SEVERE VON WILLEBRAND'S DISEASE WITH ABNORMAL PLATELET
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A 17-year-old boy with a life long history of easy
bruising, epistaxis, subcutaneous haemostasis and prolonged
bleeding time from minor injuries, was initially diagnosed as
having von Willebrand's disease, whose manifested episodes at 2
years of age. Since his initial diagnosis, he has been
treated with cryoprecipitate on many occasions to correct his
bleeding tendency. The laboratory findings in the patient and
his family are summarized in the table. The patient's mother,
father and one brother have not complained any bleeding
tendency.

Bleeding time VIII:C RfIcof RIPA Platelet
propositus 260 <12.5 5 Abn. Abn.
father 2 95 100 45 88 N N
mother 6 100 110 104 N Abn.
brother 5 5 100 112 100 N N

Multimeric analysis of vWF using SDS agarose gels showed
absence of large multimers in the patient's plasma, decreased
large multimer in mother's and brother's plasma. When the
patient's PRP was tested for aggregation and release of ATP
by ADP, epinephrine and collagen, only limited aggregation
and platelet aggregation was abnormal as shown by disaggregation
and almost no large multimer in mother's and brother's plasma. When the
platelet aggregation was tested in the supernatant, ATP contents of platelet
was abnormal aggregation of normal platelet. Washed platelets of the patient
in normal plasma did not aggregate normally, but washed normal
platelets in the patient's plasma aggregate normally. No
inhibitor of vWF could be demonstrated in the patient's
plasma. Glut retraction was normal. These findings suggest
that our patient has inherited vWD from materal side and the
platelet aggregation defect, probably a kind of storage pool
disease, from the paternal side of the family.

ABSENCE OF A BLEEDING TENDENCY IN SEVERE ACQUIRED DEFICIENCY
OF PLASMA VON WILLEBRAND FACTOR (vWF)/F.VIII WITH NORMAL
PLATELET vWF/F.VIII INDICES. J. Drouin (1), R. Lilliecrap (1),
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A 67 year old male with IgA myeloma has been investigated
for a severe deficiency of plasma vWF/F.VIII but normal
platelet vWF/F.VIII. He has no personal history nor family
history of bleeding problems. He was initially investigated for
a prolonged APTT of 43 secs. (25-40) obtained in a
prospecive clotting screen. During this investigation he
was found to have IgA myeloma. In retrospect, an APTT prior
to uneventful coronary artery bypass surgery two years
previously had been prolonged. Routine investigation has
shown that platelet count and bleeding time have been
repeatedly normal. Plasma F.VIII:C is 0.08 u/ml, F.VIII:Cag
0.07 u/ml, vWF:Ag 0.05 u/ml and ristocetin cofactor 0.09
u/ml. In contrast, platelet values for vWF:Ag of 53 units/10
platelets and F.VIII:Cag of 43 units/10^9 platelets are within
the normal ranges for our laboratory. The platelet lysate vWF
multimer pattern is also normal. Patient's plasma shows
imhibitory activity against vWF but not against either
F.VIII:C or ristocetin cofactor activity. When patient plasma
is incubated for 60 mins at 37°C with vWF and analysed by
colloidal immunoelectrophoresis (CIE) for vWF:Ag, a double arc
precipitin line is observed with marked retardation of the first
arc. A similar vWF:Ag CIE double precipitin arc is seen following the infusion of cryoprecipitate. T 1/2 for F.VIII:C and vWF:Ag are both reduced following the infusion of
cryoprecipitate = F.VIII:C 2 hrs, vWF:Ag 3 hrs. No secondary
rise in F.VIII:C is seen at 24 hrs. Despite severe deficiency of
plasma vWF/F.VIII, this man does not have a clinical
bleeding tendency. We postulate that his plasma vWF/F.VIII
deficiency is the result of his IgA myeloma, a soluble protein with vWF, resulting in premature clearance of the
vWF/F.VIII complex. This case further emphasizes the role of
platelet associated coagulation factors in maintaining normal
haemostasis.

HYPOTHYROIDISM AND ACQUIRED VON WILLEBRAND'S DISEASE
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A diagnosis of type IA von Willebrand's disease was made in
these patients presenting with a mild bleeding tendency.
Previously unrecognized hypothyroidism was also confirmed in
two patients. In the third, hypothyroidism was diagnosed four
years after initial presentation. In all three patients, thyroidine therapy was associated with correction of the
haemostatic defect and resolution of the bleeding tendency.
The association of von Willebrand's disease and hypothyroidism prompted us to examine the relationship between
thyrocrphin (TSH), T3, T4 and components of the factor
VIII complex in 12 patients with clinical and biochemical
hypothyroidism. Factor IX was also studied. Mean VIII:C
(measured by 2 stage assay) was 0.90 u/ml (range 0.35 - 1.14);
mean vWF:Ag 0.83 u/ml (range 0.44 - 1.64); mean VIII:Rcof 0.75
(range 0.65 - 1.55); mean factor IX 0.72 (range 0.39 - 1.19).
Multimeric analysis of vWF:Ag performed in samples from 8
patients was normal. VIII:Rcof levels were significantly lower
than those of normal controls. A significant inverse
relationship was correlated between TSH and factor IX and T4 and
vWF:Ag. Although there is a definite inverse relationship
between TSH and factor IX, this is not evident with respect to
factor VIII and a different mechanism is probably responsible for the modest reduction of vWF:Ag and the occurrence of
clinically-evident von Willebrand's disease which we have
demonstrated in a small proportion of hypothyroid patients.

Even though it is generally held that cryoprecipitate (cryo)
and fraction 1-0 correct the prolonged bleeding time (BT) in
patients with von Willebrand disease (vWD), perusal of reported
data indicates that the correction is usually short lasting and
often partial. We decided to do a controlled study of the
relationship between the multimeric structure of von Willebrand
Factor (vWF) (in 5 patients with severe vWD) after infusion of
three plasma concentrates: "wet" cryo, lyophilized (lyo) cryo,
and fraction 1-0 given in random order. The dosage of concentrates was tailored to achieve post infusion levels of
RCoF above the lower normal limit (50 u/ml) for at least 3
hours. The post-infusion BT values are shown in the table.

Bleeding time (min.)

<table>
<thead>
<tr>
<th>patients</th>
<th>BH1</th>
<th>ZG</th>
<th>CR</th>
<th>TA</th>
<th>DFE</th>
</tr>
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<tbody>
<tr>
<td>MEL CRYO</td>
<td>5</td>
<td>20</td>
<td>24</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>LYO CRYO</td>
<td>14</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>FRACTION 1-0</td>
<td>15</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

These findings indicate that the attainment of a normal BT is
the exception rather than the rule after infusion of three plasma
concentrates used for treatment of severe vWD. In all the
concentrates the proportions of large vWF multimers, calculated by
scanning the electrophoretic gels, were the same as in normal
standard plasmas. An intact multimeric structure was recovered in
post-infusion plasma of patients treated with wet cryo, whereas
there was post infusion loss of large multimers after lyo and
fraction 1-0. In conclusion, an intact multimeric structure in
post-infusion plasma is necessary but not sufficient to sustain a
normal BT in vWD patients.