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The Clinical Features of Chinese Children with von Willebrand Disease: The Experience of a Tertiary Institute

ZQ ***Zhang,*** GCF ***Chan,*** CCK ***Lam,*** JCC ***So,*** DKL ***Cheuk,*** AKS ***Chiang,*** SY ***Ha***

Abstract The information related to the clinical spectrum of von Willebrand disease (VWD) in Chinese patients remains very limited. We conducted a retrospective chart review on the clinical and haematological features of VWD among Chinese patients at a tertiary paediatric centre in Hong Kong. Ten patients (6 females, 4 males) were diagnosed to have VWD from 1989 to 2005. They underwent treatment in our unit, with a cumulative follow up of 102 patient-years within this 16-year period. Among them, 4 were type 1, 5 were type 2 and 1 was type 3 VWD. Six of the 10 patients had a positive family history of bleeding tendencies. A variety of bleeding manifestations were observed in these patients while mucocutaneous bleeds in the form of frequent epistaxis and easy bruising were the commonest presenting features. Severe bleeding in the form of intracranial haemorrhage occurred in 2 patients. Eight patients underwent desmopressin (DDAVP) test at diagnosis and all were responsive to DDAVP without associated thrombocytopenia. Three patients required frequent DDAVP (intravenous or subcutaneous) and 2 required occasional intermediate purity factor VIII concentrate for bleeding control. In conclusion, majority of Chinese paediatric VWD patients are inherited and acquired form is extremely rare in childhood. Patients with either type 1 or 2 VWD can develop severe bleeding in childhood. In our patient cohort, DDAVP appears to be effective and safe for our patients with either type 1 VWD or non-2B type 2 VWD without inducing thrombocytopenia.

Key words Chinese children; Epidemiology; von Willebrand disease

Department of Paediatrics, Union Hospital, Wuhan, China

ZQ **Zhang** (張志泉) *MD, HUST*

Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong, China

GCF **Chan** (陳志峰) *MD, FRCPCH, FHKAM(Paed)*
DKL **Cheuk** (卓家良) *MBBS, FHKAM(Paed)*
AKS **Chiang** (蔣國誠) *MBChB, PhD, FRCPCH*
SY **Ha** (夏修賢) *MBBS, FRCPCH, FRCPath*

Department of Pathology, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong, China

CCK **Lam** (林志傑) *MBBS, FHKAM(Path)*
JCC **So** (蘇志超) *MBBS, FHKAM(Path)*

Correspondence to: Prof. GCF **Chan**

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Introduction

von Willebrand disease (VWD) is the most common inherited bleeding disorder caused by either a qualitative or quantitative defect of the von Willebrand factor (VWF). VWF is a high molecular weight glycoprotein that plays an essential role in the early phase of haemostasis by enhancing platelet adhesion to the subendothelium leading to subsequent platelet aggregation under a high shear stress condition.[1] VWF also binds factor VIII (FVIII) in the plasma and prevents FVIII from early degradation, therefore deficiency of VWF can impair the intrinsic blood coagulation. In majority of cases, VWD is inherited in an autosomal dominant fashion but rarely, an autosomal recessive inheritance can be found. Patients with VWD may have a mild, moderate or even severe bleeding tendency since early childhood. The severity is usually affected by the

degree of the VWF defect, either in a quantitative or qualitative manner.

Though VWD is a common disease, most patients have type 1 defect (quantitative defect) with mild bleeding tendency clinically and therefore remain undiagnosed. Many patients with this disorder are found only when an index patient in the family is identified. However, this clinical information is mainly derived from Western literature on Caucasian populations. Up to the current moment, published data related to VWD in Chinese paediatric patients are very limited. We reviewed the records of our patients with VWD diagnosed in our hospital from 1989 to 2005 and compared their clinical phenotypes with those described in the literature.

Patients and Methods

We reviewed our haematology/oncology patient database which captured all patients with haematological diseases diagnosed in our unit since 1989. Patients with VWD diagnosed in our unit between 1989 and 2005 were selected for review and their records were analysed. Demographic and clinical data including sex, age at initial diagnosis, family history, bleeding symptoms and laboratory investigations were captured. The laboratory investigations for the diagnosis of VWD included prothrombin time (PT), activated partial thromboplastin time (APTT), factor VIII:C (FVIII:C) assay, VWF antigen (VWF:Ag) and ristocetin cofactor activity (VWF:RCo).[1] PT, APTT, and FVIII:C one stage assays[2] were performed by semi-automated coagulometer. VWF:Ag levels were estimated by ELISA method[2] using commercial kits and VWF:RCo by using fixed platelets.[2] Skin bleeding time was not performed in our predominantly paediatric patient cohort. Family screening for VWD was offered to all patients.

DDAVP challenge test was performed in all except one patient, according to established protocol. In brief, DDAVP (0.3 ug/kg) was administered as a continuous infusion in 100 ml of normal saline over 30 minute. Blood pressure and pulse rate were recorded at 15 minute intervals during the infusion and 30 minute afterwards. Venous blood samples were collected before infusion and at 1 & 2 hours after infusion for FVIII:C, VWF:Ag, and VWF:RCo.[3] An optimal response to DDAVP was defined as VWF:RCo and FVIII:C plasma levels rising to above 0.3 IU/mL at 1 hour after DDAVP administration and at least greater than threefold increase over the baseline values.[4]

Results

In this study cohort, 12 patients were identified but 2 of them were referred from overseas for diagnostic purpose only. These 2 patients were a pair of ethnic Chinese twin brothers with frequent nose bleeding and were diagnosed to have type 2 VWD. They were excluded from our analysis. The other 10 patients were local residents (Table I) and the male to female ratio was 4 to 6. The median age at diagnosis was 7.5 years (ranged from 1 to 13 years). Of all the VWD patients, 4 were type 1, 5 type 2 and 1 type 3. Six of the 10 patients had a positive family history of bleeding tendencies. A variety of bleeding manifestations were observed in these patients and severe catastrophic bleeding in the form of intracranial haemorrhage was the presenting feature in 2 patients (both type 1). One patient survived without long term complications related to the bleeding episode. The other patient had autism and mental retardation with chromosomal abnormality might have suffered from further deterioration in her mental function after the haemorrhage.

Mucocutaneous bleeds in the form of epistaxis and easy bruising were common among most patients. However, the nose bleeding in all patients became static when they reached adolescent age. Their characteristics were summarised in Table 1. Another interesting observation is that petechiae were rarely seen in our VWD patients although many of them did have a tendency of cutaneous bruises.

For epistaxis, 6 patients had frequent bleeding up to ≥2 times weekly which was difficult to control by local pressure. Three out of these 6 patients required intermittent haemostatic treatment. One patient received subcutaneous DDAVP at home per demand basis. As high dose nasal DDAVP (Stimate) is not routinely available locally due to its high cost, none of these patients used this preparation. Other patients responded to tranxanemic acid orally when bleeding occurred. For female patients who reached the adolescent age, most had some degree of menorrhagia but only one patient required frequent tranxanemic acid treatment and she was also put on hormonal therapy. Two patients received intermediate factor VIII concentrate therapy as treatment for episodic profuse bleeding related to trauma or surgery, and 3 required no treatment all along.

Interestingly, 3 of the 10 patients had normal or near normal APTT, therefore a normal APTT result did not exclude the diagnosis of VWD. We noted that type 2 VWD was relatively more than expected in our patient cohort. However, except for 2 patients who underwent 2D crossed-immunoelectrophoresis, the diagnosis of type 1 and 2 in our patients were mainly based on the ratio among the factor

VIII:C (FVIII:C) assay, VWF antigen (VWF:Ag) and ristocetin cofactor activity (VWF:RCo) (Table 2). Therefore the definite subtypes of VWD could not be confirmed.

Nine patients underwent DDAVP test and all showed response to DDAVP including one type 3 patient (#9, Table 1). However, this type 3 patient failed to achieve a 3 folds increase in both her VWF:Ag and FVIII:C levels. One of our patients (#6, Table 1) has lowish platelet count at presentation, his platelet count also dropped slightly with DDAVP challenge test (from 143 x 10^9/L to 104 x 10^9/L). He is likely to be a type 2B patient based on the result of hyperaggregability with low dose ristocetin using his platelet rich plasma. Hyeraggregability with low dose ristocetin was also demonstrated when patient's plasma was mixed with normal lyophilized platelet.

Discussion

The reported incidence of VWD varies in different study, ranges from 3 to 4 per 100,000 to as high as 1.3% of the population.[5-7] Accurate assessment of disease burden is difficult because of the variable genetic expression and penetrance. The exact incidence of VWD in Chinese remains unknown. VWD is a very heterogeneous disorder and patients with mild forms of VWD are often

Table 1 The clinical features and laboratory findings in VWD paediatric patients

No.	Sex	Age at diagnosis (years)	Family history	Bleeding symptoms	Platelet (10^9/L)	PT (sec)	APTT (sec)	FVIII:C (iu/ml)	VWF:RCo (iu/ml)	VWF:AgD (iu/ml)	DDAVP test	Subtype
1	F	1	P	easy bruising	328	11.6	28.3	0.46	0.08	0.33	Response	Type 2
2	M	7	P	epistaxis	457	12.4	43.1	0.28	0.02	0.12	Response	Type 2
3	F	1	P	intracranial haemorrhage	469	12.0	32.7	0.74	0.25	0.25	NA	Type 1
4	F	6	N	intracranial haemorrhage	284	14.0	45.7	0.7	NA	0.37	Response	Type 1
5	F	13	P	easy bruising	204	10.4	33.5	0.56	0.42	0.35	Response	Type 1
6	M	6	N	epistaxis	143	12.8	40.6	0.48	0.48	0.40	Response	Type 2
7	F	8	P	epistaxis	269	10.0	26.0	0.33	0.05	0.29	Response	Type 2
8	M	7	N	epistaxis	312	13.2	42.6	0.52	0.01	0.22	Response	Type 2
9	F	12	P	epistaxis, easy bruising	267	11.4	33.7	0.30	0.02	<0.01	Response	Type 3
10	M	8	N	epistaxis, easy bruising	227	14.1	29.8	0.79	0.45	0.54	Response	Type 1

F=female; M=male; N=negative; NA=not available; No.=number; P=positive

Table 2 Findings of haematological tests on different subtypes of VWD

	VWF:Ag	VWF:RiCo(RCoF)	FVIII	VWF structure	Underlying Pathology
Type 1	↓	↓	Normal or ↓	Normal	↓ amount of circulating VWF
Type 2A	↓	↓↓↓	Normal or ↓	↓ HMW VWF	↓ amount of HMW VWF
Type 2B	↓	↓	↓	Normal	↑ binding of platelet with VWF
Type 2M	↓	↓↓↓	↓	Normal	↓ binding of platelet with VWF
Type 2N	↓	↓	↓↓↓	Normal	↓ binding of FVIII with VWF
Type 3	Absent	Absent	↓↓↓	Absent	Total absent of VWF

Test for VWF structure is not available in local setting.

HMW=high molecular weight multimer

undiagnosed. The heterogeneity can be due to the relatively high variability of diagnostic tests for VWD.[8-10] It can also be affected by the physiological changes of VWF within the same individual so intrapersonal variation exists at different time points. Since our study is a single centre study, we will not be able to comment on either the incidence or prevalence of VWD among Chinese children in our locality. Comparing with the total number of haemophilia patients diagnosed in our unit within the same time period, the ratio is approximately 3 haemophilia to 1 VWD patient, this is higher than that of the usual ratio of one VWD to 8 to 10 haemophilia patients in other haemophilia centres overseas. Such differences can be caused by variation in the referral pattern.

The revised classification of VWD defined two major categories, namely quantitative (type 1 and 3) or qualitative (type 2) VWF defects.[11] Many type 1 VWD patients have mild clinical bleeding unless they encounter a major haemostatic challenge such as tooth extraction or surgery. This form of VWD is often missed and may explain why in our patient cohort, type 1 patients were even less than type 2 patients. We speculate that most of our type 1 patients remained undiagnosed in our community, part of them may be diagnosed in their adulthood when they were screened or bled during a haemostatic challenge. But one has to be aware of exceptional cases such as both of our patients with catastrophic bleeding in fact had type 1 disease so the disease phenotype and clinical phenotype may not always correlate. The diagnosis of VWD is mainly supported by the presence of the following: 1) a personal history of excessive mucocutaneous bleeding; 2) a family history of excessive bleeding; and 3) a laboratory evaluation that is consistent with a quantitative and/or qualitative defect in von Willebrand factor (VWF).

Epistaxis and bruises were the main presenting bleeding feature, which is similar to that reported in the literature for paediatric patients. Most of the patients with excessive epistaxis finally grew out from this problem without active intervention. Menorrhagia emerged as a problem when female patients entered their puberty but they are usually self-limiting and manageable. Bleeding symptoms were found to be of mild to moderate nature in most of our patients. Severe life-threatening intracranial bleeding occurred in 2 of our patient with type 1 VWD. However, none of these 2 patients had recurrence of severe bleeding and they both recovered from their neurological deficit (visual field defect and mild hemiparesis respectively). By family history, family screening and pedigree assessment, the inheritance pattern of VWD in our patients revealed that most have dominant inheritance.

As for the VWD screening tests, the platelet count is usually normal; mild thrombocytopenia may occur in patients with type 2B VWD. The skin bleeding time (BT) is usually prolonged, but may be normal in patients with mild forms of VWD such as those with type 1 and normal platelet count. The reference range of skin bleeding time in paediatric patients has not been established for local children. In addition, it is an invasive test which will inevitably leave a scar. Based on these reasons, bleeding time is not a routine test and it was only performed in some of our patients in the cohort. The prothrombin time (PT) is expected to be normal in VWD. As VWF is the major binding protein for FVIII and it prevents FVIII from being degraded prematurely, deficiency or dysfunction of VWF will lead to a drop in the FVIII level in the blood. As a consequence, the activated partial thromboplastin time (APTT) may be prolonged to a variable degree, depending on the plasma FVIII level. The APTT is an insensitive and non-specific test for the diagnosis of VWD and we expect some VWD patients may present with normal or near normal APTT. In our patient cohort, 50% of patients had normal APTT at diagnosis (3 type 1 & 2 type 2). High index of suspicion is therefore a key to diagnose VWD in children. For definitive diagnosis, the current gold standard investigations are the combined panel of VWF:Ag, VWF:RCo and FVIII:C assays.[12] Of all the VWD patients in our cohort, only a few of them can have their subtype confirmed. This highlights the difficulty in classifying patients into different subtypes as many of the required tests are not available locally[1] (Figure 1).

In patients with VWD, the goal of the treatment is to correct the dual defect of abnormal platelet adhesion and abnormal coagulation due to low FVIII levels. There are two definitive treatments of choice in VWD, namely, desmopressin and blood products replacement. Other drugs such as antifibrinolytic agents (tranxanamic acid or ε-aminocaproic acid) can be used as adjunctive or alternative therapy. Desmopressin (DDAVP) is a synthetic analog of the antidiuretic hormone L-arginine vasopressin. It increases plasma VWF and factor VIII levels through the release of stored VWF from endothelial cells, leading to stabilisation of circulating factor VIII.[13,14] In addition, DDAVP stimulates platelet adhesiveness and restores thrombin generation.[15-17] DDAVP is most effective in patients with type 1 VWD, especially for those who have normal VWF in the storage sites. In other VWD subtypes, responsiveness is variable.[18] In type 3 and in severe forms of type 1 and type 2 patients, DDAVP is often not effective

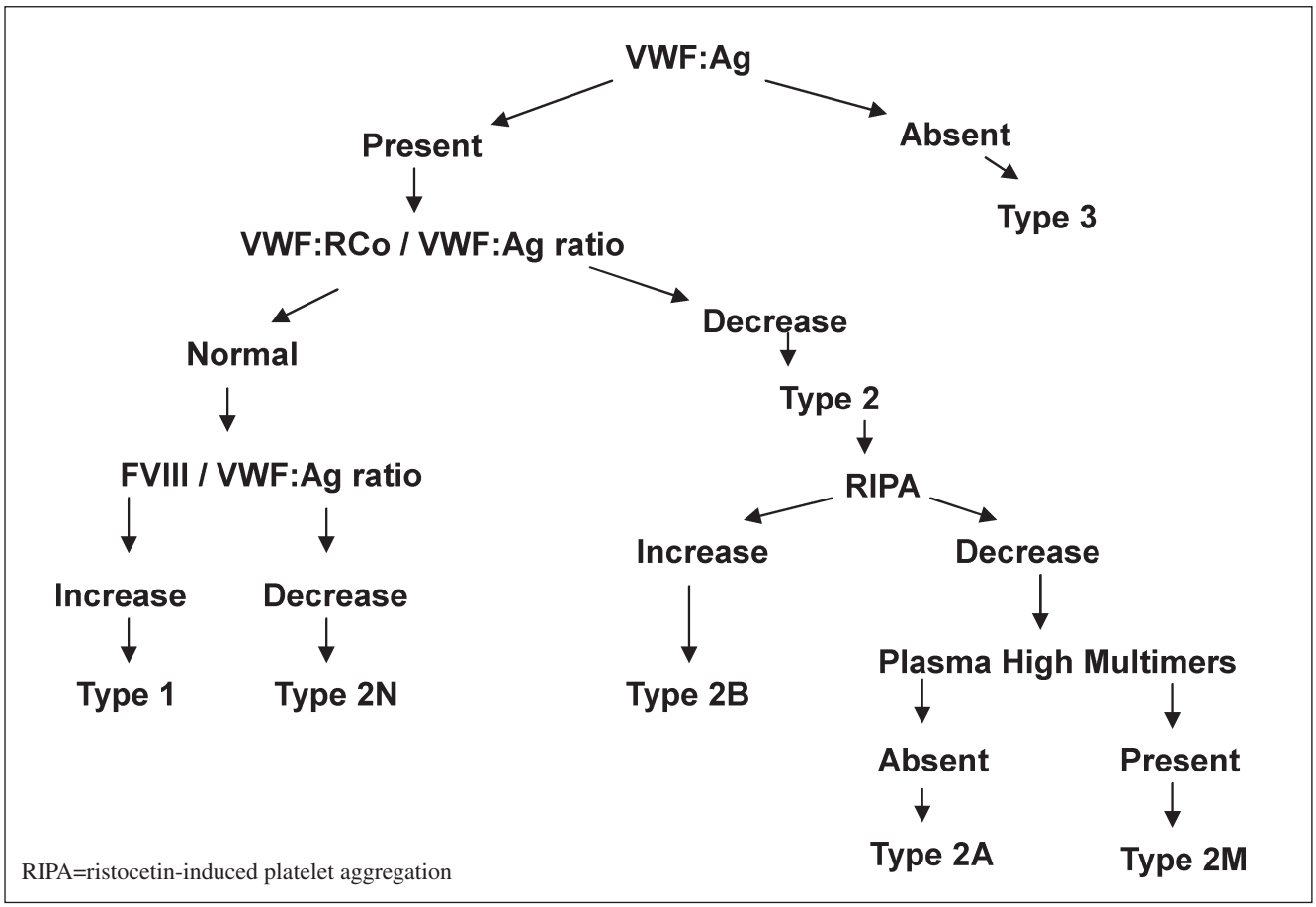

Figure 1 The simplified diagnostic approach of VWD. Modified from Federici AB, et al. Guidelines for the diagnosis and management of von Willebrand disedse in Italy. Haemophilia 2002;8:607-21.[1]

and it is necessary to resort to factor concentrates containing both FVIII and VWF. In our type 3 patient, although a rise in both VWF:Ag and FVIII:C levels was noted after DDAVP challenge, they were at suboptimal levels for effective haemostasis so it should not be used to cover any significant haemorrhage. One important point to note is that the DDAVP used in VWD is a different preparation and has a higher concentration than those used for diabetes insipidus so they should not be interchanged. Another point to note is that recombinant FVIII or very high purity plasma derived FVIII are not suitable for VWD patients with bleeding for they do not have VWF in the product. Intermediate purity plasma derived FVIII is the preferred product of choice.

In conclusion, VWD is uncommonly found in paediatric haematology unit. It is probably related to the mild phenotype of most VWD patients so they remain under-diagnosed. The diagnosis can be facilitated by a positive family history and history of excessive mucocutaneous bleeding especially in the form of epistaxis. Severe bleeding can occur in different subtypes of VWD patients. Most of our patients responded to DDAVP treatment and their bleeding tendency improved with age. We also identified 2 service gaps in the care of VWD patients locally. These include the lack of facilities in diagnosing subtype of VWD patients and the inaccessibility to high dose nasal DDAVP treatment. Future effort should be targeted on promoting collaborative data sharing and improvement in the diagnostic and therapeutic approach for this group of patients locally.

References

1. Federici AB, Castaman G, Mannucci PM; Italian Association of Hemophilia Centers (AICE). Guidelines for the diagnosis and management of von Willebrand disedse in Italy. Haemophilia 2002;8:607-21.
2. Dacie JV, Lewis SM, editors. Practical hematology. 8th ed. UK: Churchill Livingstone; 1999.

3. Nolan B, White B, Smith J, O'Reily C, Fitzpatrick B, Smith OP. Desmopressin: therapeutic limitations in children and adults with inherited coagulation disorders. Br J Haematol 2000;109:865-9.
4. Revel-Vilk S, Schmugge M, Carcao MD, Blanchette P, Rand ML, Blanchette VS. Desmopressin (DDAVP) responsiveness in children with von Willebrand disease. J Pediatr Hematol Oncol 2003;25:874-9.
5. Holmberg L, Nilsson IM. Von Willebrand disease. Clin Haematol 1985;14:461-88.
6. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand disease. Blood 1987;69: 454-9.
7. Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: A multiethnic study. J Pediatr 1993;123:893-8.
8. Salder JE, Mannucci PM, Berntorp E, et al. Impact, diagnosis and treatment of von Willlebrand disease. Thromb Haemost 2000; 84:160-74.
9. Castaman G, Federici AB, Rodeghiero F, Mannucci PM. von Willebrand disease in the year 2003: toward the complete identification of gene defects for correct diagnosis and treatment. Haematologica 2003;88:94-108.
10. Federici AB. Mild forms of von Willebrand disease: diagnosis and management. Curr Hematol Rep 2003;2:373-80.
11. Federici AB. Clinical diagnosis of von Willebrand disease. Haemophilia 2004;10 (Suppl 4):169-76.
12. Favaloro EJ, Lillicrap D, Lazzari MA, et al. von Willebrand disease: laboratory aspects of diagnosis and treatment. Haemophilia 2004;10 (Suppl 4):164-8.
13. Lethagen S. Desmopressin: a haemoststic drug: state of the art review. Eur J Anaesthesiol Suppl 1997;14:1-9.
14. Mannucci PM, Aberg M, Nilsson IM, Robertson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. Br J Haematol 1975;30:81-93.
15. Mannucci PM, Pareti FI, Holmberg L, Nilsson IM, Ruggeri ZM. Studies on the prolonged bleeding time in von Willebrand disease. J Lab Clin Med 1976;88:662-71.
16. Sakariassen KS, Cattaneo M, vd Berg A, Ruggeri ZM, Mannucci PM, Sixma JJ. DDAVP enhances platelet adherence and platelet aggregate growth on human artery subendothalium. Blood 1984; 64:229-36.
17. Balduini CL, Noris P, Belletti S, Spedini P, Gamba G. In vitro and in vivo effects of desmopressin on platelet function. Haematologica 1999; 84:891-6.
18. Mannucci PM. How I treat patients with von Willebrand disease. Blood 2001;97:1915-9.