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.

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

According to the classification by Sadler,7 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).3 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,4 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.7,8 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 purposes10–12 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 hypermegakaryocytosis 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 3%. 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.

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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).

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 hypermegakaryocytosis 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.

His chronic thrombocytopenia can be best explained by vWD type 2B rather than a chronic form of 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.

**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 herniotormy provoked massive scrotal haemorrhage despite platelet transfusions. At the age of 11 years he experienced severe posttraumatic 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., 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 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 was determined 30, 60, 120, 240 minutes and 24 hours after infusion in the patient firstly reported. nd=not done.

**Table 1**

<table>
<thead>
<tr>
<th>Time after DDAVP (min)</th>
<th>Bleeding time &gt;30</th>
<th>F VIII:C (%)</th>
<th>vWF:Ag (%)</th>
<th>RiCoF (%)</th>
<th>Platelet count (× 10^9/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>nd</td>
<td>80</td>
<td>54</td>
<td>14</td>
<td>85</td>
</tr>
<tr>
<td>30 min</td>
<td>nd</td>
<td>190</td>
<td>79</td>
<td>70–112</td>
<td>40</td>
</tr>
<tr>
<td>60 min</td>
<td>9</td>
<td>165</td>
<td>90</td>
<td>nd</td>
<td>64</td>
</tr>
<tr>
<td>120 min</td>
<td>6</td>
<td>150</td>
<td>&gt;100</td>
<td>nd</td>
<td>44</td>
</tr>
<tr>
<td>240 min</td>
<td>&gt;30</td>
<td>94</td>
<td>87</td>
<td>nd</td>
<td>49</td>
</tr>
<tr>
<td>24 hours</td>
<td>&gt;30</td>
<td>61</td>
<td>56</td>
<td>nd</td>
<td>70</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Time after transfusion (min)</th>
<th>F VIII:C (%)</th>
<th>vWF:Ag (%)</th>
<th>RiCoF (%)</th>
<th>Platelet count (× 10^9/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>37</td>
<td>42</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>30 min</td>
<td>80</td>
<td>52</td>
<td>112</td>
<td>30</td>
</tr>
<tr>
<td>24 hours 30 min</td>
<td>58</td>
<td>85</td>
<td>56</td>
<td>33</td>
</tr>
<tr>
<td>48 hours 30 min</td>
<td>70</td>
<td>100</td>
<td>70</td>
<td>32</td>
</tr>
</tbody>
</table>

DDAVP treatment should therefore be avoided.
from that in the Tampa family. These findings suggest recessive rather than dominant inheritance similar to the description of Donner et al. 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 × 10⁹/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 but rather caused by spontaneously increased in vivo platelet aggregation. 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 physiological 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.