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Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease

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Summary. Type 3 is the most severe form of von Willebrand disease (VWD) transmitted as an autosomal recessive trait. We collected data on the clinical manifestations of type 3 VWD by examining 385 patients from 300 Iranian kindreds, who were compared with 100 age-matched patients with severe haemophilia A. Joint and muscle bleeding was less frequent than in haemophiliacs, perhaps because factor VIII levels were in general higher (median value 4% vs. 1% or less). Mucosal tract haemorrhages such as epistaxis and menorrhagia were the most prevalent symptoms in VWD. Post-circumcision and oral cavity bleeding occurred frequently when prophylactic replacement therapy was not carried out or was inadequate. The course of pregnancy was usually uneventful, but increased bleeding occurred at parturition when affected women were treated with replacement therapy for less than 3–4 d. Ten of 385 (2·6%) of these multitransfused patients developed an alloantibody to VWF and 55% are chronically infected with the hepatitis C virus.

Keywords: von Willebrand disease, von Willebrand factor.

von Willebrand disease (VWD) is a congenital bleeding disorder characterized by a defect of platelet adhesion to the vascular subendothelium that is reflected by a prolonged skin bleeding time and is accompanied by hypocoagulability as a result of low plasma levels of factor VIII coagulant activity (FVIII:C) (for a review, see Sadler *et al*, 2000). VWD is due to quantitative and/or qualitative abnormalities of von Willebrand factor (VWF), a large multimeric glycoprotein that circulates in plasma in complex with factor VIII and functions as its stabilizer. The most severe form of VWD is type 3, which is transmitted as an autosomal recessive trait and is characterized by unmeasurable plasma levels of VWF that contrast with low but measurable levels of FVIII:C. These patients usually need lifelong replacement therapy, although usually less frequently than patients with severe haemophilia A. Patients with type 3 VWD are homozygous or double heterozygous for abnormal VWF genes inherited from asymptomatic parents (see Sadler *et al*, 2000).

With an estimated prevalence of 0·55–3·2 per million in Western countries (Mannucci *et al*, 1984), type 3 VWD is more frequent in communities where consanguineous marriages are common (Shoa'i *et al*, 1977). In Iran, a national registry of inherited coagulation disorders lists 600 patients, with a prevalence as high as 6·0 per million. In contrast, registries kept in Italy and in the UK, countries that like Iran have populations of approximately 60 million but that unlike Iran have fewer consanguineous marriages, list 61 and 55 patients respectively (prevalence approximately 1 per million).

Because of the rarity of type 3 VWD, there is relatively little information on the type and severity of bleeding manifestations. Published cases are likely to reflect exceptionally severe bleeding in highly selected patients, so that the findings are not representative. In this study, we tried to collect more accurate information on clinical manifestations and side-effects of replacement therapy by examining an Iranian sample of 385 patients, including 182 women with type 3 VWD. The unusually large group of affected women allowed us to evaluate the frequency and type of complications associated with pregnancy and childbirth and to relate them to the use of prophylactic replacement therapy.

PATIENTS AND METHODS

Type 3 VWD was diagnosed when VWF was unmeasurable as immunoreactive protein (Laurell's electroimmunoassay

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Table I. Percentage of Iranian patients with type 3 von Willebrand disease ($n = 385$) and severe haemophilia A ($n = 100$) who had a given bleeding symptom at least once.

Bleeding symptom	In type 3 VWD (%)	In haemophilia A (%)	Statistical significance*
Haemarthrosis	141/385 (37)	86/100 (86)	$P < 0{\cdot}0001$
Muscle haematoma	200/385 (52)	93/100 (93)	$P < 0{\cdot}0001$
Oral cavity bleeding	296/385 (70)	55/85 (64)	$P = 0{\cdot}31$
Post-operative bleeding	83/203 (41)	26/70 (36)	$P = 0{\cdot}58$
Post-partum bleeding	15/100 (15)	NA	–
Menorrhagia	90/130 (69)	NA	–
Epistaxis	296/385 (77)	20/100 (20)	$P < 0{\cdot}0001$
Haematuria	4/385 (1)	12/100 (12)	$P < 0{\cdot}0001$
Gastrointestinal bleeding	74/385 (20)	10/100 (10)	$P = 0{\cdot}03$
Central nervous system bleeding	7/385 (2)	4/100 (4)	$P = 0{\cdot}25$

*Chi-squared test or Fisher's exact test.
NA, not applicable.

using rabbit anti-VWF antiserum supplied by Laboratoire Stago, Asniers, France). Pooled normal plasma from 50 normal individuals (25 men and 25 women not taking oral contraceptives, with blood groups representing the distribution of the general Iranian population) was used as a reference standard and was given an arbitrary value of 100%. The lower limit of sensitivity of the immunoassay was 6%. FVIII:C was measured by an activated partial thromboplastin time (aPTT)-based assay using substrate plasma from a severely deficient patient with haemophilia A. All patients had FVIII:C values ranging between 1% and 9% (median value 4%) and very prolonged Ivy bleeding times that did not stop during the observation time (at least 15 min). Ristocetin cofactor activity was introduced only recently as a diagnostic test, and results are available so far in only approximately one-third of the patients (in all it was unmeasurable). Serological markers for the hepatitis viruses B and C and for the human immunodeficiency virus (HIV) were sought using commercially available enzyme immunoassays for the hepatitis B surface antigen and antibody (HBs-Ag and anti-HBs), the antibody to the hepatitis C virus (anti-HCV) and anti-HIV.

Three hundred and eighty-five patients from 200 kindreds (age 2–72 years, 182 females and 203 males, 64% of all registered patients) who met the aforementioned criteria were examined in Teheran by the same physician. Most of these patients (67%) were born from consanguineous marriages and the asymptomatic parents had, on average, half of the normal levels of VWF:Ag, but normal FVIII:C levels and skin bleeding times. Alloantibodies to VWF were identified by analysing the capacity of patients' plasma to inhibit *in vitro* ristocetin-induced aggregation of normal platelet-rich plasma, as previously described (Mannucci *et al*, 1976).

A few criteria were established before the study to evaluate whether or not symptoms reported by the patients had to be accepted as valid. Epistaxis qualified only when it had occurred spontaneously more than five times in the patient's life, from both nostrils, lasted more than 10 min or required hospital admission. Menorrhagia, evaluated in 130 women of reproductive age, was defined by menstrual blood losses large enough to require the therapeutic use of combined oestrogen–progestogen preparations or to cause iron deficiency. Bleeding in the gastrointestinal and urinary tracts and in the central nervous system had to be documented by hospital records. Muscle haematomas and haemarthroses qualified if they occurred spontaneously or following minor traumas and caused at least transient signs of functional joint or muscle impairment. Bleeding symptoms occurring after dental extractions or other surgical operations (including circumcision) were considered only when they occurred in patients who had not received prophylactic replacement therapy, usually before the coagulation defect was diagnosed. Oral bleeding had to have lasted for more than 10 min or to have required the intervention of an oral surgeon, whether caused by dental extractions or by bites to lips, cheeks and tongue. Surgical bleeding and post-partum bleeding qualified only if they caused a delay in discharge from hospital or required blood transfusion. We also collected information on complications of childbirth, such as early or late term bleeding, occurrence of miscarriages, outcome of delivery and post-partum bleeding. Easy bruising was not considered because the evaluation of this symptom by patients was considered too subjective.

RESULTS

The main bleeding symptoms of Iranian patients with type 3 VWD are shown in Table I. The percentage of patients who had bleeding symptoms as defined above were compared with those found in 100 patients with severe haemophilia A (FVIII:C 1% or less) matched for age with VWD patients. As expected, among haemophiliacs the most prevalent symptoms were joint, muscle and post-operative haemorrhages, whereas bleeding in mucosal tracts was relatively rare. Among patients with type 3 VWD, only 37% had spontaneous haemarthroses and 52% muscle haematomas, perhaps because FVIII:C levels were in general higher than

Table II. Prevalence of serological markers for hepatitis B and C and the human immunodeficiency virus in 385 Iranian patients with type 3 von Willebrand disease and in 100 patients with severe haemophilia A.

	In type 3 VWD	In haemophilia A	Statistical significance*
HBs-Ag	2%	2·6%	$P = 0{\cdot}70$
Anti-HBs	50%	65%	$P = 0{\cdot}007$
Anti-HCV	55%	90%	$P < 0{\cdot}0001$
Anti-HIV	1%	5%	$P = 0{\cdot}02$

*Chi-squared test or Fisher's exact test.

HBs-Ag, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; anti-HCV, the antibody to the hepatitis C virus; anti-HIV, the antibody to the human immunodeficiency virus.

in haemophiliacs. Abnormal post-operative bleeding was observed in 83 of 203 VWD patients (41%) who underwent surgery without replacement therapy, of similar frequency to that in haemophiliacs (37%). Particularly frequent was oral cavity bleeding (70% in VWD patients), occurring not only when teeth were extracted or shed without coverage with replacement therapy but also as a consequence of traumatic lacerations to the tongue or lips. Mucosal-type haemorrhages such as epistaxis and menorrhagia were frequent in type 3 VWD (77% and 69%), the latter often causing iron-deficiency anaemia that could usually be controlled only by the sustained intake of oral contraceptives. Gastrointestinal bleeding was relatively more frequent in type 3 VWD than in haemophilia, whereas haematuria was definitely rarer. Life-endangering haemorrhages in the central nervous system were rare in type 3 VWD.

No prophylactic replacement therapy was given during pregnancy. Fifteen of 100 VWD women (15%) who delivered at least one child had abnormal post-partum bleeding. At parturition, they were usually treated with fresh-frozen plasma, cryoprecipitate or, more recently, with factor VIII concentrates. Abnormal bleeding usually occurred when this treatment was suboptimal in dosage or was given for a too short time period (for 1 d instead of 3–4 d). There was no evidence that the primary haemostasis and coagulation defects present in type 3 VWD reduced fertility in affected women, nor did they cause single or recurrent miscarriages with frequencies higher than those seen in the general Iranian population (data not shown).

This study has also evaluated the prevalence of the most important complications of replacement therapy in multitransfused patients with inherited bleeding disorders, i.e. the development of alloantibodies to deficient factors and infections with blood-borne viral agents. Ten of 385 patients, all transfused at least five times, developed anti-VWF antibodies (2·6%). The majority of them (8 of 10) had anaphylactic reactions of varied severity at the time of replacement therapy, and this complication was often the event that led to the detection of alloantibodies. Table II shows that 55% of patients had HCV antibodies compared with 90% in severe haemophilia, whereas the prevalence of HBV and HIV infections was much less and was substantially similar in haemophilia and VWD patients.

DISCUSSION

This study demonstrated that the clinical manifestations of severe VWD differ substantially from those seen in severe haemophilia. Soft tissue bleeding is less frequent in VWD, probably because patients usually have measurable levels of FVIII:C and therefore behave like patients with moderate haemophilia. As expected, the impairment of primary haemostasis typical of VWD led to more frequent bleeding from mucosal tracts. The large series of affected women evaluated in this series indicate that, whereas fertility and the course of pregnancy do not differ from those in normal women, the risk of bleeding at parturition is considerable unless patients are given replacement therapy for at least 3–4 d.

Alloantibodies to VWF that render ineffective replacement therapy with VWF-containing plasma fractions and cause severe anaphylactic reactions have been reported so far in 21 patients with type 3 VWD (Mannucci & Federici, 1995). The prevalence of such antibodies among patients with type 3 VWD has been estimated to be 7·5% and 9·5%, respectively, in two relatively large surveys (Mannucci *et al*, 1984; Mannucci & Federici, 1995), somewhat lower than the 15% prevalence of factor VIII antibodies usually quoted for patients with severe haemophilia. This study of the largest and most homogeneous series of patients ever investigated systematically for the presence of anti-VWF antibodies gave a lower prevalence rate (2·6%). Differences are perhaps due to the fact that when anti-VWF antibodies are present at low potency the simple screening test used in Iran, based upon the inhibition by test plasma of ristocetin-induced aggregation in normal platelet-rich plasma, may not be sensitive enough. As reported before (Mannucci & Federici, 1995), anaphylactic reactions of varied severity developed at the time of replacement therapy. We also confirmed previous data (reviewed by Mannucci & Federici, 1995) that the presence of the complication is strictly associated with the presence of large or complete VWF gene deletions or stop codons (Baronciani *et al*, 2000).

In the past, in Iran bleeding episodes were generally treated using inexpensive measures such as locally produced fresh-frozen plasma and cryoprecipitate (Shoa'i *et al*, 1977). In the 1980s and early 1990s, non-virally inactivated, intermediate-purity lyophilized factor VIII concentrates produced locally from unpaid blood donors have been used more extensively. As a result of this, many patients are currently infected with HCV, even though infection with HIV and HBV was relatively rare both in type 3 VWD and in severe haemophilia patients. At the moment, therefore, virally inactivated lyophilized concentrates containing both factor VIII and VWF are imported from Europe and are being used instead of cryoprecipitate and the local concentrate.

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