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Von Willebrand's disease in the Western Cape

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Objective. To establish the prevalence of the various subtypes of Von Willebrand's disease (VWD) among patients with bleeding disorders in the Western Cape and to review appropriate treatment strategies.

Design. A systematic clinical and laboratory study.

Setting. Haemophilia clinics at two tertiary referral hospitals (Groote Schuur Hospital and Red Cross War Memorial Children's Hospital) in the Western Cape.

Patients. Twenty-two patients (14 females, 8 males; ages 3 - 55 years) were studied. Those studied were selected for reasons of convenience, as they were compliant and regular attenders at the clinics.

Main outcome measures. History of a bleeding tendency; bleeding time measurements; factor VIII assays, von Willebrand factor (VWF) antigen assays; ristocetin co-factor assays and VWF multimer analysis.

Results. Fourteen patients had typical type I VWD; 2 had type II and 5 had type III variants, and there was 1 unclassifiable variant. Analysis of local factor VIII concentrates showed the presence of high-molecular-weight VWF multimers.

Conclusion. The results are similar to patterns reported elsewhere in the world. Locally produced factor VIII concentrates, unlike a number of commercially produced concentrates, contain sufficient multimers for use as appropriate replacement therapy.

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Von Willebrand's disease (VWD) is a mild-to-moderately severe bleeding disorder characterised by mucosal bleeding such as epistaxis, gingival bleeding, gastro-intestinal bleeding and menorrhagia. Haemarthroses, deep subcutaneous and intramuscular haematomas, typically seen in the severe haemophilias, are uncommon. The bleeding increases markedly in association with trauma and surgery. The disorder results from a deficiency of Von Willebrand factor (VWF), a glycoprotein (Gp) present in plasma, platelets and endothelial cells. VWF is an adhesive protein which facilitates platelet adhesion to damaged vessel walls; the haemostatic effect is achieved by the VWF's acting as a bridge between platelets and vessel wall components such as collagen. The protein circulates as a complex multimeric structure with factor VIII, and has a stabilising effect on the latter.

Three types of VWD are recognised: type I, with a moderately decreased plasma concentration of normal VWF; type II, with qualitatively abnormal VWF at normal or near normal levels; and type III, with a very low or undetectable concentration of VWF. Typically, types I and II show a dominant pattern of inheritance with a mild-to-moderate bleeding tendency, while type III is recessive and can be associated with severe haemorrhage.[1] Although this classification is an over-simplification, it forms a useful clinical basis.

VWD is probably one of the commonest congenital bleeding disorders. In northern Italy the prevalence is estimated at 1 in 100, although lower prevalences have been reported elsewhere.[1,2] Most of the reported differences in prevalence probably relate to the availability of proper facilities to diagnose the disorder. In South Africa there are only 250 patients recorded on the National Haemophilia Register, which indicates a relatively low prevalence. However, this may be the result of under-reporting and under-diagnosis.

The laboratory diagnosis depends upon the demonstration of a prolonged bleeding time using a standardised template in the presence of a normal platelet count. There is no current assay that measures the level of VWF directly, but this can be inferred by measurement of the VWF antigen level, factor VIII activity and ristocetin co-factor activity. Ristocetin is an antibiotic which was found to agglutinate normal platelets but does not have an effect on platelets from patients with VWD. The ristocetin co-factor (RiCof) assay measures the ability of plasma to agglutinate fixed platelets and is therefore regarded as an indirect measure of VWF activity. Qualitative analysis of VWF antigen (VWF-Ag) is required for proper identification of variants and is achieved by separation of the VWF multimers (in plasma or platelets) by SDS-agarose electrophoresis followed by staining with a radiolabelled antibody to VWF antigen. Other diagnostic procedures may include ristocetin-induced platelet aggregation (RIPA) of the patient's platelets and response to desmopressin (a synthetic analogue of vasopressin) or specific factor VIII concentrates.

Little has been published concerning the prevalence and subtypes of VWD in South Africa. This paper is the result of a systematic study of patients with a presumptive diagnosis of VWD who attended the haemophilia clinic at Groote Schuur Hospital and Red Cross War Memorial Children's Hospital.

Materials and methods

Twenty-two people from 11 families with a history of VWD were studied. There were 14 females and 8 males, ranging in age from 3 to 55 years. Fifteen were of mixed racial origin while the remainder were white. Their bleeding histories were carefully documented and full blood counts and platelet counts were performed on a Coulter S Plus IV. The bleeding time was measured with a standard template (Simplate II, General Diagnostics, USA) and the factor VIII

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activity by a one-stage clotting method that used a manual tilt tube.[3] VWF-Ag was assayed by an enzyme-linked immunosorbent assay (ELISA),[4] and ristocetin co-factor was measured with fixed platelets and an aggregometric technique supplied in kit form (General Diagnostics, USA).[5] VWF-Ag was qualitatively analysed by separation of the multimers in SDS-agarose (1.8%) followed by immunofixation with a radiolabelled antibody to VWF.[6] RIPA had also previously been performed in some patients.

Results

Fourteen patients from 5 families appeared to conform to the typical type I pattern (Table I). They had mild bleeding tendencies, and plasma concentrations of the VWF-related proteins were moderately decreased, generally all to a similar degree, although disparate levels were noted in a couple of patients. On multimeric analysis, the VWF-Ag structure was normal (Fig. 1).

Table I. Type I variants

	Bleeding time (min.)	Factor VIII (%)	VWF-Ag (%)	RiCof (%)
Normal	1 - 9.5	60 - 200	50 - 200	45 - 200
Mean	9.6	49	25	19
Range	4 - >15	17 - 65	15 - 57	10 - 40

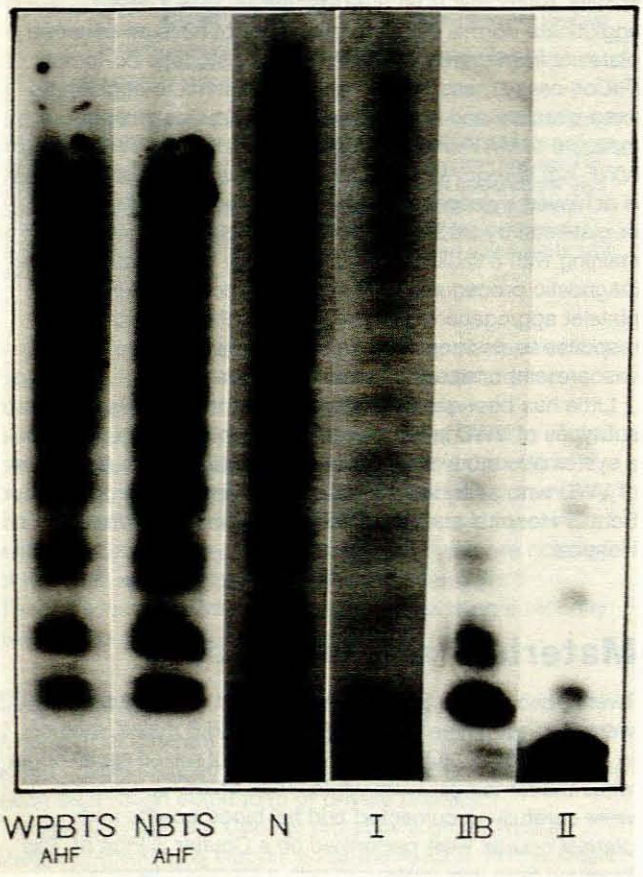

Fig. 1. VWF multimer analyses of normal plasma, VWD variants and factor VIII therapeutic concentrates.

Two patients from 2 families were diagnosed as type II variants. Both had prolonged bleeding times and mildly decreased or normal factor VIII, VWF-Ag levels and ristocetin co-factor values. Both lacked the high-molecular-weight multimers (Fig. 1). In 1 patient there was enhanced sensitivity of the patient's own platelets to ristocetin and he therefore probably belongs to the type IIB category, in which there is enhanced binding of the VWF to Gp-binding sites on the platelet, specifically the Gp-1b receptor. RIPA was not performed in the other patient but the triplet structure of the multimers appears to be abnormal and he may therefore belong to the type IIC category. Further high-resolution multimer studies are indicated. Both patients have mild-to-moderate bleeding tendencies.

Five patients from 3 families appear to have the type III variant (Table II) in that they all had virtually undetectable levels of VWF-Ag and ristocetin co-factor, together with low levels of factor VIII. Multimeric assays not surprisingly showed a complete absence of bands. Family history in 2 of the families we were able to screen comprehensively also indicated a recessive inheritance in that both parents showed some measurable abnormalities of the VWF/factor VIII complex, but were clinically normal. Interestingly, although most publications describe these patients as suffering from periodic haemophilia-like haemorrhages with soft-tissue bleeding, the patients in this study had a history of mainly mucosal bleeding easily controlled by administration of appropriate plasma products.

Table II. Type III variants

	Bleeding time (min.)	Factor VIII (%)	VWF-Ag (%)	RiCof (%)
Normal	1 - 9.5	60 - 200	50 - 200	45 - 200
Mean	15	5	3	0
Range	12 - >15	3 - 8	0 - 14	0

Finally, there is 1 patient who remains unclassifiable: he has a persistently prolonged bleeding time, normal factor VIII and VWF-Ag and absent ristocetin co-factor. The multimeric analysis of the plasma showed normal multimeric structure, but platelet multimers have not been assayed. Clinically, he has had recurrent episodes of unexplained gastro-intestinal bleeding, although he is symptom-free at present. Unfortunately the patient's parents were not available for testing, but his children have no bleeding problems, although some showed mild abnormalities on laboratory testing.

Discussion

In agreement with other studies, the classic type I VWD variant was the most common form, affecting 60% of all patients tested. This compares fairly well with the 70 - 75% incidence in other studies.[7] The type II variants are the least common at 10% while 5 type III patients make up the remaining 30%. This is somewhat higher than that reported in other studies, but our sample was relatively small. It is notable that there were no black patients in our study; this is also reflected in the figures from the National Haemophilia Register and probably indicates that this condition is uncommon in blacks.

As noted earlier, however, VWD is probably underdiagnosed in South Africa since most other studies from more developed countries report a higher prevalence. Definitive diagnosis is occasionally difficult, especially in mild cases, since the levels of VWF and factor VIII are known to fluctuate in healthy people and repeat determinations of the different variables may therefore be required. It is not necessary to undertake all the investigations performed in this study. Any patient presenting with a predominantly mucocutaneous bleeding tendency should have a platelet count followed by a bleeding time test if the platelet count is normal. The type II B variant is sometimes associated with a moderate thrombocytopenia and patients with persistent unexplained mild-to-moderate thrombocytopenias should be tested for VWD. Factor VIII assay, VWF-Ag and ristocetin co-factor assays are required to confirm the diagnosis. Further tests need only be considered if a variant type is suspected or if the results are difficult to interpret. Clearly such patients need to be referred to a specialist centre for these assays. If the diagnosis is questionable or borderline it is best not to label the patient as having VWD since they may then be inappropriately treated with blood components.

When patients with VWD bleed or are to undergo surgery, the main goal of treatment is to correct the bleeding time and factor VIII defects. Clinical studies have demonstrated that low factor VIII levels are the main determinant of postoperative haemorrhages and the more rare soft-tissue haemorrhages which are usually only seen in some type III patients. Normalisation of bleeding time is not necessarily required in these situations. However, when severe mucosal haemorrhage occurs, correction of the bleeding time is usually required.[8] In most patients with type I VWD, both factor VIII levels and bleeding time defects can be corrected by the administration of desmopressin, which is efficacious in stopping most haemorrhages. Patients given repeated infusions over a period of a few days (e.g. during and after surgery) may, however, become refractory owing to tachyphylaxis, since desmopressin acts by releasing endogenous factor VIII/VWF from storage sites. However, in patients with type III variants and in most type II variants, desmopressin is not effective; it is, in fact, contraindicated in the type IIB variant since it may cause a significant thrombocytopenia. Replacement with blood components therefore still plays an important role. Although cryoprecipitate contains all the important multimers in VWF, it is not virally inactivated as are the more purified factor VIII concentrates. Purification, however, does remove some of the high-molecular-weight multimers and some very highly purified concentrates are not suitable for treatment of VWD. In South Africa there are two concentrates available, namely the small-pool heat-treated antihaemophiliac factor (AHF) made by the South African Blood Transfusion Service and Western Province Blood Transfusion Service, and the large-pool solvent-detergent inactivated concentrate from Natal Blood Transfusion Service. Fig. 1 shows that both contain most of the important high-molecular-weight multimers and are therefore suitable for replacement therapy in VWD. If bleeding is profuse, despite replacement therapy, platelet concentrates should be given, since it has been shown that the latter may normalise the bleeding time for several hours and stop severe mucosal haemorrhage: this emphasises the important role of platelet VWF in normal haemostasis.[9]

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