Type IIA von Willebrand Disease With Apparent Recessive Inheritance

By Akio Asakura, Janet Harrison, Edward Gomperts, and Charles Abildgaard

Type IIA von Willebrand’s Disease (vWD) is the most common type II variant, and all reported cases (56 individuals in 26 families) have had autosomal dominant inheritance. An eight-year-old female with an increased bleeding tendency since infancy was found to have laboratory values typical of type IIA vWD, but her parents and siblings were asymptomatic. With the exception of uniformly decreased levels of ristocetin cofactor in relation to von Willebrand factor antigen, the results of family studies were normal including the presence of large multimeric forms of von Willebrand factor antigen. These findings are consistent with the proposition having the homozygous state of an autosomal recessive trait. Desmopressin infusion in the propositus was followed by a significant increase of factor VIII coagulant and von Willebrand factor antigen but a limited change in ristocetin cofactor with no development of large multimers.

parents and three siblings (6, 14, and 16 years) are living and well, and all members of the family were evaluated.

MATERIALS AND METHODS

Computations of bleeding times were performed by the Ivy method. Blood collection, plasma preparation and storage, as well as methods for factor VIII coagulant activity (one-stage partial thromboplastin time method), vWF:Ag (Laurell), multimer analysis (sodium dodecyl sulfate agarose gel electrophoresis using 1.5% and 3.0% gels), and RCo (macroscopic agglutination technique using formalin-fixed platelets) have been described previously. Ristocetin-induced platelet aggregation (RIPA) was measured by the method of Weiss et al.

RESULTS

The results of plasma studies of the propositus, her parents, and three siblings are shown in Table 1. The propositus had a prolonged bleeding time (>20 minutes), significantly decreased vWF:Ag (22%) and RCo (3%), and normal RIPA. The only abnormality noted in the parents and siblings was a uniformly decreased amount of RCo in relation to vWF:Ag. The ratios of RCo to vWF:Ag for the parents and siblings were 0.47, 0.60, 0.49, 0.61, and 0.67 (mean, 0.57). For comparison, mean ratios of RCo to vWF:Ag in normal individuals and other vWD subjects studied in our laboratory are as follows: normals (26), 1.02; type I vWD (15), 1.21; type IIA (14), 0.51, and type IIB (9), 1.19.

The multimer patterns of vWF:Ag on 1.5% and 3.0% agarose gel electrophoresis are shown in Fig 1A and B. On 3.0% gel the propositus has a repeating five-band pattern. The child subsequently has had repeated bleeding episodes following minor injuries and has received cryoprecipitate for treatment of a laceration and for a tooth extraction. More recently she received antifibrinolytic therapy and an infusion of desmopressin in preparation for a tooth extraction, and hemostasis was satisfactory.

Her family history is negative for bleeding manifestations. Both parents and three siblings (6, 14, and 16 years) are living and well, and all members of the family were evaluated.

<p>| Table 1. Values for VIIIc, vWF:Ag, and RCo for the Propositus and Family Members |
|---------------------------------|---------------|--------------|---------------|----------------|</p>
<table>
<thead>
<tr>
<th>VIllc (%)</th>
<th>vWF:Ag (%)</th>
<th>RCo (%)</th>
<th>RCo/vWF:Ag</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Propositus</td>
<td>58</td>
<td>22</td>
<td>3</td>
<td>.14</td>
</tr>
<tr>
<td>Mother</td>
<td>144</td>
<td>89</td>
<td>42</td>
<td>.47</td>
</tr>
<tr>
<td>Father</td>
<td>100</td>
<td>73</td>
<td>44</td>
<td>.60</td>
</tr>
<tr>
<td>Brother (1)</td>
<td>100</td>
<td>107</td>
<td>53</td>
<td>.49</td>
</tr>
<tr>
<td>Brother (2)</td>
<td>120</td>
<td>95</td>
<td>58</td>
<td>.61</td>
</tr>
<tr>
<td>Sister</td>
<td>98</td>
<td>73</td>
<td>49</td>
<td>.57</td>
</tr>
<tr>
<td>Normal</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>1.02*</td>
</tr>
<tr>
<td>Normal range</td>
<td>50-150</td>
<td>50-150</td>
<td>50-150</td>
<td>0.72-1.59</td>
</tr>
</tbody>
</table>

*Mean ratio of 26 normal individuals.

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resulted in increases of factor VIII coagulant activity (18% to 128%) and vWF:Ag (23% to 114%), whereas RCo only increased from 3% to 17%. Plasma vWF:Ag multimers were analyzed before and after desmopressin infusion in the propositus; patterns are shown in Fig 2. On 1.5% gel only a few of the smaller intermediate multimers appeared following desmopressin infusion. An increase in density of the smallest multimers was noted on 3.0% gel.

Fig 2. Before and after desmopressin infusion studies of the propositus plasma on (A) 1.5% and (B) 3.0% agarose gels. On 1.5% gel, the postinfusion sample in the center lane reveals a slight increase of intermediate multimers (normal plasma on the right). On 3.0% gel, an increased density of small multimer bands is seen in the postinfusion sample in the center lane (normal plasma on the right).

REFERENCES

5. Hill FGH, Enayat MS, George AJ: Investigation including VIII R:Ag multimeric analysis of a large kindred with type II A von Willebrand's disease showing a dominant inheritance and similar gene expression in four generations. Thromb Haemost 50:735, 1983
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