMW multimers (in which case patient suffers type 2A) and, that the reduction in VWF:Ag level is equivalent to the VWF:RCo level. On the other hand, ongoing debate has focused on whether a diagnosis of VWD type 1 should justifiably be applied in persons with a record of no symptoms or a mildly increased tendency to bleeding and levels of VWF greater than 35% of normal. Quite large epidemiological studies have demonstrated that relatively decreased VWF levels plus a positive history of bleeding occur in 0.7–1.3% of populations,<sup>7–9</sup> placing VWD into a context of quite common disorders. Accounting for the prevalence data VWD appears to be either under-reported or alternatively, a mild bleeding risk with no tendency to serious bleeding is erroneously being assigned with a disease diagnosis. The proposed prevalence figures further contrast with actual numbers of VWD patients registered in most countries. At the lower-end of the reference range some individuals may be diagnosed with

VWD if a positive bleeding history is presented. Since the level of VWF is relatively lower in persons with blood group O as compared to non-O, it has been discussed whether patient's VWF level should be compared to a reference population with same ABO blood group to improve the accuracy of the VWD diagnosis. Previous publications<sup>10,11</sup> as well as recent data from a major European study on type 1 VWD<sup>12</sup> illustrate that amongst persons with a VWD type 1 disorder there is over-representation of blood group O as compared to non-O. Thus, an increased risk of bleeding in blood group O may be caused solely by the tendency to lower levels of VWF in plasma as a simple biological phenomenon. Contributing to this discussion, Sadler<sup>13</sup> recently argued that many patients with a diagnosis of type 1 VWD really do not suffer from a well-defined haemorrhagic disorder, and further proposed that a reduced level of von Willebrand factor might be regarded a mild risk factor for bleeding in a biological continuum, rather than a disease state. Hence, it appears more appropriate to adopt a risk based rather than a diagnostic terminology. It is well known that VWF levels tend to increase with age and bleeding symptoms to wean off. Until clarification from studies of mutations in type 1 families and linkage it seems preferable to adopt a bleeding risk based approach in management of a patient with mildly lowered quantitative deficiency of VWF.

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### **Time for a new classification system?**

During 2004, a group of members of the von Willebrand Factor Subcommittee of the Scientific and Standardisation Committee of ISTH have contributed to an e-mail based discussion forum, presenting several aspects and proposals for a new classification system. Amongst these, some will be brought to attention here.

#### ***Classification based on laboratory features only***

Since bleeding symptoms are quite difficult to assess objectively and no evidence based scoring system exists, the diagnosis of VWD in type 1 is predominantly based on laboratory findings with the ristocetin cofactor level representing the important determinant for diagnostic purposes in most centers. With the exception of the picture in the severe type 3 VWD variant, however, no correlate has been established between the level of VWF:RCo and bleeding symptoms, and it is doubtful whether such a correlation exists at all. Supposedly, the factor VIII:C level might be a better candidate for bleeding risk assessment. In terms of type 2 and 3 variants, the loss of high molecular weight forms or all forms of VWF multimers provides us with a well understood mechanistic problem with

the anchoring of platelets to the wound. Even here, bleeding symptoms vary considerably amongst biochemically comparable cases.

#### ***Classification based on molecular genetics***

Most logically a new classification system could account for molecular genetics of the disease variants. In quite many subtype 2 variants, the multimeric pictures provide some information concerning the site of mutation. However, there is still insufficient genetic data in type 1 (and type 3) to establish a platform for a novel classification based on mutation in general terms. For instance, in the same phenotypic variant subgroup there are examples with decreased synthesis of VWF while others are caused by increased clearance.

Further, a mildly increased bleeding tendency may not always co-segregate with VWF levels in families, and linkage studies are only at an early stage. Until more data become available from the ongoing major studies in Europe and Canada, VWF protein/function determinations will still represent a stronghold in diagnosis.

#### ***Classification based on simplified diagnostic procedures***

With the universal geographic occurrence of VWD, many patients today are diagnosed by means of quite simple laboratory methods. Accounting for this, a revised classification system should be more simplistic to assist less well-equipped laboratories in providing a diagnosis without the more sophisticated sub-classification requirements.

#### ***Classification based on treatment demands***

It is well known that many patients with a mild bleeding disorder may achieve effective haemostasis quite easily with antifibrinolytics alone. In others (type 1) desmopressin acetate (DDAVP) administration is efficacious in management and prevention of bleeding, while still others (type 2 and 3) need factor VIII concentrate with natural VWF. Based on these clinical grounds, a simplified classification system could be based primarily on treatment requirements.

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### **The perspective**

In a summary of the discussions of the working party presented by J.E. Sadler during the recent Scientific and Standardisation Committee meeting June 2004, the following major points were addressed (citation):

i. The classification is intended primarily to guide VWD patient treatment and genetic counselling, and

therefore must be clinically relevant;

ii. The classification should be simple, with a minimum number of formal categories;

iii. Implementation should depend mainly on laboratory tests that are widely available;

iv. The classification should be separated conceptually from specific laboratory testing protocols, so that the development of new assay methods will not render the classification obsolete;

v. A revised classification should address the dif-

ferential diagnosis of VWD, acquired von Willebrand syndrome (AVWS) and platelet-type pseudo-VWD (pseudo-VWD).

A final proposal for a revised classification scheme is expected in 2005.

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