Thrombophilia or thrombophobia
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2001

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Meinardi, J. R. (2001). Thrombophilia or thrombophobia: clinical implications of recently identified thrombophilic disorders s.n.

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CHAPTER 3

THE INCIDENCE OF VENOUS THROMBOEMBOLISM IN RELATIVES OF PATIENTS WITH THE PROTHROMBIN 20210A MUTATION

- an interim analysis -

Saskia Middeldorp, Johan R. Meinardi, Maria M.W. Koopman, Jan van der Meer, Elisabeth C.M. van Pampus, Karly Hamulyák, Martin H. Prins, and Harry R. Büller
SUMMARY

**Background:** The prothrombin 20210A mutation is a genetic defect associated with elevated levels of prothrombin and an increased risk for venous thromboembolism. When the absolute incidence of venous thromboembolism in relatives of patients known to have the mutation outweighs the disadvantages of prophylactic strategies, family screening may be necessary.

**Methods:** To determine the incidence of venous thromboembolism in carriers of the prothrombin 20210A mutation, we retrospectively studied 155 first-degree relatives of 42 heterozygous symptomatic carriers of the prothrombin 20210A mutation. Before DNA testing, information on previous venous thromboembolism and concomitant risk factors was obtained. Relatives with and without prothrombin 20210A mutation were compared.

**Results:** The annual incidence of thromboembolism in relatives of heterozygous propositi was 0.40% (95% CI 0.18-0.75) in those with the mutation and 0.28% (95% CI 0.10-0.60) in those without the mutation (relative risk, 1.4 [95% CI 0.5-4.0]).

**Conclusions:** This interim analysis was limited by the small number of observation years and exposures to exogenous risk factors that could be studied. The absolute incidence of venous thromboembolism in carriers of the prothrombin 20210A mutation seems to be comparable to that found in carriers of the factor V Leiden mutation. However, more families need to be included and the findings should be validated in prospective cohort studies.
3.1 INTRODUCTION

In recent years, relatively common genetic abnormalities leading toward a tendency for developing venous thromboembolism have been identified. Until 1994, only isolated deficiencies of physiologic inhibitors of the coagulation system, such as antithrombin, protein C, and protein S, were known as established hereditary risk factors and could be detected in about 8% of consecutive patients with documented venous thromboembolism [1]. In 1993, resistance to activated protein C, most often caused by the FV:Q^506 or factor V Leiden mutation, was shown to be a prevalent risk factor for venous thromboembolism [2-4]. In 1996, the prothrombin 20210A mutation was found to be associated with elevated plasma concentrations of prothrombin, as well as an increased risk for venous thromboembolism [5]. The prevalence of this mutation in consecutive patients with venous thromboembolism is approximately 5% [5-7], and in selected patients this may be as high as 18% [5]. The geographic distribution of the prothrombin 20210A mutation varies, with a prevalence of about 1-2% in European populations, and much lower in individuals of Asian or African descent [8, 9]. The relative risk for venous thromboembolism in heterozygous carriers of the prothrombin 20210A mutation compared with healthy controls is approximately 3 [5, 6, 10].

Because of the autosomal dominant inheritance pattern of the prothrombin 20210A allele, half of the relatives of each patient who has thrombosis and the mutation will carry the same defect. Therefore, in clinical practice, the question arises whether families of patients known to have the prothrombin 20210A mutation should be actively screened for the presence of the mutation in order to consider instituting prophylactic anticoagulant strategies, either permanently or during high-risk situations. Disadvantages of screening include the psychological stress induced among carriers, the risks associated with the prevention of thrombosis by using anticoagulant medication, and the potential problems with obtaining insurances and social security benefits.

Whether the benefits of screening outweigh the disadvantages depends largely on the absolute risk for venous thromboembolism in carriers of the prothrombin 20210A mutation. This risk needs to be weighed against the known benefits and hazards of anticoagulant prophylaxis. We therefore investigated 155 first-degree relatives of 42 patients seen at our institutions with documented venous thromboembolism and the prothrombin 20210A mutation. From all these relatives, we obtained a medical history with special emphasis on previous episodes of venous thromboembolism and the exposure to risk factors such as surgery, trauma, immobilization, pregnancy and the use of oral contraceptives. We then determined the presence or absence of the prothrombin 20210A mutation and compared the findings in family members who had the mutation with those family members with a normal genotype.
3.2 METHODS

3.2.1 Patients and study design

In the participating centers, all patients with a proven episode of venous thromboembolism are tested for the presence of an underlying coagulation disorder. A total of 42 thrombosis patients with known carriership of the prothrombin 20210A mutation were invited to participate in this project and were considered propositi.

All living first-degree relatives (parents, siblings and children older than 15 years of age), identified through pedigree analysis, formed the study cohort. Each family member was interviewed by one of the investigators using a standardized medical history form. Detailed information was obtained about previous episodes of venous thromboembolism, and exogenous risk factors such as surgical interventions, trauma, periods of immobilization and prophylactic or therapeutic use of anticoagulant drugs. For women, the obstetric history and the use of oral contraceptives were documented. Subsequently, blood was obtained and the prothrombin 20210A mutation status (normal, heterozygous, and homozygous) was determined by using a polymerase chain reaction-based assay, as described previously [11]. The institutional review boards of the participating centers approved the study, and all participants gave informed consent.

3.2.2 Definitions

A previous episode of venous thromboembolism was considered to have occurred, if it had been confirmed by venography, ultrasonography, impedance plethysmography, ventilation-perfusion lung scanning, or pulmonary angiography. When no objective testing had been done, but the patient had received full-dose intravenous heparin therapy or vitamin K antagonists for at least 3 months, he or she was considered to also have experienced a venous thromboembolic event. When required, the patients' charts were reviewed.

Episodes of increased risk for venous thromboembolism included surgery, trauma, immobilization for more than 7 days, pregnancy, and use of oral contraceptives. An episode of venous thromboembolism was considered to be related to such a risk situation when it occurred within 3 months. A relation with use of oral contraceptive use was defined as an event occurring during exposure to oral contraceptives. Observed years are all years since the age of 15 years until inclusion in the study or until the date of the first venous thromboembolic event; this time period was chosen because it was considered to reflect the duration of exposure to the risk for venous thromboembolism. The information from the medical history (and, if necessary from other sources) was classified without knowledge of the prothrombin 20210A status.
3.2.3 Statistical analysis

The overall and age-specific annual incidence of a first episode of venous thromboembolism was calculated in relatives with and those without the prothrombin 20210A mutation by dividing the number of symptomatic family members by the observed years. The relative risk for the development of a first episode of venous thromboembolism (adjusted for extremes if necessary) was calculated by dividing the incidence of venous thrombosis in family members with the mutation by the incidence in family members with the normal genotype. The 95% CIs were calculated according to normal approximation of the binomial distribution. The relative risk (and its mid-P corrected 95% CI) for pregnancy-, and surgery-related venous thromboembolism was calculated by using a Cox model. For this purpose, a risk period was considered as an unit of time, and persons who had not had a thromboembolic event by the end of their last risk period were considered to be censored. If a relative had had an episode of venous thromboembolism, all subsequent high risk situations were excluded from the analysis to avoid enhancing risk and because anticoagulant prophylaxis is often given after such an episode.

3.3 RESULTS

The pedigrees of the 42 propositi with documented venous thromboembolism and the prothrombin 20210A mutation revealed 276 first-degree family members. Nineteen relatives were younger than 15 years of age. Furthermore, 42 relatives had died prior to start of the study. Two of these died of fatal pulmonary embolism. Another 22 relatives were unavailable because they lived outside of the Netherlands. Finally, 38 relatives could not participate for various reasons, including reluctance to undergo assessment of genetic disorders, refusal to give consent, and the presence of terminal diseases. Thus, a total of 155 first-degree family members were available for the present analysis (response rate of living family members, 66%; overall response rate, 56%).

Approximately half of the 155 relatives carried the prothrombin 20210A mutation (Table 3.1). Of the 81 family members with the mutation, 3 were found to be homozygous. Six family members without the mutation and 9 family members with the mutation reported to have experienced an episode of venous thromboembolism. In the group without the mutation, 2 individuals suffered from pulmonary embolism, whereas 4 had had deep venous thrombosis. In the relatives with the mutation, these figures were 2 and 7, respectively. The absolute annual incidence of a first episode of venous thromboembolism was 0.28% (95% CI 0.10% to 0.60%) in the group with a normal genotype and 0.40% (95% CI 0.18% to 0.75%) in those with the mutation. Thus, the relative risk for a first episode of venous thromboembolism among family members with the prothrombin 20210A mutation was 1.4 (95% CI 0.5 to 4.0). In the family members with a normal genotype the
gender distribution was equal, while 2 of the 6 relatives with thrombosis were men. In the family members with the mutation, two-thirds were female, and of the 9 relatives with thrombosis, 7 were women. Two of the 9 symptomatic relatives belonged to the same family and were found to be homozygous. One was a woman who experienced a pulmonary embolism 3 days postpartum at the age of 26 years; she also had spontaneous deep-vein thrombosis two years later, but remained without venous thromboembolic complications in the next 40 years. The other homozygous relative was her brother who suffered from his first spontaneous deep venous thrombosis of the leg at the age of 70 years. All 6 relatives in the group without the prothrombin 20210A mutation had a single episode of thrombosis, whereas recurrent episodes of venous thromboembolism occurred in 2 of the 9 relatives with the mutation, one spontaneously and the other postpartum.

<table>
<thead>
<tr>
<th>prothrombin 20210A mutation</th>
<th>absent</th>
<th>present</th>
</tr>
</thead>
<tbody>
<tr>
<td>number, n (%)</td>
<td>74 (48)</td>
<td>31* (52)</td>
</tr>
<tr>
<td>male, n (%)</td>
<td>33 (51)</td>
<td>23 (35)</td>
</tr>
<tr>
<td>female, n (%)</td>
<td>35 (48)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>mean age, yr</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>(range)</td>
<td>(18-76)</td>
<td>(17-81)</td>
</tr>
<tr>
<td>parents with VTE, n</td>
<td>6</td>
<td>6**</td>
</tr>
<tr>
<td>mean age at first VTE, yr</td>
<td>41</td>
<td>56</td>
</tr>
<tr>
<td>(range)</td>
<td>(17-56)</td>
<td>(20-70)</td>
</tr>
<tr>
<td>reserved years, yr</td>
<td>2173</td>
<td>2270***</td>
</tr>
<tr>
<td>heterozygous (%)</td>
<td>0.28</td>
<td>0.40</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>(0.10-0.59)</td>
<td>(0.13-0.75)</td>
</tr>
<tr>
<td>relative risk</td>
<td>-</td>
<td>1.4***</td>
</tr>
</tbody>
</table>

* including 3 homozygous relatives
** including 2 homozygous relatives
*** including 1 heterozygous, 3 homozygous relatives
**** CI 95%
Table 3.2 shows the age-specific annual incidences of a first episode of thrombosis in relatives with a normal genotype and in those with the mutation. The absolute annual incidence in the age group of 15 to 30 years with the mutation was 0.57% (95% CI 0.2% to 1.2%), with a relative risk of 5.6 (95% CI 0.7 to 46.3) as compared with their family members without the mutation. In the age group of 30 to 45 years with the mutation no thromboembolic complications were reported. In the affected relatives aged 45 to 60 years, and those older than 60 years, the annual incidences of venous thrombosis were 0.26% (95% CI 0.006% to 1.4%) and 1.64% (95% CI 0.2% to 5.8%), respectively.

In the group with the mutation, about half of the thrombotic episodes occurred spontaneously, whereas in the group with a normal genotype, two-thirds of the episodes were provoked by exogenous risk factors (Table 3.3). The absolute annual incidence of venous thrombosis among women who had the mutation and used oral contraceptives was lower than in the women without the mutation (0.2% [95% CI 0.1% to 1.0%] and 0.9% [95% CI 0.1% to 3.2%], respectively), although this difference was not statistically significant. No pregnancy-related episodes of venous thromboembolism occurred in the group without the mutation, while in the group with the prothrombin 20210A mutation, 3 of 80 pregnancies were complicated by venous thromboembolism. All these episodes occurred in the postpartum period.
gery, immobilization, or trauma were complicated by venous thromboembolism, while in those with the mutation, 1 out of 115 risk episodes was complicated by thrombosis.
Our preliminary findings suggest that a first-degree relative of a symptomatic heterozygous propositus who also carries the prothrombin 20210A mutation has an absolute annual risk for a first episode of venous thromboembolism of 0.40% (95% CI 0.18% to 0.75%) (Table 3.1). This rate is comparable to that observed in carriers of the factor V Leiden mutation, which was found to be about 0.45% annually [12, 13]. Unexpectedly, the incidence in the relatives without the prothrombin 20210A mutation was found to be 0.28% (95% CI 0.10% to 0.60%), which is about 2 to 3 times higher than the reported population risk [14]. As a result, the relative risk for venous thromboembolism in the present study was estimated to be 1.4 (95% CI 0.5-4.0) in carriers, as compared with their non-affected family members.

Assuming that the observed rate in the family members without the prothrombin 20210A mutation is erroneously high, and would be closer to 0.1% per year, the relative risk may become about 4, which is consistent with earlier observations [5, 6, 10]. Why the rate in noncarriers is so high, is not fully understood, but may be the result of the inclusion of selected families, who potentially have combined defects that are yet unknown. Since the response rate of relatives at the time of the present analysis was only 66%, preferential investigation of symptomatic relatives may have also occurred, although it is likely that this effect would also be present in the group with the mutation.

Finally, the increased rate may be the result of chance due to the small sample size. Analysis of the age-specific incidences is also hampered by the small numbers per age group. It is interesting to note, however, that the relative risk for venous thromboembolism in carriers of the prothrombin 20210A mutation in the younger age group (15 to 30 years) is 5.6 (95% CI 0.7-46.3), as compared with noncarriers. Half of the thrombotic episodes in carriers in this age group were related to pregnancies. This observation is in agreement with earlier findings that a genetic predisposition in women, in combination with the exposure to increased levels of estrogen (either pregnancy-related or during the use of oral contraceptives) leads to the occurrence of venous thromboembolism at a younger age [15-17]. However, the relationship with the prothrombin 20210A mutation and oral contraceptive use in the present study is yet not clear.

In order to draw definite conclusions about the absolute risk of venous thromboembolism in carriers of the prothrombin 20210A mutation, both spontaneously and in relation with exogenous risk factors, more families need to be included and the findings should be validated in prospective cohort studies.
3.5 REFERENCES


