von Willebrand factor (VWF) is a large plasma glycoprotein that exists as a series of multimers of molecular weight 800-20000 kD. VWF has two main functions: as a carrier protein for coagulation factor VIII and as an adhesive protein involved in vessel wall-platelet interaction. Its function as an adhesive protein is most important in situations of high shear stress. Inherited defects in VWF may, therefore, cause bleeding by impairing either platelet adhesion or fibrin clot formation.

Von Willebrand disease (VWD) is defined as a deficiency of VWF function causing impaired haemostasis. VWD is generally recognised as the most common human inherited bleeding disorder. However, precise data regarding prevalence are not available reflecting the extreme variability in clinical symptoms of milder forms of VWD. Western population based studies give an estimate of clinically significant VWD at a prevalence of 125 per million. This is approximately the same incidence as haemophilia A. However, up to 1 per cent of these populations may have VWD if defined simply by reduced levels of VWF. The majority of such cases are due to mild, quantitative deficiencies of VWF. Severe forms of VWD due a virtual absence of VWF affects 1.4-1.6 per million.

The most common symptoms of VWD are mucosal bleeding (epistaxis, bleeding after tooth extraction, gingival bleeding, menorrhagia), prolonged bleeding from skin wounds, and post-operative bleeding. The diagnosis of VWD is suspected in individuals with such symptoms and a family history of bleeding. The haemorrhagic tendency is highly variable and depends upon type and severity of disease. VWD most commonly presents as a mild to moderate bleeding disorder, however, when there is complete deficiency of VWF, the bleeding symptoms are severe. Consequently the most severe forms of VWD usually present in childhood whilst the mild forms may not present until after a significant haemostatic challenge, often in adulthood. In the absence of such a significant challenge, some patients remain asymptomatic and undiagnosed. In the mild forms there is considerable overlap with normality.

The diagnosis of VWD cannot confidently be made in the absence of phenotypic data. The diagnosis can be divided into three stages: (i) identification of patients at risk of VWD based upon clinical and family history and basic laboratory identification; (ii) diagnosis of VWD and type by specific laboratory tests; and (iii) discrimination of sub-type where appropriate by further laboratory analysis. However, uncertainty regarding the relationship between clinical features, laboratory assays and function in vivo means that diagnosis is frequently difficult. Despite an increasing understanding of the pathophysiology of VWD, the investigation and diagnosis of patients with possible VWD can vary widely.

VWD has been defined as an inherited bleeding disorder caused by a quantitative or qualitative defect of VWF secondary to a mutation in the VWF gene. However, it is now clear that many other genetic loci exert quantitative and qualitative influences over plasma VWF so that VWD is a genetically and clinically heterogeneous disorder with variable penetrance.
Historically the classification of VWD has been complex and a major source of confusion. The old classification system had many different subtypes and subclassifications of limited clinical relevance. Today a simpler classification is used\(^3\). VWD is now subclassified into three major categories (Table I), one of which, (type 2) is subclassified into four variants dependent upon the type of functional defect present (Table II). The six categories correspond to distinct pathophysiological mechanisms and are important in determining therapy.

According to the International Society on Thrombosis and Haemostasis (ISTH) classification, the diagnosis of VWD hinges on defining quantitative and qualitative deficiencies of VWF\(^3\).

In this issue, Trasi et al\(^4\) have examined the prevalence and spectrum of VWD in western part of India using a full range of laboratory assays. In contrast to the expectations, they have shown that in their tertiary centre the most common forms of VWD seen are type 3, with type 1 and type 2 of approximately equal proportions. They conclude that VWD is probably an underdiagnosed entity in India. So why is type 3 more common in their practice? In part this is likely a reflection of the referral patterns - more severe cases are referred on for diagnosis and follow up. However, there is also likely to be a genuinely higher incidence of type 3 VWD in India due to the prevalence of consanguous marriages in some states.

But why is type 1 so much less frequently observed than in Western populations? Type 1 VWD is a heterogenous disorder that ranges from a disorder with frequent bleeding problems to a very mild disorder with infrequent bleeding problems. As the authors suggest in milder forms of type 1 VWD the bleeding pattern is relatively infrequent and mild and, if there are relatively low levels of awareness of the potential diagnosis of VWD, this will be considered as normal. In this setting the more frequent milder cases will not be sent on for formal investigation - only the less frequent more severe type 1 cases will be picked up.

The underdiagnosis of VWD is in some ways a self fulfilling prophesy - it is not common, and therefore not considered and not frequently diagnosed. We are now seeing the flip side of this coin in the UK. Whilst the number of new registrations of patients with VWD are rising year on year, as awareness about VWD increases, increasing understanding that a set of normal coagulation screening test results do not exclude the diagnosis and also the increasing understanding that VWD is very prevalent in women being investigated for significant menorrhagia.

The diagnosis of type 1 VWD in milder forms can also be very problematic. It is essential that a full range of tests are available if the diagnosis is to be established\(^5\). The possibility, as the Trasi et al\(^4\) suggest, that significant numbers of patients with VWD are diagnosed in India as mild haemophilia A due to lack of specific testing is very real. Even with the right assays available diagnosis can be difficult. VWF levels are significantly affected by blood group, hormonal status, intercurrent illness and age. Disentangling these compounding factors in milder cases of VWD from the normal is complex. Guidelines have been published to aid diagnosis\(^5\).

Type 2 VWD can produce significant symptoms and has historically been thought to account for about 20-25 per cent of cases of VWD. However, now it is increasingly recognized, largely through studies on the
molecular biology of type 1 VWD, that many cases of apparent autosomal dominant type 1 VWD are in fact type 2 variants that have been previously overlooked. Perhaps what we have learnt for this is that the diagnosis of type 1 VWD requires as much attention to detail as type 2.

VWD is likely to emerge as the most common bleeding disorder in India as awareness about it increases and more cases are investigated. It is also likely that the relative balance will move away from type 3 being the most common subtype. These severe cases are those most likely to be investigated first. Undoubtedly type 1 will be diagnosed more frequently. Whether type 1 or type 2 will emerge as the most frequent is another matter and will be informed by our increasing understanding of the genetics of VWD.

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### References


