Possible Effect of Secretor Locus on Plasma Concentration of Factor VIII and von Willebrand Factor

By Karen Helene Ørstavik, Leif Kornstad, Howard Reisner, and Kåre Berg

A significant fraction (30%) of the genetically determined variance in plasma concentration of the von Willebrand factor antigen (vWF:Ag) has been shown to be related to ABH determinants. Individuals with blood group O, who have the highest amounts of blood group H substance, have the lowest concentration of vWF:Ag. The Lewis substances, Le\(^a\) and Le\(^b\), are biochemically closely related to the ABH substances as both can be produced from the same precursor substance. We studied the effect of the presence of the Lewis antigens on the plasma concentration of vWF:Ag and factor VIII antigen (VIII:Ag) in 323 individuals of different ABO groups from a series of twins and in 58 blood donors of blood group O. Among persons belonging to blood group O, those with the Le\(^a\) antigen had a higher concentration of both vWF:Ag and VIII:Ag than individuals lacking Le\(^a\). Le\((a+b-)\) people are nonsecretors and Le\((a-b+)\) people are secretors of ABH substance. Thus, the lowest concentration of vWF:Ag and VIII:Ag was found in group O secretors. The effect is most likely due to an effect of the secretor locus. This finding may be of importance for the detection of carriers of hemophilia A and for the diagnosis of type I von Willebrand disease.

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MATERIALS AND METHODS

Material. Plasma samples were examined from 323 twins and 58 blood donors. The twins had previously been examined in a study of the effect of genetic factors on the plasma concentrations of vWF:Ag and VIII:Ag, and included 74 identical pairs, 84 like-sexed fraternal pairs, and seven twins where the cotwin was lacking. The twins were bled in their homes or in the laboratory after an overnight fast. Blood was collected into Vacutainer tubes containing 1/10 vol 3.13% sodium citrate. The blood donors all belonged to ABO blood group O, and the samples were selected to give about the same number of individuals of each of the three Lewis phenotypes. The blood donors were bled at the end of ordinary blood donations and were not fasting. Blood was collected into Vacutainer tubes containing 1/100 vol 15% EDTA. All donors were retested in the Lewis system on this occasion and the phenotypes were in all cases confirmed. The twins were either 33 to 39 or 57 to 62 years old, with approximately the same number of individuals in each age group. The blood donors were between 22 and 61 years old with a mean of 40 years in all three Lewis phenotypes.

vWF:Ag and VIII:Ag. vWF:Ag was determined by an electroimmunoassay using a rabbit antibody, and VIII:Ag was determined by a radioimmunoassay using a human antibody, as previously described. For some individuals plasma was not available for the VIII:Ag assay. The concentration was given relative to a standard plasma pool defined to contain 100 U/dL.
SECRETOR LOCUS AND VIII-vWF COMPLEX

and A, while there are no problems of this kind when testing groups and the vWf:Ag and VIII:Ag concentrations are described in standard textbooks.

The donors were typed at the National Blood Group Reference Laboratory using antisera prepared at the laboratory.

Statistical methods. vWf:Ag and VIII:Ag concentrations were not normally distributed, but normality was obtained after logarithmic transformation. Natural logarithms were therefore used for all statistical analyses. t Tests and z scoring were performed as described in standard textbooks.

RESULTS

Twin series. The relationships between the Lewis blood groups and the vWf:Ag and VIII:Ag concentrations are shown in Tables 1 and 2. Many anti-Le6 sera give weak and unreliable results with red cells of ABO groups other than O and A1, while there are no problems of this kind when testing for Lea. Therefore, the material was divided into one group having and one group lacking the Lea antigen on their erythrocytes. A significantly higher concentration of vWf:Ag and VIII:Ag was found in Le(a+) compared with Le(a−) persons belonging to blood group O. There was no difference in the vWf:Ag and VIII:Ag concentrations of group A, Le(a+) and Le(a−) persons. The number of persons with ABO group other than O and A1 was too small for statistical analysis. A difference in vWf:Ag and VIII:Ag concentration between Le(a+) and Le(a−) persons was not found when all ABO blood groups were examined.

A positive correlation between age and concentration of vWF and F VIII has been shown in many studies, and was confirmed in this material. The relationship between Lewis blood group and vWf:Ag and VIII:Ag concentration was therefore also examined on values for vWf:Ag and VIII:Ag that had been corrected for age effect by z transformation as described previously. The same results were obtained as for the uncorrected values (results not shown).

Blood donor series. In order to study the effect of the relatively infrequent le/le genotype and to evaluate the relative importance of the Lewis and the ABH secretor loci for the vWf:Ag concentration, blood samples were collected from nearly the same number of blood donors of all three Lewis phenotypes. The donors were all of blood group O. This selection was made to rule out the possibility of any erroneous results of the Leb typing. No difference in vWf:Ag concentration was found between Le(a−b−) and Le(a−b+) individuals (Table 3). The higher concentration in persons with the Lea antigen found in the twin series was also observed in the blood donors (P = .034).

DISCUSSION

We have previously shown that the ABO locus is a major locus for the determination of plasma vWf:Ag concentration. In the present study two independent series also showed an effect of the Lewis groups. The effect was related to the presence or absence of the Lea antigen, with a higher concentration in Le(a+b−) people belonging to blood group O. A lower vWf:Ag concentration was found in the donors compared with the O group twins. However, blood was obtained differently in the two series and therefore they cannot be compared directly. Samples from the blood donors were obtained after ordinary blood donation. This may explain the low mean vWf:Ag concentration in the blood donor series.

The difference between individuals with and without the Lea antigen could be due to an effect of the Lea antigen itself or an effect of the secretor locus. One reason why a direct effect of Lea substance seems unlikely is that people with the Le(a−b+) red cell phenotype nevertheless have the Lea

### Table 1. Plasma Concentration of vWf:Ag(U/dL) in Lewis(a+) and Lewis(a-) Individuals Within Different ABO Blood Groups

<table>
<thead>
<tr>
<th>ABO Blood Group</th>
<th>vWf:Ag</th>
<th>In vWf:Ag</th>
<th>Le (a+b-)</th>
<th>Le (a-b+)</th>
<th>Le (a-b-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean ± SD</td>
<td>(No.)</td>
<td>Median</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>O</td>
<td>125</td>
<td>4.89 ± 0.76</td>
<td>(21)</td>
<td>98</td>
<td>4.60 ± 0.47</td>
</tr>
<tr>
<td>A1</td>
<td>152</td>
<td>5.05 ± 0.69</td>
<td>(6)</td>
<td>111</td>
<td>4.84 ± 0.63</td>
</tr>
<tr>
<td>A2</td>
<td>130</td>
<td>4.91 ± 0.60</td>
<td>(26)</td>
<td>145</td>
<td>5.00 ± 0.57</td>
</tr>
<tr>
<td>B</td>
<td>155</td>
<td>4.80 ± 0.38</td>
<td>(11)</td>
<td>145</td>
<td>4.96 ± 0.42</td>
</tr>
<tr>
<td>A1B</td>
<td>—</td>
<td>—</td>
<td>(0)</td>
<td>145</td>
<td>5.01 ± 0.62</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>4.93 ± 0.65</td>
<td>(64)</td>
<td>118</td>
<td>4.82 ± 0.56</td>
</tr>
</tbody>
</table>

*Test within O blood group: P = .028.

### Table 2. Plasma Concentration of VIII:Ag(U/dL) in Lewis(a+) and Lewis(a-) Individuals Within Different ABO Blood Groups

<table>
<thead>
<tr>
<th>ABO Blood Group</th>
<th>VIII:Ag</th>
<th>In VIII:Ag</th>
<th>Le (a+b-)</th>
<th>Le (a-b+)</th>
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*Test within O blood group: P = .028.
antigen in secretions, although in smaller amounts than Le(a+b-) individuals. The phenotypes Le(a+b-) and Le(a-b+) both require the presence of the Le gene, while the absence of this gene gives the phenotype Le(a-b-). As Le(a-b+) and Le(a-b-) people have similar vWf:Ag concentrations, lower than the average concentration in Le(a+b-) persons, the vWf:Ag concentration is not likely to be determined by the Le gene. A main characteristic of the Le(a+b-) people is that they are all nonsecretors of ABH substance, while all Le(a-b+) and about 80% of the Le(a-b-) persons carry the Se gene.

The mechanism for the effect of the ABO locus on the plasma concentration of the VIII/vWf complex is not known, but could relate to an effect on secretion from the site of synthesis or to an effect on the catabolism of the complex. Blood group A, B, and H oligosaccharide structures have been found in purified VIII/vWf complex preparations. Vascular endothelial cells are the site of synthesis of vWF, and we have previously shown that the effect of the ABO locus is mainly an effect on this part of the VIII/vWf complex, and not in the catabolism of the complex. Blood group A, B, and H oligosaccharide structures have been found in purified VIII/vWf complex preparations.

In a recent paper Gill et al. found an increased number of group O individuals in patients with type I von Willebrand disease. They discussed the possibility that there is a subset of patients with decreased concentration of vWF on the basis of blood group rather than on specific inherited abnormal vWF production. It seems probable that in these patients there will be an increased number of group O secretors since these are the individuals with the lowest plasma concentration of vWF:Ag.

**REFERENCES**


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