Lower Factor VIII Coagulant Activity in Daughters of Subjects With Hemophilia A Compared to Other Obligate Carriers

By Juan Chediak, Margaret C. Telfer, Thiti Jaojaroenkul, and David Green

Studies of factor-VIII-related activities were performed in 62 obligate carriers of hemophilia A, comparing 23 daughters of hemophilic men (paternal carriers) with 39 mothers of hemophilic sons whose fathers were normal by history (maternal carriers). Nineteen of the maternal carriers were mothers of at least 2 hemophiliacs and 20 were mothers of one, but from families whose other close male members were known to be affected. Fifty-three control subjects (age range 1-65, the same as the carriers) were also evaluated for factor VIII coagulant (VIII:C), factor-VIII-related antigen (VIIIR:Ag), and the ratio VIII:C to VIIIR:Ag. As expected, VIII:C was lower and VIIIR:Ag was higher in the carrier group than in control subjects, and the mean of the carrier VIII:C to VIIIR:Ag ratio was about 50% of the mean VIII:C to VIIIR:Ag ratio of the control group (0.47 and 0.97, respectively). Within the carrier group there were statistically significant differences in VIII:C levels; lower values were found in paternal carriers as compared to maternal carriers (p < 0.02). Paternal and maternal carriers had similar mean values of VIIIR:Ag; the differences found in mean VIII:C level between paternal and maternal carriers were reflected in the VIII:C to VIIIR:Ag ratio (p < 0.02). These findings were more pronounced when daughters of severely affected subjects were compared to the mothers of equally severely affected individuals (p < 0.001). No statistically significant differences in VIII:C, VIIIR:Ag, and ratio were found when either paternal or maternal carriers were subclassified according to the severity of hemophilia in their offspring. Similarly, no difference in age, VIII:C, VIIIR:Ag, or the VIII:C to VIIIR:Ag ratio were observed when maternal carriers were subdivided into those who were mothers of more than one hemophilic son and those who were mothers of one hemophilic son and had a family history of this disorder on the maternal side. The difference between paternal and maternal carriers could not be attributed to pubertal status, age of the carrier (although the paternal carrier group was significantly younger than the maternal), or greater number of severe hemophilic families in the paternal group. The lower VIII:C levels in paternal carrier women may indicate dominance of the father's affected X chromosome during X-chromosome selection in embryogenesis.

Female carriers of classical hemophilia (factor VIII deficiency) have been shown by family studies to have a single sex chromosome (X) carrying the defect and are expected to have approximately half as much coagulant factor VIII activity (VIII:C) as normal females. This is because in each somatic cell of the carrier, one of the X chromosomes will be genetically defective, affecting the biosynthesis of VIII:C. The statistical chance that this defective X chromosome will be the inactive chromosome in any given cell is 50:50—the Lyon hypothesis. However, because the inactivation of the X chromosome is a random event, there results a broad range of VIII:C activity in carrier females. Factor-VIII-related antigen (VIIIR:Ag) levels, on the other hand, are determined by autosomal chromosomes; normal to increased values have been reported in hemophilia A carriers. The mean ratio of VIII:C to VIIIR:Ag in carriers will, therefore, be less than unity and approaches 0.5, while in normal female or male subjects, the mean ratio is close to one.

Detection of female carriers is important, and knowledge of the multiple factors that affect the biosynthesis of VIII:C and VIIIR:Ag is essential. Factor VIII:C and VIIIR:Ag levels range from 50% to 150% in normal subjects. Both values are elevated in response to stress, exercise, pregnancy, and hyperthyroidism. Certain drugs also affect the levels of VIII:C and VIIIR:Ag in normal or mildly affected subjects with hemophilia or von Willebrand disease. There has been a suggestion that factor VIII:C changes with age; however, in other reports, age was not found to have a significant effect on factor VIII:C. Although there is some overlap between carriers and normals, measurements of VIII:C, VIIIR:Ag, and the ratio have been shown to be useful parameters in carrier detection. Carriers have been classified as obligate or possible carriers considering the family pedigree. Furthermore, female carriers may inherit their genetically defective X chromosome either from hemophilic fathers (daughters of patients with hemophilia A or paternal carriers) or from carrier mothers (maternal carriers). Other studies of carrier detection have not considered the type of inheritance of the abnormal X chromosome; therefore, in this investigation, we have attempted to ascertain whether the levels of VIII:C, VIIIR:Ag, and the ratio VIII:C to VIIIR:Ag are different in paternal as compared to maternal carriers.
FACTOR VIII IN HEMOPHILIA A CARRIERS

MATERIALS AND METHODS

Carrier Group

Obligate carriers of hemophilia A were studied once the genetic information of a particular subject was obtained and her pedigree evaluated. The severity of the hemophilia A was established by measuring factor VIII:C in the affected male relative of the subject to be studied. Other information obtained included the age of the carriers, child-bearing status, and bleeding history. Sixty-two obligate carriers of hemophilia A were analyzed, comparing 23 daughters of hemophilic men (paternal carriers) with 39 mothers of hemophilic sons whose fathers were normal by history (maternal carriers). Nineteen of the maternal carriers were mothers of at least two hemophiliacs and 20 were mothers of one but from families whose other members were known to be affected. Data from obligate carriers who were pregnant or in the immediate postpartum period were not utilized for this analysis. If the daughter of a hemophilic subject was at the same time the mother of one or more hemophilic sons, she was included in the paternal carrier group. Four of the 23 paternal carriers were in this category. No carrier was taking oral contraceptives or suffering from acute or chronic illness, including thyroid disease.

Control Group

Fifty-three healthy females from 1 to 65 yr of age, who were not taking oral contraceptives or other medications, constituted the normal control group. Their past history and family history were negative for bleeding disorders. None of them were pregnant or suffering from acute or chronic illness at the time of this study.

Blood Collection

Venous blood from the carrier and control groups was obtained by venipuncture with a 19-gauge scalp vein needle without a tourniquet, using the 2-syringe technique. The blood was collected in a plastic syringe and immediately mixed with 3.8% sodium citrate in a ratio of 9:1 (blood to citrate). The blood was then centrifuged at 4000 rpm, 4°C, for 15 min to obtain platelet-poor plasma (PPP). The plasma was tested immediately for VIII:C activity, and a portion quick-frozen for subsequent determination for factor VIII:Ag concentration.

Methods

The activated partial thromboplastin time (APTT) was done as previously described. The determination of VIII:C was done by the one-stage APTT, using at least 3 dilutions of the patient's plasma, as described.15 The two-stage method was also used to measure VIII:C in 12 carriers; values were similar to those obtained with the one-stage method. Factor VIII:Ag was measured within 30 days of blood collection, using the Laurell "rocket" immunoelectrophoresis method as previously described. All determinations were done in duplicate.

Statistical Methods

The initial analysis included comparisons of VIII:C, VIII:Ag, and VIII:C to VIII:Ag ratio among control, paternal, and maternal groups, using standard statistical methods.17 A second step was then implemented, which consisted of classifying paternal and maternal carriers according to the severity of the hemophilia of their fathers or sons, respectively. A hemophiliac was considered mild if the plasma concentration of factor VIII:C was over 3%-4%, whereas the hemophilia was severe if the percentage was less than 1%-2%. This laboratory classification correlated with the degree of clinical severity. Correlation coefficients (r) were calculated using standard formulas.18 Simple linear regression plotting VIII:C, VIII:Ag, and VIII:C to VIII:Ag ratio with age was done in the control, paternal, and maternal carrier groups using the SPSS package on a Perkin-Elmer Interdata Computer (Oceanport, N.J.). The following formula was applied: Factor VIII:C = A + B age + ϵ, where A is the intercept (distance above or below the origin of coordinates); B is the slope of the line; and ϵ is the error. Similar formulas were used for VIII:Ag and ratio. The number of outliers for each determination was then examined as well as the presence or absence of skewness. A nonparametrical test (rank sum test) was performed according to the method of Wilcoxon.

RESULTS

Control Group

Fifty-three female subjects, aged from 1 to 65 (mean 38 yr), were considered in this group. Mean VIII:C levels were 104% ± 5.2% (SEM); mean VIII:Ag was 119% ± 7.5%. Factor VIII:C levels in the control group ranged from 50% to 195%, whereas factor VIII:Ag ranged from 43% to 270%. The factor VIII:C to VIII:Ag ratio ranged from 0.40 to 1.88, with a mean value of 0.97 ± 0.05. A comparison of 8 prepubertal controls (whose ages ranged from 1 to 11 yr) with 45 postpubertal women revealed no significant differences in factor VIII:C, factor VIII:Ag, or the VIII:C to VIII:Ag ratio (Table I).

Obligate Carriers

Sixty-two obligate carriers of hemophilia A were studied. Their ages ranged from 1 to 83 yr with a mean age of 36 yr. The levels of VIII:C were lower than normal, averaging 56% ± 3.1% (SEM), with a range of 14%-128%. On the other hand, VIII:Ag levels were higher than those of the control subjects, averaging 136% ± 8.3%, with a range of 50%-330%. The ratio of VIII:C to VIII:Ag ranged widely in the carrier group from 0.13 to 1.5. As expected, mean values of the ratio of factor VIII:C to VIII:Ag of carriers were significantly lower than in the control (0.47 and 0.97, respectively). Twenty-three obligate carriers were daughters of hemophilic men, whereas 39 were maternal carriers (fathers of these carriers were normal by history and we assumed that the inheritance of the abnormal X chromosome came from the maternal side). Four of the 23 paternal carriers were also mothers of hemophilic patients, but they were considered only in the paternal subgroup. Equal numbers of maternal carriers were seen when they were classified as those with one hemophilic son and a positive family history of a close male relative and those who were mothers of more than two hemophilic sons. Significant differences in the mean age of the paternal carrier subgroup was found when compared to the maternal carrier subgroup. As expected, the
Table 1. Mean Values and Standard Error of the Mean (SEM) for Age, Factor VIII Coagulant (VIII:C), Factor VIII-Related Antigen (VIIIR:Ag), and the VIII:C to VIILR:Ag Ratio in Control and Obligate Carriers. In Parentheses are the Range Values.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age (yr) ± SEM</th>
<th>VIII:C (%) ± SEM</th>
<th>VIIIR:Ag (%) ± SEM</th>
<th>Ratio ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>53</td>
<td>28 ± 1.9</td>
<td>104 ± 5.2</td>
<td>119 ± 7.5</td>
<td>0.97 ± 0.05</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>8</td>
<td>6.3 ± 1.5</td>
<td>117.6 ± 16.4</td>
<td>141.5 ± 18.2</td>
<td>0.86 ± 0.11</td>
</tr>
<tr>
<td>Postpubertal</td>
<td>45</td>
<td>31.8 ± 1.7</td>
<td>101.1 ± 5.5</td>
<td>115.6 ± 8.2</td>
<td>0.98 ± 0.05</td>
</tr>
<tr>
<td>Obligate carriers</td>
<td>62</td>
<td>36 ± 2.3</td>
<td>56 ± 3.1</td>
<td>136 ± 8.3</td>
<td>0.47 ± 0.03</td>
</tr>
<tr>
<td>Paternal</td>
<td>23</td>
<td>18 ± 2.6</td>
<td>41.5 ± 3.3</td>
<td>131.6 ± 14.9</td>
<td>0.36 ± 0.003</td>
</tr>
<tr>
<td>Maternal</td>
<td>39</td>
<td>46 ± 2.1</td>
<td>64.1 ± 3.9</td>
<td>140.5 ± 9.8</td>
<td>0.53 ± 0.04</td>
</tr>
</tbody>
</table>

*Range values.
†Significant differences between paternal and maternal carriers (p < 0.02).

The effect of pubertal status was analyzed in the

paternal subgroup was younger (mean age 18 yr) than the maternal subgroup (mean age 46 yr). A significant difference in factor VIII:C levels was found between those carriers who inherited the abnormal X chromosome from their fathers and those who presumably inherited it from their mothers. The daughter subgroup had lower levels of VIII:C than the maternal subgroup. This difference was significant at a p value of <0.02. Calculated mean values for paternal and maternal carriers were 41 ± 3.3 (SEM) and 64 ± 3.9 (SEM), respectively. Both subgroups had similar VIIIR:Ag values. The differences in VIII:C were reflected in the VIII:C to VIIIR:Ag ratio in the two subgroups (p < 0.02) (Table 1).

Paternal and maternal carriers were then subdivided according to the severity of hemophilia in their fathers and sons, respectively. Equal percentages of severely affected individuals were found in each group: 74% of paternal carriers were daughters of severely affected individuals and 72% of maternal carriers were mothers of severely affected hemophiliacs (Table 2). Again, statistically significant differences for VIII:C and the ratio of VIII:C to VIIIR:Ag were found when carriers of the severe subgroup were compared; no such differences were noted for VIIIR:Ag. The factor VIII:C of daughters of severely affected hemophiliacs had a mean value of 39 ± 3 (SEM), whereas the mean value of VIII:C of mothers of severely affected hemophiliacs was 66 ± 4 (SEM) (p < 0.001). This difference was also reflected in the ratio, which was 0.33 ± 0.02 for paternal carriers and 0.60 ± 0.06 for maternal carriers (p < 0.001). The numbers of carriers whose relatives have mild hemophilia in either group was too small to allow us to make comparisons between paternal and maternal carriers of milder condition or to compare carriers of severe and mild hemophilia in the maternal or paternal groups.

The 39 maternal carriers could be subdivided into two subgroups: 19 carriers were the mothers of more than one hemophilic son, and 20 carriers were mothers of one hemophilic son with a positive family history of this condition in either a brother, a nephew, or an uncle. No significant differences were found in means for age, VIII:C, VIIIR:Ag, and the VIII:C to VIIIR:Ag ratio between these two subgroups (Table 3). The low number of carriers who were mothers of more than one severely affected hemophilic son did not allow us to subclassify those with from those without a family history of hemophilia.

The effect of pubertal status was analyzed in the
paternal carrier group as was done in the control group. Twelve daughters of hemophiliacs were under the age of 15, with a mean age of 7.8 ± 1.3 (SEM), whereas 11 daughters were over the age of 17, with a mean age of 29.3 ± 2.3 (SEM). Mean VIII:C values were 40 ± 4.8 (SEM) and 43 ± 4.6 for the prepubertal and postpubertal individuals, respectively (p > 0.1). Mean values for VIIIR:Ag also showed insignificant differences, and the range of values in both groups was similar. Lastly, no statistically significant differences were observed for the ratio in prepubertal versus postpubertal paternal carrier subgroups (Table 4).

Correlation coefficients (r) were then calculated in order to assess the influence of age in factor VIII:C and VIIIR:Ag determinations in the controls (group 1), paternal (group 2), and maternal (group 3) carriers. With the possible exception of VIIIR:Ag in group 2, where a p value of 0.03 was calculated, age did not significantly influence VIII:C, VIIIR:Ag, or the ratio of VIII:C to VIIIR:Ag in any of the groups (Table 5).

An additional analysis of the effect of age on VIII:C, VIIIR:Ag, and ratio in the 3 groups was performed using simple linear regression with the formula described in Materials and Methods. The results showed that age had no significant impact (0.1 < p < 0.05) on the amount of factor VIII:C, VIIIR:Ag, and VIII:C to VIIIR:Ag ratio in control subjects or in the carrier groups.

There were two outliers for age in the maternal group and none in the other two groups (control and paternal). There were three outliers for VIII:C, one in the paternal group and two in the maternal; factor VIIIR:Ag had three outliers, one in the control group and two in the paternal carriers; finally, VIII:C to VIIIR:Ag ratio showed the presence of four outliers, two each in the paternal and maternal carrier groups. All these outliers reach significant p values of <0.05.

The presence of skewness was also investigated; it showed that values for VIII:C, VIIIR:Ag, and ratio in the three groups were skewed to the right (positive) but did not reach significant levels.

Because of the presence of outliers and the finding of a positive skewness in the carrier group, a nonparametrical test was performed according to the method of Wilcoxon; the level of significance using this formula was 0.0003 for VIII:C, 0.37 for VIIIR:Ag, and 0.0085 for VIII:C to VIIIR:Ag ratio. These results indicate again that there were significant differences in factor VIII:C between maternal and paternal carrier group, but there were no significant differences in VIIIR:Ag. Furthermore, the differences

Table 3. Mean and SEM Values for Age, Factor VIII Coagulant (VIII:C), Factor VIII-Related Antigen (VIIIR:Ag), and the VIII:C to VIIIR:Ag Ratio in Two Subgroups of Maternal Carriers

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age</th>
<th>VIII:C (%)</th>
<th>VIIIR:Ag (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal carriers</td>
<td>39</td>
<td>46 ± 2.1</td>
<td>64.1 ± 2.9</td>
<td>140.5 ± 9.8</td>
<td>0.53 ± 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(21-83)*</td>
<td>(21-128)</td>
<td>(55-275)</td>
<td>(0.13-1.5)</td>
</tr>
<tr>
<td>Mothers of more</td>
<td>19</td>
<td>46.5 ± 2.5</td>
<td>67.7 ± 6.5</td>
<td>142.5 ± 14.4</td>
<td>0.56 ± 0.07</td>
</tr>
<tr>
<td>than one hemophilic son</td>
<td></td>
<td>(32-75)</td>
<td>(21-128)</td>
<td>(60-254)</td>
<td>(0.14-1.5)</td>
</tr>
<tr>
<td>Mothers of one</td>
<td>20</td>
<td>44.75 ± 3.31</td>
<td>60.7 ± 4.64</td>
<td>138.65 ± 13.88</td>
<td>0.50 ± 0.04</td>
</tr>
<tr>
<td>hemophilic son and</td>
<td></td>
<td>(21-83)</td>
<td>(38-119)</td>
<td>(55-275)</td>
<td>(0.13-0.99)</td>
</tr>
<tr>
<td>positive family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of hemophilia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significance NS NS NS NS NS

*NS, not significant.

Range values.

Table 4. Mean Values and Standard Error of the Mean (SEM) for Age, Factor VIII Coagulant (VIII:C), Factor VIII-Related Antigen (VIIIR:Ag), and the Factor VIII:C to VIIIR:Ag Ratio in Paternal Carriers According to Pubertal Status

<table>
<thead>
<tr>
<th>Pubertal status</th>
<th>No.</th>
<th>Age (yr)</th>
<th>VIII:C (%)</th>
<th>VIIIR:Ag (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paternal carriers</td>
<td>23</td>
<td>18 ± 1.6</td>
<td>41.5 ± 3.3</td>
<td>131.6 ± 14.9</td>
<td>0.36 ± 0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1-45)*</td>
<td>(14-75)</td>
<td>(50-330)</td>
<td>(0.15-0.75)</td>
</tr>
<tr>
<td>Pubertal status</td>
<td>12</td>
<td>7.8 ± 1.3</td>
<td>40.1 ± 4.8</td>
<td>113.4 ± 10.2</td>
<td>0.39 ± 0.04</td>
</tr>
<tr>
<td>Prepubertal</td>
<td></td>
<td>(1-15)</td>
<td>(14-75)</td>
<td>(50-300)</td>
<td>(0.16-0.75)</td>
</tr>
<tr>
<td>Postpubertal</td>
<td>11</td>
<td>29.3 ± 2.3</td>
<td>42.9 ± 4.6</td>
<td>151.5 ± 21.4</td>
<td>0.32 ± 0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(17-45)</td>
<td>(24-72)</td>
<td>(69-330)</td>
<td>(0.16-0.64)</td>
</tr>
</tbody>
</table>

Significance S NS NS NS NS

S, significant; NS, not significant.

*Range.
in VIII:C were also reflected in the ratio but to a lesser degree.

**DISCUSSION**

The major finding of this study is that paternal carriers of hemophilia A have significantly lower levels of VIII:C than maternal carriers. This difference was more evident when daughters of severely affected hemophiliacs were compared to mothers of equally severely affected subjects.

Factors that are known to influence the biosynthesis of VIII:C and VIIIR:Ag, such as exercise, adrenergic stimulators, hyperthyroidism, oral contraceptives, renal and liver disease, carcinomatosis, and pregnancy, were excluded in subjects of our study. In addition, since VIII:C and VIIIR:Ag vary within a broad range in a normal population, we closely followed ideal conditions for a reproducible determination.

There is incomplete agreement in published reports on the influence of age on factor VIII activities in normal and in carrier subjects. Nilsson et al. studied 30 normal female subjects and found mean VIII:C levels to be higher than normal. Younger controls were not studied and no mention of drug history was given. Preston and Barr studied 178 normal female subjects followed ideal conditions for a reproducible determination.

Several statistical methods were applied in order to assess the influence of age in VIII:C, VIIIR:Ag, and ratio in the three groups of subjects. Simple linear regression was negative for such influence in both groups; additionally, nonparametric tests showed that age did not affect the results of VIII:C, VIIIR:Ag, or ratio in controls nor in the carrier group. The last type of analysis eliminates the influence of outliers or skewness. It is of great interest that the significant differences in VIII:C and in the ratio between paternal and maternal carriers were enhanced by the exclusion of carriers of mild disease or daughters of carriers who were only mildly affected (Table 2).

An explanation for the reduced VIII:C of paternal carriers might be that the X chromosome from a severe hemophilic subject is responsible for the production of less VIII:C than the X chromosome from a milder hemophilic, and that more of our patients were daughters of hemophiliacs from severely affected families. We found, however, that the percentage of our
maternal carriers who were from severely affected families was the same as that in paternal carriers (72% and 74%, respectively).

An alternative explanation for the higher mean VIII:C values of maternal carriers is that some of these women might not really be carriers, but have had mutations leading to the birth of more than one hemophilic son. This is unlikely but possible in a minimal number of the maternal carriers with no other relatives with hemophilia, i.e., mothers of two hemophilic sons. This type of carrier could have received the gene from a single mutated ovum, in which case her mother would not be a carrier, or she could have received a single mutated sperm from her father, although he is not hemophilic. Unfortunately, the number of carriers who are mothers of two hemophilic sons with a negative family history are too small to compare with mothers of more than one hemophilic son with a positive history of hemophilia. A mutation could be manifested in maternal carriers who are mothers of one hemophilic son with a positive history of hemophilia in a close male relative. However, when maternal carriers were further subdivided into those with more than one hemophilic son versus those with one hemophilic son and a positive family history, there were no significant differences in the mean age, VIII:C, VIIIR:Ag, and ratio.

Careful scrutiny of our data reveals that the VIII:C levels in our obligate carriers conform to the values anticipated according to the Lyon hypothesis of random inactivation of the X chromosome, i.e., mean VIII:C levels approximate half those of normal women (56% and 104% in the carrier and control groups, respectively). However, paternal carriers, especially daughters of severely affected individuals, had levels of VIII:C lower than the mean value of 50% predicted by the Lyon hypothesis, whereas maternal carriers had higher values.

Biggs and Rizza, in an earlier study, made a similar observation, but did not comment on its significance. Other reports of carrier detection did not subclassify obligate carriers. Of interest is a study by Eyster et al. of two families of carriers with low levels of VIII:C. There were four paternal and six maternal carriers. The mean values of VIII:C were markedly different in these two subgroups being 27% for paternal carriers and 76% for maternal carriers. Furthermore, the mean values of the ratio VIII:C to VIIIR:Ag in paternal and maternal carriers in the Eyster group were similar to values observed in our study.

A last possibility is that there is an unbalanced lyonization in the paternal carriers, with the father’s X chromosome having favored status at the expense of the normal maternal X chromosome. This would result in fewer cells capable of producing VIII:C and explain the lower values for VIII:C in the paternal carriers. Support for this hypothesis will come if it is discovered that a selective advantage of the paternally derived X chromosome occurs not only in hemophilia but in other X-linked disorders as well.

ACKNOWLEDGMENT

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