# Management of severe chronic thrombocytopenia in von Willebrand's disease type 2B

C Mauz-Körholz, U Budde, H Kruck, D Körholz, U Göbel

**Abstract**

**Two patients with a long history of unexplained thrombocytopenia, eventually diagnosed with von Willebrand's disease (vWD) type 2B are reported. In one patient with platelet counts of 80 × $10^9$/l 1-desamino-8-D-arginine vasopressin (DDAVP) had a favourable effect during bleeding episodes. The second patient received intermediate purity von Willebrand's factor (vWF)/factor VIII concentrate (Haemate HS), which helped haemostasis during tooth extraction. It increased platelet counts from 15 to 30 × $10^9$/l, whereas platelet transfusions produced no increase, nor prevented severe bleeding during abdominal surgery. Thus the treatment of vWD type 2B might depend on the degree of thrombocytopenia. It is recommended that in patients with mild to moderately decreased platelet counts, DDAVP treatment can be tried, whereas in patients with severely decreased platelet counts intermediate purity vWF/factor VIII concentrate substitution is preferred.**

**In addition, vWD type 2B should be considered in the differential diagnosis of any child with chronic thrombocytopenia as the treatment strategy is different.**

(*Arch Dis Child* 1998;**78**:257–260)

Keywords: von Willebrand's disease type 2B; chronic thrombocytopenia; DDAVP; F VIII/von Willebrand's factor plasma concentrates

**Department of Paediatric Haematology/Oncology, Heinrich-Heine University Medical Centre, Düsseldorf**
C Mauz-Körholz
H Kruck
D Körholz
U Göbel

**Blood Centre, General Hospital, Hamburg-Harburg, Germany**
U Budde

Correspondence to:
Dr Ulrich Göbel, Department of Paediatric Haematology/Oncology, Heinrich-Heine-University Medical Centre, Moorenstr 5, 40225 Düsseldorf, Germany.

Accepted 17 August 1997

According to the classification by Sadler,[1] von Willebrand's disease (vWD) type 2B is a rare subtype, accounting for fewer than 5% of all patients with vWD. It is characterised by the presence of an abnormal von Willebrand's factor (vWF) with an enhanced affinity to glycoprotein Ib on the platelet surface.[2] Therefore platelet-rich plasma of these patients aggregates at low ristocetin concentrations.[3] In addition, their plasma lacks high molecular weight multimers.[4]

Most patients with vWD can be effectively and safely treated with 1-desamino-8-D-arginine vasopressin (DDAVP).[5] This vasopressin analogue is able to normalise both factor VIII coagulant activity (F VIII:C) and prolonged bleeding time, thus correcting the underlying haemostatic defect. F VIII:C is variably increased in all subtypes of the disease, apart from patients with vWD type 3. However DDAVP has been shown to induce thrombocytopenia in vWD type 2B,[6] so has been considered contraindicated in these patients. The treatment of choice in patients with vWD types 2B and 3 is generally considered to be replacement with intermediate purity plasma concentrate.[7–9] Bleeding time, F VIII:C, and vWF levels can be corrected effectively thereby. Unexpected bleeding or symptoms of thrombosis, however, have never been reported in patients with vWD type 2B in whom DDAVP had been infused for investigational purposes[10–13] or to prevent surgical bleeding.[14–16]

We report our treatment strategies in two patients with vWD type 2B and different degrees of thrombocytopenia.

## Case reports

CASE 1

The patient, now 8 years old, was the first son of a healthy Vietnamese couple with no bleeding history. At the age of 2 years he was admitted to hospital with severe bleeding and platelet count of 25 × $10^9$/l. Bone marrow aspirate showed normocellularity with no evidence of malignancy. In addition, no hypermegakariocytosis was observed. A search for platelet associated autoantibodies was negative. Despite these findings the patient was treated with corticosteroids. His response was very slow and short lived, and repeated courses of steroids were given. With intravenous immunoglobulin (IVIg) his platelet count initially rose from 80 to 140 × $10^9$/l. However, repeated administration of IVIg was ineffective subsequently.

He required nasal tamponade and blood transfusions for severe epistaxis and coagulation analysis revealed very low vWF activity of 33%. Subsequently he was given DDAVP and epistaxis immediately stopped. Multimer analysis of vWF revealed the pattern of vWD type 2 with a lack of high molecular weight multimers. An increased ristocetin induced platelet aggregation at low concentration of ristocetin (0.6 μg/ml) favoured the diagnosis of vWD type 2B. We demonstrated that DDAVP at a concentration of 0.3 μg/kg body weight, given intravenously, significantly reduced bleeding time. In addition, a rise of vWF antigen in the plasma (table 1) was associated with a partial restoration of previously absent vWF multimers (fig 1). Platelet counts, as expected, dropped from 80 × $10^9$/l to as low as 44 × $10^9$/l, but returned to 70 × $10^9$/l 24 hours after DDAVP (table 1). He did not bleed and no adverse effect occurred after repeated DDAVP application.

Laboratory testing of his parents showed normal coagulation parameters, a full range of plasma vWF multimers, and a normal ristocetin induced platelet aggregation test and platelet counts.

*Table 1 Effects of DDAVP on haemostasis of a patient with vWD type 2B*

| *Time after DDAVP* | *Bleeding time (min)* | *F VIII:C (%)* | *vWF:Ag (%)* | *RiCoF (%)* | *Platelet count (× 10⁹/l)* |
|---|---|---|---|---|---|
| 0 min | >30 | 80 | 54 | 14 | 85 |
| 30 min | nd | 190 | 79 | 70–112 | 40 |
| 60 min | 9 | 165 | 90 | nd | 64 |
| 120 min | 6 | 150 | >100 | nd | 44 |
| 240 min | >30 | 94 | 87 | nd | 49 |
| 24 hours | >30 | 61 | 56 | nd | 70 |

DDAVP (0.3 µg/kg body weight) was administered as a 30 minute infusion. Subsequently, bleeding time, vWF:Ag, F VIII:C, ristocetin cofactor (RiCoF), and platelet counts were determined 30, 60, 120, 240 minutes and 24 hours after infusion in the patient firstly reported.
nd=not done.

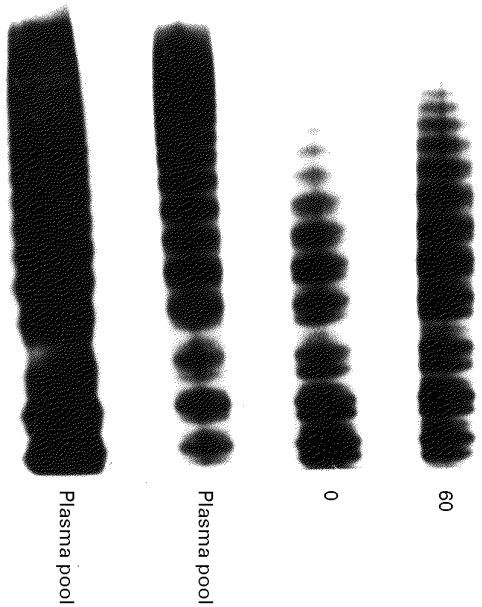


*Figure 1 Effect of DDAVP on multimer analysis in case 1. Multimer analysis was performed by western blotting before DDAVP infusion and 60 minutes later. DDAVP qualitatively increased high molecular weight multimers, but could not restore the full range of the normal multimer pattern.*

CASE 2

The patient was 17 years old at the time of this report and was the first son of a healthy German couple with no bleeding history. Platelet counts had been below $20 \times 10^9$/l since birth. Bone marrow aspirate showed normal megakaryopoiesis and diagnostic testing for antiplatelet antibodies and anti-HLA antibodies was negative. Congenital infection was ruled out and corticosteroid treatment failed to show any effect. At the age of 2 years inguinal herniotomy provoked massive scrotal haemorrhage despite platelet transfusions. At the age of 11 years he experienced severe post-traumatic muscle haemorrhage. Coagulation analysis showed very low ristocetin cofactor activity (14%) and both decreased factor VIII (47%) and vWF (49%) activity. Multimer analysis of vWF showed absence of high molecular weight multimers (fig 2). Neither ristocetin induced or spontaneous platelet aggregation nor circulating platelet aggregates, according to the method described by Wu *et al*,[17] could be determined because of severe thrombocytopenia. At the age of 17 years dental extraction was carried out under intermediate purity factor VIII/vWF plasma concentrate (Haemate HS) without blood loss. After infusion of plasma concentrate platelet counts rose from 15 to over $30 \times 10^9$/l (table 2). As expected, vWF multimer analysis showed nearly the full range of plasma multimers after infusion (fig 2).

*Table 2 Effects of plasma concentrate transfusion on haemostasis of a patient with vWD type 2B*

| *Time after transfusion* | *F VIII:C (%)* | *vWF:Ag (%)* | *RiCoF (%)* | *Platelet count (× 10⁹/l)* |
|---|---|---|---|---|
| 0 min | 37 | 42 | 14 | 12 |
| 30 min | 80 | 52 | 112 | 30 |
| 24 hours 30 min | 58 | 83 | 56 | 33 |
| 48 hours 30 min | 70 | 100 | 70 | 32 |

Haemate HS (30 IU/kg body weight) was infused for three subsequent days. Coagulation analysis including F VIII:C, vWF:Ag, ristocetin cofactor (RiCoF), and platelet counts was performed 30 minutes after infusion.

As in the first patient, laboratory testing of his parents was completely normal.

## Discussion

The first patient had originally been diagnosed with idiopathic thrombocytopenic purpura (ITP), as he had responded to IVIg treatment, even though the bone marrow aspirate had not shown hypermegakariocytosis and no platelet associated autoantibodies had been detectable. However, his subsequent clinical course was unusual for chronic ITP. Although platelet counts had been higher than $50 \times 10^9$ /l, the patient had presented with severe bleeding episodes. In addition, coagulation studies revealed characteristic findings for vWD type 2B. Thus, his chronic thrombocytopenia can be best explained by vWD type 2B rather than a chronic form of ITP. However, we cannot explain satisfactorily the initial response at age 2 to IVIg treatment unless the thrombocytopenic episode was caused by an acute immune mediated event, not uncommon in young children. The absence of response to repeated courses of IVIg and steroids is against the diagnosis of chronic ITP.

In this patient DDAVP was given during an episode of severe nasal bleeding. The treatment appeared to be safe and bleeding ceased immediately.

We observed increased thrombocytopenia after giving DDAVP, with a nadir four hours after infusion; platelet counts returned to pretreatment levels within 24 hours and no haemorrhage occurred.

The abnormal vWF multimers in patients with vWD type 2B have been reported to show an increased affinity to glycoprotein Ib on the platelet surface which results in an increased aggregation of platelets. Casonato *et al* could demonstrate this mechanism by the use of a monoclonal antiglycoprotein Ib. This antibody effectively blocked the interaction of vWD type 2B multimers with platelets leading to an inhibition of platelet aggregation in vitro.[10] Gralnick *et al* demonstrated platelet aggregation in vivo in patients with vWD type 2B and this could increase the concentration of abnormal multimers by DDAVP administration.[18] DDAVP treatment should therefore be avoided

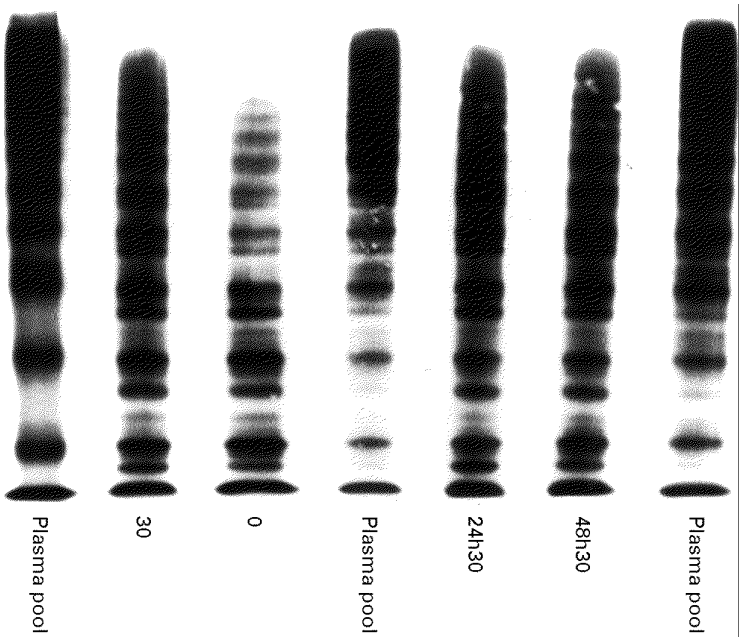


*Figure 2 Effect of an intermediate purity factor VIII/vWF concentrate infusion on multimer analysis in case 2. Multimer analysis was performed before and on three occasions after transfusion. Infusion of Haemate HS led to a nearly complete normalisation of the multimer pattern, except for the very high molecular weight multimers.*

in patients with vWD type 2B who have low basal platelet counts.

In the second case, severe congenital thrombocytopenia had been the presumed diagnosis until vWD type 2B was confirmed at the age of 14 years by multimer analysis. Laboratory findings, clinical symptoms, and the patient's history were not characteristic of any particular disease associated with chronic thrombocytopenia: the history revealed no evidence of inherited disease and the lack of response to steroids excluded the diagnosis of chronic ITP. Laboratory findings showed normal immunoglobulin concentrations, normal leucocyte and erythrocyte counts, and bone marrow aspirate showed a normal number of megakariocytes.

Mild to moderate thrombocytopenia is a common finding in patients with vWD type 2B.[3–6] In contrast, our patient had severe thrombocytopenia with platelet counts never above $20 \times 10^9$/l. A small subpopulation of patients with vWD type 2B can present with severe chronic thrombocytopenia. For example a family with vWD type 2B and severe thrombocytopenia was first described by Saba *et al*, who named this subtype vWD 2B Tampa.[19] The platelet counts of the propositus were between 9 and $30 \times 10^9$ /l. This was explained by in vivo platelet aggregation. In this family an enhanced ristocetin induced platelet aggregation, an enhanced bleeding time, and a lack of high molecular weight vWF multimers were found, indicating vWD type 2B. The RIPA test and circulating platelet aggregates could not be determined in our second patient because of his very low platelet counts. Laboratory testing of his parents was normal. In contrast, in the Tampa family the propositus and four of his children had abnormal laboratory tests. Thus, the inheritance pattern in our family differs from that in the Tampa family. These findings suggest recessive rather than dominant inheritance similar to the description of Donner *et al*.[20] These authors reported a recessive disorder in two families with vWD type 2B. In these patients thrombocytopenia was present during infancy. However, platelet counts improved with time and were never below $50 \times 10^9$/l. Thus, we here describe a patient with severe chronic thrombocytopenia with multimer analysis featuring vWD type 2B, who neither completely fits to the description of Donner *et al* nor to the Tampa vWD subtype 2B suggesting a different variant of vWD type 2B.

Despite platelet transfusion a major haemorrhagic episode occurred in our patient after surgery for an inguinal hernia. This supports the hypothesis that thrombocytopenia in vWD type 2B patients is not a laboratory artefact, as suggested by Castaman and Rodeghiero[21] but rather caused by spontaneously increased in vivo platelet aggregation.[19] Therefore the administration of intermediate purity F VIII/vWF concentrate might be the treatment of choice in vWD type 2B with extremely low platelets. In our patient, infusion of an intermediate purity F VIII/vWF plasma concentrate (Haemate HS) not only prevented bleeding during dental surgery, but also increased platelet counts. Thus, normal vWF obtained from a plasma concentrate might compete with the pathological vWF for glycoprotein Ib binding sites on platelets. Molecular analysis of the abnormal vWF and recombinant production of mutant proteins could give further clues in the pathogenesis of thrombocytopenia in patients like ours.

Severe thrombocytopenia can be associated with typical clinical findings such as splenomegaly, giant haemangiomata, or absent radii. In addition, some patients present with signs of bleeding only. In these patients thrombocytopenia might be caused by a chronic immune mediated mechanism or a genetic defect of thrombocyte membrane glycoproteins (Bernard-Soulier syndrome) or defective thrombopoietin production. Since vWD type 2B requires distinct management to prevent severe bleeding during surgery such as vWF/factor VIII concentrate transfusion, vWD type 2B should be considered in the differential diagnosis of any child with chronic thrombocytopenia and an inappropriate bleeding tendency.

C Mauz-Körholz was supported by a grant from "Elterninitiative Kinderkrebsklinik Düsseldorf e.V.

1 Sadler JE. A revised classification of von Willebrand disease. *Thromb Haemost* 1994;**71**:520–5.
2 Ruggeri ZM, Zimmerman TS. von Willebrand factor and von Willebrand disease. *Blood* 1987;**70**:895–907.
3 Ruggeri ZM, Pareti FI, Mannucci PM, *et al*. Heightened interacion between platelets and F VIII/von Willebrand factor in a new subtype of von Willebrand's disease. *N Engl J Med* 1980;**302**:1047–51.
4 Ruggeri ZM, Zimmerman TS. Variant of von Willebrand's disease: characterization of two subtypes by analysis of multimeric composition of F VIII/von Willebrand factor in plasma and platelets. *J Clin Invest* 1980;**65**:131–5.
5 Rodeghiero F, Castaman G, Mannucci PM. Clinical indication for desmopressin (DDAVP) in congenital and acquired von Willebrand disease. *Blood Rev* 1991;**5**:155–61.
6 Holmberg L, Nilsson IM, Borge L, *et al*. Platelet aggregation induced by 1-desamino-8D-arginine vasopressin

(DDAVP) in type IIB von Willebrand's disease. *N Engl J Med* 1983;**309**:816–21.
7 Scharrer I. The treatment of von Willebrand's disease. In: Lusher JM, Kessler CM, eds. *Hemophilia and von Willebrand's disease in the 1990s*. Amsterdam: Excerpta Medica/Elsevier 1991: 463–9.
8 Scharrer I, Vigh T, Aygören-Pürsün E. Experience with Haemate P in von Willebrand's disease in adults. *Haemostasis* 1994;**24**:298–303.
9 Kreuz W, Menzer D, Becker S, *et al*. Haemate P in children with von Willebrand's disease. *Haemostasis* 1994;**24**:304–10.
10 Casonato A, Fabris F, Girolami A. Platelet aggregation and pseudothrombocytopenia induced by 1-desamino-8D-arginine vasopressin (DDAVP) in type IIB von Willebrand's disease. *Eur J Haematol* 1990;**45**:36–42.
11 Kyrle PA, Niessner H, Dent J, *et al*. IIB von Willebrand's disease: pathogenetic and therapeutic studies. *Br J Haematol* 1988;**69**:55–9.
12 Casonato A, Sartori MT, de Marco L, *et al*. 1-Desamino-8D-arginine vasopressin (DDAVP) infusion in type IIB von Willebrand's disease: shortening of bleeding time and induction of a variable thrombocytopenia. *Thromb Haemost* 1990;**64**:117–20.
13 McKeown LP, Connaghan G, Wilson O, *et al*. 1-Desamino-8-arginine-vasopressin corrects the hemostatic defects in type 2B von Willebrand's disease. *Am J Hematol* 1996;**51**: 158–63.
14 Casonato A, Pontara E, Dannhauser D, *et al*. Re-evaluation of the therapeutic efficacy of DDAVP in type IIB von Willebrand's disease. *Blood Coagul Fibrinolysis* 1994;**5**:959–64.
15 Mannucci PM, Ruggeri ZM, Pareti FI, *et al*. DDAVP in haemophilia. *Lancet* 1977;**ii**:1171–2.
16 Fowler WE, Berkowitz LR, Roberts HR. DDAVP for type IIB von Willebrand's disease. *Blood* 1989;**74**:1859–60.
17 Wu KK, Hoak JC. A new method for quantitative detection of platelet aggregates in patients with arterial insufficiency. *Lancet* 1974;**ii**:924–7.
18 Gralnick HR, Williams SB, McKeown LP, *et al*. Von Willebrand's disease with spontaneous platelet aggregation induced by an abnormal von Willebrand factor. *J Clin Invest* 1985;**76**:1522–9.
19 Saba HI, Saba SR, Dent J, *et al*. Type IIB Tampa: a variant of von Willebrand's disease with chronic thrombocytopenia, circulating platelet aggregates, and spontaneous platelet aggregation. *Blood* 1985;**66**:282–6.
20 Donner M, Holmberg L, Nilsson IM. Type IIB von Willebrand's disease with probable autosomal recessive inheritance and presenting as thrombocytopenia in infancy. *Br J Haematol* 1987;**66**:349–54.
21 Castaman G, Rodeghiero F. Desmopressin and type IIB von Willebrand's disease. *Hemophilia* 1996;**2**:73–7.