Spectrum of Inherited Bleeding Disorder with Special Reference to von Willebrand Disease in Eastern India

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Abstract

Background The objective of this study is to study the prevalence, clinical spectrum, and hematological profile of inherited bleeding disorder with special reference to von Willebrand disease in eastern India.

Materials and Methods This prospective study was done in a tertiary care center in the eastern part of India over 2 years. Detailed history and clinical findings were noted in a proforma. Laboratory analysis included prothrombin time, activated partial thromboplastin time, bleeding time, and fibrinogen assay along with tests related to specific factor assay.

Results One hundred and five patients were diagnosed as suffering with the inherited bleeding disorder out of a total of 1,204 patients. The age of patients ranged from 13 days to 35 years. The most common presenting clinical feature was prolonged bleeding after cut (76.19%). Out of 105 patients, 97 patients (92.38%) had coagulation defect, 5 patients (4.76%) had von Willebrand disease (vWD), and 3 patients (2.85%) had platelet defect. Most common coagulation defect was hemophilia A (84 cases), followed by hemophilia B (8 cases). Other rare congenital factor deficiencies were seen in five cases (5.15%). Only platelet defect was Glanzmann's thrombasthenia (GT). The age of vWD patients ranged from 4.5 years to 24 years. Forty percent patients with vWD disease were type 1 followed by 40% of type 2N and 20% of type 3 vWD.

Conclusion vWD was not so common in eastern India. vWD was present only in 4.76% cases in this study. The most common coagulation defect was hemophilia A (86.59%) in our study. GT was present in only 2.85% cases.

Keywords
- bleeding
- Glanzmann's thrombasthenia
- hemophilia
- von Willebrand disease

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Introduction

Bleeding disorders are a group of disorders that result from defect in any one of the components of hemostasis including defect in vessel wall, platelets, or coagulation factor. Inherited bleeding disorders result from genetic transmission, that is, they are passed from a parent to their child. The most frequent inherited hemostatic defects are hemophilia A, hemophilia B, and von Willebrand's disease (vWD).[1] Hereditary deficiencies of other coagulation factors are significantly less common, ranging in prevalence from 1 per 500,000 to 1 per million. All are autosomal recessive. These include afibrinogenemia, hypofibrinogenemia, hypoprothrombinemia, and deficiencies of factor V, VII, X, XI, XII, and XIII. These recessively inherited bleeding disorders are more common in those geographic or ethnic populations where consanguineous marriages are common.

vWD is the most common inherited bleeding disorder that affects both platelet adhesion (primary hemostasis) and factor VIII level (secondary hemostasis), therefore presenting with a mixed bleeding profile. vWD affects 1.3% of the population.[2,3] It is caused by a quantitative (reduced amount) or qualitative (abnormal function) deficiency in von Willebrand factor (vWF), combinations of which result in the various vWD subtypes. vWD commonly presents as a mild-to-moderate bleeding disorder, typically with easy bruising or bleeding from mucosal surfaces.[4]

Hemophilia A and B are inherited in an X-linked fashion, with males being carriers of the mutant gene afflicted with the bleeding diathesis and females being obligate carriers. The incidence is 1 in 10,000 live births for hemophilia A and 1 in 25,000 live births for hemophilia B.[5] Glanzmann's thrombasthenia (GT) is an autosomal recessive disease that is caused by the lack of expression of or qualitative defects in one of the two glycoproteins forming the integrin αIIb/β3.[6] There are very few studies from India especially in this region of eastern India regarding the characterization of vWD and other inherited bleeding disorders.

Aims and Objectives

The present study was conducted with the following aims and objectives:

1. To study the prevalence, clinical spectrum, and hematological profile of inherited bleeding disorders in this area of eastern India.
2. To study the prevalence and characterizations of vWD among the inherited bleeding disorders that are diagnosed during the study.

Materials and Methods

The present study was performed in the Department of Pathology, Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi, for a period from June 2011 to June 2013. All the patients with abnormal bleeding, referred to us from the various departments of Sir Sundarlal Hospital, IMS, BHU or from outside, were investigated to detect the cause of bleeding. For this purpose, an informed consent was obtained and detailed proforma containing the nature of bleeding episodes, age of onset, frequency of bleeding, family history, mode of inheritance, and history of prior medications including blood transfusion was made along with detailed physical examination. For coagulation and platelet disorders, blood was collected in a blue cap vacutainer containing 3.2% sodium citrate in the ratio of nine parts of blood to one part of citrate (i.e., 0.5 mL of anticoagulant and 4.5 mL blood). Two milliliter of blood in ethylenediaminetetraacetic acid vial was taken for the complete blood count (CBC) including the platelet count. Finger prick smears were made and stained by Leishman's stain for general blood picture and platelet morphology. Platelet-rich plasma was prepared by 600 rpm for 3 minutes for the platelet profile, while platelet-poor plasma was prepared by 2,500 rpm for 10 minutes for the coagulation profile. All the tests of hemostasis were performed within 4 hours of blood collection. Coagulation test was done either manually or by a semi-automatic analyzer. CBC was performed by five parts automatic hematology analyzer (Mindray, China). The screening tests performed for coagulation were prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time. Correction experiment was also performed to know the specific factor deficiency or inhibitors present, with normal plasma, normal-aged serum, and Al(OH)3 adsorbed plasma. On the basis of these assay, specific factor assay was performed further. If all the coagulation tests were normal, then factor XIII assay (urea solubility test) was performed. Test for vWD included Von Willebrand factor antigen (vWFAg) by enzyme-linked immunosorbent assay (Diagnostica Stago, France), ristocetin-induced platelet aggregation (RIPA) using platelet aggregometer (Chronolog Dual channel model 700) with agonists, ristocetin cofactor assay (RiCoFAssay) using a kit by Diagnostica Stago, France, Factor VIII Assay, and bleeding time by the Ivy method. Low-dose RIPA (0.5 mg/mL) was also done wherever indicated to differentiate vWD type 2B and platelet type (Pseudo vWD). Platelet aggregation test with adenosine diphosphate (ADP) and adrenaline was done to detect platelet function defects. On the basis of these tests, all the coagulation disorders, vWD and its variant, and platelet defects were identified in this study.

Observations and Results

Patients with abnormal bleeding coming to the hematology laboratory of the Department of Pathology, IMS, BHU, from June 2011 to June 2013 were investigated. After detailed clinical, personal, and family history and performing appropriate investigation, a total of 1,204 patients were enrolled in our study. Out of 1,204 patients, 105 patients were diagnosed as suffering with an inherited bleeding disorder, while in the rest 1,099 patients, an acquired cause of abnormal bleeding was detected (►**Table 1**). The age of patients ranged from 13 days to 35 years. The maximum number of patients was in the age group of 1 to 5 years (►**Table 2**). There were predominantly males (95.23%) in the study group, while

Table 1 Total number of patients investigated for abnormal bleeding

Total no. of patients	Inherited bleeding disorder Number (%)	Acquired bleeding disorder Number (%)	vWD among inherited bleeding disorder Number (%)
1,204	105 (8.72)	1,099 (91.28)	5 (4.76)

Table 2 Age and sex distribution of patients with inherited bleeding disorders ($n = 105$)

Serial no.	Age group (y)	Male		Female		Total	
		No.	%	No.	%	No.	%
1.	< 1	5	4.76	0	0	5	4.76
2.	1–5	29	27.61	2	1.90	31	29.52
3.	6–10	24	22.85	0	0	24	22.85
4.	11–15	21	20.00	0	0	21	20.00
5.	16–20	10	9.52	0	0	10	9.52
6.	21–30	8	7.61	3	2.85	11	10.47
7.	> 30	3	2.85	0	0	3	2.85
	Total	100	95.23	05	4.76	105	100

4.6% patients were females (►**Table 2**). Family history was present for 22.85% of patients. Consanguinity was present in 2.85% of patients, while 1.9% consanguineous patients gave positive family history for a bleeding disorder. The most common presenting clinical feature was prolonged bleeding after cut (76.19%) (►**Table 3**).

The mean value of PT was 14.01 ± 1.40 seconds with a *p*-value of 0.0001, which was highly significant. The standard error of difference was 0.147. The mean value of APTT was 78.84 ± 25.62 seconds, with *p*-value 0.0001, which was highly significant. The standard error of difference was 2.507. Isolated increase in APTT was seen in 91.42% of patients. Isolated increase in PT was not seen in any patient. Both PT and APTT were increased in two patients (1.90%). The mean value of factor VIII was 10.49 ± 2.62 IU/dL with a *p*-value of 0.0001, which was highly significant. The standard error of difference was 4.233. Factor VIII was reduced in 84 Patients. The mean value of factor IX was 90.76 ± 60.56 IU/dL with a *p*-value of 0.2959, which was not significant. The standard error of difference was 12.870. Factor IX was reduced in eight patients. The mean value of vWF was 95 ± 86.7 IU/dL with a *p*-value of 0.7956, which was not significant. vWF was reduced in 5 patients out of 14 cases in which vWD was suspected. The PF3 availability test was reduced in two patients and was normal in six patients. Aggregation with ADP and adrenaline was abnormal (increased) in three patients.

Table 3 Frequency of bleeding symptoms in patients of inherited bleeding disorder ($n = 105$)

Clinical symptoms	No. of patient	Percentage (%)
Prolonged bleeding on cut/trauma	80	76.19
Ecchymosis/bruise	46	43.80
Hemarthrosis	38	36.19
Hematoma	30	28.57
Petechiae	12	11.42
Epistaxis	8	7.61
Gum bleeding	8	7.61
Bleeding after tooth extraction	4	3.80
Menorrhagia	4	3.80
Post-circumcision bleeding	3	2.85
Umbilical bleeding	3	2.85
Hematuria	2	1.90
Hematemesis	1	0.95

Out of 105 patients, 97 (92.38%) had coagulation defect, 5 (4.76%) had vWD, and 3(2.85%) had platelet defect. The most common coagulation defect was hemophilia A (86.59%) followed by hemophilia B (8.25%), factor XIII deficiency (2.06%), and factor X deficiency, factor I deficiency, and factor VIII carrier (1.03% each) (►**Table 4**). In this study, only platelet defect was GT (100%), which was seen in all three patients.

The most common age group in hemophilia A patients was 1 to 5 years followed by 6 to 10 years. The most common presenting clinical feature in hemophilia A patients was prolonged bleeding on cut/trauma (95.23%) followed by ecchymosis/bruise (42.85%), and hemarthrosis (42.85%). More than half (53.57%) of the patients of hemophilia A had less than 1% factor VIII concentration. In hemophilia B, the most common age group was 11 to 15 years (50%). A single case of factor X deficiency was diagnosed in a 13-day-

Table 4 Incidence of coagulation disorders ($n = 97$)

Coagulation disorder	Number ($n = 97$)	Percentage as total coagulation defect ($n = 97$)	Percentage (%) as of total cases ($n = 105$)
Hemopholia A	84	86.59	80
Hemophilia B	8	8.25	7.61
Factor X deficiency	1	1.03	0.95
Factor I deficiency	1	1.03	0.95
Factor XIII deficiency	2	2.06	1.90
Factor VIII carrier	1	1.03	0.95

male baby with deficient factor X activity. Two cases of factor XIII deficiency were diagnosed with the positive urea solubility test. A single case of factor I deficiency was diagnosed with prolonged PT, APTT, thrombin time, and decreased factor I activity. A single case of factor VIII carrier was diagnosed in a 28-year-old female with a positive family history of hemophilia A, reduced factor VIII activity and normal factor IX, and vWF level.

Out of total 105 cases of inherited bleeding disorders, five patients (4.76%) were diagnosed as a case of vWD. The age ranged from 4.5 years to 24 years. The most common age group was 1 to 5 years (60%) followed by 6 to 10 years (20%) and 21 to 25 years (20%). Gender wise 60% of vWD patients were males, while 40% were females. Most of the vWD patients had the onset of clinical symptoms in the age group of 1 to 5 years (80%). The most common presenting clinical feature in vWD patients was prolonged bleeding on cut/trauma (100%) followed by epistaxis (20%), gum bleeding (20%), and menorrhagia (20%). Eighty percent of vWD patients had factor VIIIc concentration between 1 and 5%, and 60% of patients had between 5 and 50% vWFAg concentration. Low-dose RIPA was absent in 100% cases. RiCoFAssay performed in two out of five cases was 0 and 48%. Bleeding time was in the range of 7 for more than 15 minutes. Forty percent of patients of vWD disease were type 1, 40% were type 2N, and 20% were type3 vWD. Out of total 105 cases of inherited bleeding disorders, GT was diagnosed in three patients (2.85%). All three cases show increased platelet aggregation with ADP and adrenaline.

Discussions

Abnormal bleeding is a common clinical presentation, and the approach to the diagnosis of inherited bleeding disorder necessitates a comprehensive history, thorough physical examination, and systematic laboratory work-up. A total number of 1,204 patients with abnormal bleeding manifestations were investigated in this study. Among these, 8.72% (105/1,204) patients were diagnosed as suffering from inherited bleeding disorders, whereas in other 91.27% (1,099/1,204) cases, an acquired cause of abnormal bleeding was discerned.

Among the inherited bleeding disorder, the age of presentation of disease was 13 days to 35 years. In total, 77.13% (81/105) patients belonged to the pediatric age group. The mean age was 11.25 ± 8.84 years, the median age was 10 years, and the mode was 15 years. In a study done by Gupta et al, the age at presentation ranged from 2 to 47 years with a median age of 32.2 years.[7] In a study by Sajid et al from Pakistan, the age of presentation ranged from 3 to 57 years with a median age of 17 years.[8] Only patients with mild deficiency were diagnosed in the adult age group. In the present study, the male-to-female ratio was 20:1. In a study by Gupta et al, the male-to-female ratio was 4:3, while in the study of Sajid et al the male-to-female ratio was 4:1.[7,8] In the present study, 92.38% (97/105) patients had coagulation defect, 4.76% (5/105) had vWD, and 2.85% (3/105) had platelet function defect. Ahmad et al reported 72.23% (1,138/1,576) coagulation defect including vWD and 27.77% (438/1,576) inherited platelet disorders.[9] Manisha et al reported 94.59% (598/630) coagulation defect (including 10.8% vWD) and 5.07% (32/630) had platelet function defect.[10] These findings were comparable to our study.

In the present study, the most common inherited bleeding disorder was hemophilia A with a frequency of 80% (84/105) followed by hemophilia B with the frequency of 7.61% (8/105). Apart from these, two cases of factor XIII deficiency 1.90% (2/105), one case each of factor X deficiency, afibrinogenemia, and factor VIII carrier were also seen in the present study (0.95% each). vWD was seen in 4.76% (5/105) of patients only. Slightly different observations were seen in the study by Manisha et al who reported hemophilia A in 70.5%, hemophilia B in 14%, and vWD in 10.8% of cases.[10] Although vWD has been described as the most common inherited bleeding disorder with a prevalence of 1%, in the present study, we found hemophilia A as the most common bleeding disorder. It suggests that hemophilia A is more severe as compared to vWD, which is mild, so in a developing country like ours maximum patients ignore mild symptoms and they do not visit hospitals unless they develop severe symptoms. In the present study, vWD comprised 4.76% (5/105) and GT 2.85% (3/105) cases. Gupta et al reported 16.8% cases of vWD (94/560) and 8.9% cases of GT (28/ 312) patients with platelet function defect.[7]

In the present study, five patients of vWD were diagnosed. The age of the patients ranged from 4.5 to 24 years. The mean age was 9 ± 8.27 years. The most common age group was 1 to 5 years (60%), followed by 6 to 10 years (20%) and 21 to 25 years (20%). In our study, for most of the vWD patients, the age of onset of clinical symptoms was the age group of 1 to

Table 5 Studies on the prevalence of vWD (among inherited bleeding disorder) and frequency of its different subtypes in India

Authors (y of study)	Total cases of inherited bleeding disorder	Number and (%) of vWD	Type-1 vWD *n* (%)	Type-2 vWD *n* (%)	Type-3 vWD *n* (%)
Gupta et al (2005)	224	64 (28.6)	14 (21.9)	28 (43.3)	22 (34.8)
Trasi et al (2005)	822	81 (9.8)	15 (18.5)	16 (19.7)	50 (61.8)
Gupta et al (2007)	872	94 (16.8)	20 (21.3)	42 (44.7)	32 (34)
Ahmad et al (2008)	1,576	136 (8.6)	29 (21.3)	73 (53.6)	33 (24.3)
Kumar et al (2010)	230	40 (17.34)	17 (42.5)	11 (27.5)	12 (30)
Present study (2013)	105	5 (4.76)	2 (40)	2 (40)	1 (20)

5 years (80%). It was 5 days to 77 years in study done by Trasi et al, 5 months to 45 years in study done by Kumar et al, and 1.6 to 40 years in study done by Borhany et al.[11–13] The male-to-female ratio for vWD was 1.5:1. Trasi et al[11] reported the male-to-female ratio of 1.2:1, while Borhany et al[13] reported the male-to-female ratio of 0.83. In the present study, the most common clinical feature in vWD patient was prolonged bleeding on cut/trauma (100%), followed by epistaxis (20%), gum bleeding (20%), and menorrhagia (20%).Trasi et al reported mucocutaneous bleeding along with ecchymoses, epistaxis, and gum bleeding being common clinical findings among these patients, which was similar to our study.[11] Since vWD affects the process of coagulation at both levels, that is, primary and secondary hemostasis, it presents with a variety of clinical manifestation; however, mucocutaneous bleeding was much more common in vWD than the coagulation type of bleeding such as hemarthrosis and hematoma in these patients. Although exact categorization in different subtypes was not possible due to the limitation of laboratory assay and the lack of multimer study, based upon the available laboratory parameters, we have categorized them in different subtypes as type 1 in 40% (two out of five), type 2 in 40% (two out of five), and type 3 in 20% (one out five) of cases. Both the type 2 patients were further categorized into type 2N type depending upon the concentration of factor VIIIc and vWFAg. However, vWFAg:FVIIIc binding was not done for confirmation due to the limitation of assay. One single case of type 3 vWD patient was having RiCoFAssay concentration 0 (zero), and vWFAg concentration of 1% indicates the severity of the disease. Most of the studies from India report a high prevalence of type 2 and type 3 vWD, that is, much more severe forms of the disease than type 1 vWD. ►**Table 5** shows important studies on the prevalence of vWD among the inherited bleeding disorder and the frequency of its different subtypes in India.

Most of the studies from the west report a high prevalence of type1 vWD as compared with type 2 and type 3 vWD. Scheibel in his study also recorded similar findings. Out of 250 patients diagnosed as having vWD, type 1was seen in 194 cases, type 2A in 21 cases, type 2B in 15 cases, type 2N in 2 cases, type 3 in 11 cases, and 7 cases were of unknown type.[14] Awidi studied 65 cases of vWD and reported type 1 in 36 cases (59%), type 2A in 7 cases (11.5%), type 2B in 11 cases (18%), and severe type 3 in 7 cases (11.5%).[15] Diez-Ewald et al reported 96 cases of vWD in which 88% were of type 1, 2% were of type 2B, and 4.1% were of type 3.[16] Five cases were not classified.[16] Chuamary and Santosa et al reported 34 patients of vWD, of which 11 cases (32.35%) were of type 1 and 23 cases (67.65%) were of type 2.[17] No type 3 vWD was observed in their study.[17]

Although according to the literature, vWD is the most common inherited bleeding disorder; however, this remains an undiagnosed entity in developing countries like India because of many reasons. Since most of the western literature describes type 1 vWD as the most common type which has milder symptoms, these symptoms are ignored by the patient as people in these regions are not aware of their health status, they lack proper knowledge, and they are of low socio-economic status. Also, there is a lack of screening in healthy people due to poor resources and limitation of each laboratory assay, all these in combination rendering delay in diagnosing this disease. Only patients with severe symptoms come to hospitals, which signify the increased frequency of type 2 and type 3 in this region.

Conclusion

In this study, we reported the prevalence and characterization of vWD along with the clinical and hematological characteristics of 105 patients with inherited bleeding disorders. We found that vWD was not so common in eastern India. A large number of patients with inherited bleeding disorders remain undiagnosed because of the limitation of coagulation laboratories and lack of awareness among health care professionals and family members and so the figures presented in this study do not reflect the actual burden of the crippling disorders in our community. An epidemiological study in the general population needs to be done to assess the magnitude of this disease in this area.

Conflict of Interest
None declared.

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