G20210A Mutation in the Prothrombin Gene and the Risk of Recurrent Venous Thromboembolism

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OBJECTIVES

The study was done to determine whether the G20210A mutation in the prothrombin gene increases the risk of recurrent venous thromboembolism (VTE), both alone and in combination with factor V Leiden.

BACKGROUND

Several inherited defects of coagulation are associated with increased risk of first VTE, including a recently identified G20210A mutation in the prothrombin gene. However, whether the presence of this mutation confers an increased risk of recurrent venous thromboembolism is controversial.

METHODS

A total of 218 men with incident venous thromboembolism were genotyped for the prothrombin mutation and for factor V Leiden and were followed prospectively for recurrent VTE over a follow-up period of 7.3 years.

RESULTS

A total of 29 men (13.3%) suffered recurrent VTE. Five of the 14 carriers of the prothrombin mutation developed recurrent VTE (35.7%; incidence rate \( \frac{8.70}{100 \text{ person-years}} \)), while 24 of 204 individuals who did not carry the prothrombin mutation developed recurrent VTE (11.8%; incidence rate \( \frac{1.76}{100 \text{ person-years}} \)). Thus, presence of the G20210A mutation was associated with an approximate fivefold increased risk for recurrent VTE (crude relative risk [RR] 4.93; 95% confidence interval [CI] 1.9–12.9; \( p = 0.001 \)); age-, smoking-, and body mass index-adjusted RR 5.28; 95% CI 2.0–14.0; \( p = 0.001 \)). In these data, recurrence rates were similar among those with an isolated mutation in the prothrombin gene (18.2%) as compared to those with an isolated factor V Leiden mutation (19.2%). However, all three study participants who carried both mutations (100%) suffered a recurrent event during follow-up.

CONCLUSIONS

In a prospective evaluation of 218 men, the presence of prothrombin mutation was associated with a significantly increased risk of recurrent VTE, particularly among those who co-inherited factor V Leiden. (J Am Coll Cardiol 2001;37:215–8) © 2001 by the American College of Cardiology

Individuals with inherited defects of coagulation are at increased risk for deep venous thrombosis and pulmonary embolism. In particular, carriers of either a G20210A mutation in the prothrombin gene (1–4) or the factor V Leiden mutation (5–8) have an increased lifelong risk of first venous thrombosis compared to unaffected individuals. However, whether genetic carriers of these defects are at significantly increased risk for recurrent venous thromboembolism (VTE), and thus might benefit from lifelong anticoagulation, is controversial. For example, while some prospective studies report a significantly increased risk of recurrent VTE among carriers of factor V Leiden (9,10), other studies suggest these risks may be small and limited to individuals with multiple inherited and/or acquired defects of hemostasis (11,12).

With respect to the prothrombin mutation, data concerning the risk of recurrent VTE are scant and inconsistent. For example, although two prospective studies have shown no increase in the risk of recurrent VTE in association with the prothrombin mutation (12,13), De Stefano and colleagues have recently demonstrated in a retrospective study that the rate of recurrent VTE among carriers of the prothrombin mutation was increased only among those who also were carriers of factor V Leiden (14). Thus, whether an isolated mutation in the prothrombin gene increases the risk of recurrent venous thromboembolism remains unclear. To provide further data on this issue, we evaluated the role of the G20210A mutation as a potential risk factor for recurrent venous thromboembolism among a cohort of 218 men followed over an average period of 7.3 years.

METHODS

Study subjects included 218 participants in the Physicians’ Health Study (PHS) who had a documented VTE and were then followed for recurrent thromboembolic events. As
prothrombin mutation, 29 (13.3%) were carriers of factor V Leiden, and 3 (1.4%) were carriers of both mutations. No patients were homozygous for either the prothrombin mutation or factor V Leiden. Overall, 29 participants (13.3%) developed recurrent VTE over a mean follow-up period of 7.3 years.

As shown in Table 1, (35.7%) of the 14 study participants heterozygous for the prothrombin mutation developed recurrent VTE (incidence rate = 8.70 per 100 person-years), whereas 24 (11.8%) of the 204 individuals who did not carry the mutation developed a recurrent event (incidence rate = 1.76 per 100 person-years). Thus, the RR for recurrent VTE associated with the prothrombin mutation was 4.93 (95% confidence interval [CI] 1.9–12.9; p = 0.001); in multivariate analyses controlling for age, smoking and BMI, the adjusted RR was 5.28 (95% CI 2.0–14.0; p = 0.001).

Among individuals in whom the initial VTE was classified as idiopathic, 4 of the 7 carriers of the prothrombin mutation developed a recurrent event (57.1%, incidence rate = 12.79 per 100 person-years), as compared to 17 of the 94 without the prothrombin mutation (18.1%; incidence rate = 2.44 per 100 person-years) (Table 2). Thus, the RR for recurrent VTE in this subgroup (5.24; 95% CI 1.8–15.6; p = 0.003) was similar to that observed in the cohort as a whole.

The effects of isolated versus combined mutation on rates of recurrent VTE are shown in Figure 1. As displayed, of the 178 study participants who carried VTE and the date of death. No participants were lost to follow-up.

Incidence rates of recurrent VTE for patients with and without the prothrombin mutation were computed as the number of recurrent events divided by the total exposure time for each group. The relative risk (RR) of recurrent VTE associated with mutation was computed as the ratio of the incidence rate among genetically affected men divided by the incidence rate among those unaffected. Adjusted estimates of risk were computed by use of Poisson regression models that controlled for age, smoking habit, and body mass index (BMI). All probability values are two-sided.

**RESULTS**

Of the 218 study participants, the first episode of venous thromboembolism was classified as idiopathic in 101 (46%). Fourteen of the 218 participants (6.4%) were carriers of the prothrombin mutation, 29 (13.3%) were carriers of factor V Leiden, and 3 (1.4%) were carriers of both mutations. No patients were homozygous for either the prothrombin mutation or factor V Leiden. Overall, 29 participants (13.3%) developed recurrent VTE over a mean follow-up period of 7.3 years.

**Table 1.** Incidence Rates of Recurrent Venous Thromboembolism Among 218 Men According to Presence or Absence of the G20210A Mutation in the Prothrombin Gene

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>N</th>
<th>Recurrent Events, n (%)</th>
<th>Person Time (years)</th>
<th>Incidence Rate*</th>
<th>Incidence Rate Ratio (Crude)</th>
<th>p Value</th>
<th>Incidence Rate Ratio (Adjusted)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>218</td>
<td>29 (13.3)</td>
<td>1418.3</td>
<td>2.04</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PT present</td>
<td>14</td>
<td>5 (35.7)</td>
<td>57.5</td>
<td>8.70</td>
<td>4.93</td>
<td>0.001</td>
<td>5.28</td>
<td>0.001</td>
</tr>
<tr>
<td>PT absent</td>
<td>204</td>
<td>24 (11.8)</td>
<td>1360.8</td>
<td>1.76</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
</tbody>
</table>

*Incidence rates calculated per 100 person-years of exposure. Incidence Rate Ratios derive from a comparison of the incidence rate among those with the prothrombin mutation to those without mutation (referent group). Variables included in adjusted analyses are age at index event, body mass index and smoking habit (past, current, never). PT = prothrombin mutation.
neither the prothrombin mutation nor factor V Leiden, 19 (10.7%) suffered a recurrent event. By contrast, recurrent VTE occurred among 2 (18.2%) of the 11 participants with isolated prothrombin mutation, 5 of 26 (19.2%) with isolated factor V Leiden mutation, and 3 of 3 participants heterozygous for both mutations (100%). Similar effects were observed in the subgroup of those who initially presented with idiopathic VTE.

Among the total cohort, the mean time between initial and recurrent VTE was 37.6 months (range 3 to 98 months). Carriers of the prothrombin mutation developed recurrent VTE at a mean time of 30.4 months (range 9 to 98 months) after their initial event, whereas those without the prothrombin mutation developed recurrent VTE at an average of 33.2 months (range 3 to 87 months). The times between initial and recurrent VTE for the three participants who carried both the prothrombin mutation and factor V Leiden were 12, 21, and 98 months, respectively. Of the three participants who suffered more than one recurrent event during follow-up, one carried the prothrombin mutation.

DISCUSSION

In this prospective study of 218 men with a first episode of VTE, carriers of the G20210A mutation in the prothrombin gene were at significantly increased risk for recurrent thromboembolic events. Specifically, over a mean follow-up period of 7.3 years, the recurrence rate was 35.7% among carriers of the prothrombin mutation as compared to 11.8% among unaffected individuals (RR = 4.97; p = 0.001). In these data, the highest recurrence rates were observed among those with both the prothrombin mutation and factor V Leiden (100%), intermediate rates were observed among those with isolated mutations (18% to 20%), and the lowest rates were observed among genetically unaffected individuals (10%). Similar findings were present in the subgroup of study participants in whom the index VTE was classified as idiopathic. In the present study, virtually all events occurred after cessation of oral anticoagulant therapy.

Co-inheritance of coagulation defects. Prior prospective studies have not reported an increase in risk of recurrent VTE among carriers of the prothrombin mutation (12,13). However, these studies were limited to follow-up periods between 24 and 48 months. By contrast, mean follow-up in our study was 7.3 years. Thus, we believe our data provide important long-term evidence regarding the role of inherited hypercoagulability in the pathogenesis of VTE. In addition, the current prospective data provide further evidence that co-inheritance of multiple hypercoagulable defects results in significantly increased risks of recurrent venous thromboembolism, corroborating recent retrospective findings among carriers of both the prothrombin mutation and factor V Leiden (14,16). As such, the current data additionally extend prior work describing gene-gene and gene-environment interactions (17) between several defects of anticoagulation including hyperhomocysteinemia.

Table 2. Incidence Rates of Recurrent Venous Thromboembolism Among the Subgroup of Men With an Initially Idiopathic Event, According to Presence or Absence of the G20210A Mutation in the Prothrombin Gene

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>N</th>
<th>Recurrent Events, n (%)</th>
<th>Person Time (years)</th>
<th>Incidence Rate*</th>
<th>Incidence Rate Ratio (Crude)</th>
<th>p Value</th>
<th>Incidence Rate Ratio (Adjusted)*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>101</td>
<td>21 (20.8)</td>
<td>728.2</td>
<td>2.88</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PT present</td>
<td>7</td>
<td>4 (57.1)</td>
<td>31.3</td>
<td>12.79</td>
<td>5.24</td>
<td>0.003</td>
<td>5.74</td>
<td>0.002</td>
</tr>
<tr>
<td>PT absent</td>
<td>94</td>
<td>17 (18.1)</td>
<td>696.9</td>
<td>2.44</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
</tbody>
</table>

PT = prothrombin mutation.

*Incidence rates calculated per 100 person-years of exposure. Incidence Rate Ratios derive from a comparison of the incidence rate among those with the prothrombin mutation to those without mutation (referent group). Variables included in adjusted analyses are age at index event, body mass index and smoking habit (past, current, never).

Figure 1. Rates of recurrent venous thromboembolism (VTE) based on the presence or absence of the prothrombin and factor V Leiden mutations.
(18) and relative deficiencies of protein C, protein S, and anti-thrombin III (2).

Clinical implications. From a clinical perspective, the increase in risk of recurrent thromboembolic events associated with the prothrombin mutation has several implications. On the one hand, randomized clinical trials demonstrate that, among individuals with a first thromboembolic event, anticoagulation with full-dose warfarin for a period of six months reduces the rate of recurrent VTE compared to regimens of three months or less (19). Similarly, “indefinite” therapy with full-dose warfarin has shown efficacy among those with idiopathic events (20) and among those with a history of multiple prior episodes of thrombosis (21). Thus, on the basis of these data, one might hypothesize that genetically susceptible individuals should be targeted for more aggressive anticoagulation regimens.

On the other hand, conflicting reports for both the prothrombin mutation (12,13) and factor V Leiden (9–12) indicate that there is no current consensus that genetically affected individuals are necessarily at levels of risk high enough to warrant such an approach. This issue is of particular importance because studies of full-dose warfarin have consistently demonstrated increased risks of hemorrhage such that the net benefit-to-risk ratio for lifelong anticoagulation remains uncertain, even among the highest-risk subgroups.

Need for clinical trials. Given this situation, whether or not genetically affected individuals require more prolonged anticoagulation to prevent recurrent VTE is unknown. Thus, in this context, we believe the current data strongly support the need for aggressive enrollment of both genetically affected and unaffected patients into ongoing clinical trials designed to evaluate directly the net benefit-to-risk ratio associated with long-term anticoagulation (22). Optimal such trials should include consideration of low-dose warfarin regimens, such as the target international normalized ratio range of 1.5 to 2.0 currently being tested in the Prevention of Recurrent Venous Thromboembolism Trial (PREVENT), an ongoing federally funded project enrolling VTE patients with and without genetic determinants of hypercoagulability (23).

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REFERENCES