The Risk of Mortality and the Factor V Leiden Mutation in a Population-based Cohort

Bastiaan T. Heijmans1, 2, Rudi G. J. Westendorp2, 3, Dick L. Knook1, 2, Cornelis Kluft3, P. Eline Slagboom1

From the 1Gaubius Laboratory, TNO Prevention and Health, Leiden, The Netherlands, 2Section of Gerontology and Geriatrics, Department of General Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands, 3Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

Summary

The factor V Leiden mutation (conferring resistance to activated protein C) has been implicated in the risk of arterial thrombosis and is a well-established risk factor for venous thrombosis especially in the elderly. We studied whether the disease association of the factor V mutation is reflected in an increased all-cause and cause-specific mortality.

First, the prevalence of the factor V Leiden mutation was determined in a population-based study among subjects aged 85 years and over (4.7%, n = 660) and was found to correspond to the prevalence in young subjects aged 18 to 40 years (5.0%, n = 321). Secondly, we studied the association of factor V Leiden with the risk of all-cause mortality and specific causes of death in the elderly cohort during a 10-year follow-up period. Neither the all-cause mortality risk (RR 1.0; 95% CI, 0.7-1.5), nor the risk of death due to cardiovascular disease (RR 0.9; 95% CI, 0.5-1.7) were increased in elderly subjects heterozygous for factor V Leiden. Our study thus indicates that heterozygosity for factor V Leiden does not affect population mortality.

Introduction

The factor V Leiden mutation is the most common genetic predisposition to venous thrombosis with a prevalence of heterozygous carriers of 3% to 6% (1, 2). The mutation leads to an arginine-506 to glutamine amino-acid substitution at the cleavage site for activated protein C (APC), which results in a 10-fold decreased inactivation rate of the variant factor V (3). As a consequence, individuals with the mutation have a poor anticoagulant response (APC-resistance). Heterozygous carriers have a 3.5- to 7-fold increased risk of venous thrombosis (1, 2). The majority of studies did not demonstrate associations of factor V Leiden with arterial thrombosis (2, 4, 5) although the factor V mutation was found to be associated with myocardial infarction in smoking women younger than 45 years (6).

The disease association with factor V Leiden raises the concern that the mutation confers excess mortality among carriers due to an increased risk of thromboembolic complications. If the factor V mutation were to have a deleterious effect on mortality risk, this would probably be observed in the elderly since the relative contribution of arterial and venous thrombosis to total mortality is greater with advancing age. Moreover, the incidence of venous thrombosis among factor V Leiden carriers has been found to increase with age at a significantly greater rate than among subjects without the mutation and increases especially after the age of 70 years (7).

We studied the association of the factor V Leiden mutation with mortality in a population-based study among subjects aged 85 years and over (Leiden 85-plus Study). First, the association with all-cause mortality was assessed by comparing the prevalence of the factor V mutation in the elderly cohort with that in subjects aged 18 to 40 years, since excess mortality would be reflected in a reduced frequency of the mutation in older age-groups. Secondly, the association of factor V Leiden with all-cause mortality and specific causes of death in old age was studied in the elderly cohort over a 10-year follow-up period.

Methods

The Leiden 85-plus Study is a population-based study in which all the inhabitants of Leiden, The Netherlands, aged 85 years and over were invited to take part (8). Out of a total of 1258 eligible subjects, 221 died before the enrolment which lasted from December 1, 1986, to March 1, 1988. Of the 1037 remaining subjects, 977 (94%) participated and were medically interviewed at home. After the exclusion of subjects with a non-Dutch (n = 29) or unknown (n = 69) place of birth, sufficient cell material was available from 660 (186 men/474 women) subjects for the present genetic study. DNA was extracted and the presence of factor V Leiden detected by the PCR-amplification of a 220 bp fragment containing the G1691- to-A transition, followed by digestion with MnlI as previously described (1). The factor V genotype was independently assessed by two observers and the sample was reamplified if their observations did not match. The study was approved by the Medical Ethics Committee of Leiden University and informed consent was obtained from all participants.

In the cross-sectional analyses, subjects aged 85 years and over were compared with a control population which consisted of 320 (191 men/129 women) blood donors of Dutch descent aged 18-40 years. All participants in the Leiden 85-plus Study were followed up for mortality until October 1, 1996. Among the 660 subjects of the cohort studied, 2 were lost to follow-up. Primary causes of death were obtained from the Dutch Central Bureau of Statistics and categorized for cardiovascular disease (ICD-9 390-519), ischemic heart disease (410-414), cerebrovascular disease (430-438), cancer (ICD-9 140-239) and all causes (ICD-9 000-999). Death from infection was coded as previously described (9).

In the cross-sectional analyses, distributions of genotypes were compared by the \( \chi^2 \)-test, and mortality risks and 95% confidence intervals (CI) were estimated using the exposure odds ratio. In the prospective follow-up study, survival times for subjects were computed from the date of the home visit to the date of one of the following events: death from a specific cause, death from any cause or October 1, 1996. Survival was estimated using the Kaplan-Meier product limit method and compared with the log-rank test. Adjusted mortality risks and 95% CIs were estimated with Cox proportional hazards models.
Results

The prevalence of factor V Leiden among subjects aged 85 years and over (31/660, 4.7%) corresponded with that among young controls aged 18-40 years (16/321, 5.0%; $X^2_{df=1} = 0.04; P = 0.84$). Both populations were in Hardy-Weinberg equilibrium and no homozygotes for the factor V mutation were identified. The all-cause mortality risk up to the age of 85 years, as estimated with the exposure odds ratio, associated with carrying factor V Leiden was estimated at 1.1 (95% CI, 0.6-2.0). For men the risk was estimated at 0.9 (95% CI, 0.4-2.1) and for women at 1.1 (95% CI, 0.7-1.8).

During the 10 years follow-up period, 587 (89.2%) deaths occurred in the 85-plus cohort investigated in this study (n = 660; 2 subjects lost to follow up). The mortality of carriers of the factor V Leiden mutation was similar to that of non-carriers (RR 1.0; 95% CI, 0.67-1.46; adjusted for age and gender; Fig. 1). The estimates were similar for men (RR 0.9; 95% CI, 0.5-1.7; adjusted for age) and women (RR 1.1; 95% CI, 0.7-1.8; adjusted for age). The mortality risk associated with heterozygosity for factor V Leiden was 0.7 (95% CI, 0.3-1.6) in smokers (n = 109) and 1.1 (95% CI, 0.7-1.8) in non-smokers (n = 524).

The mortality risks for specific causes of death were not significantly different for factor V Leiden carriers as compared to non-carriers (Table 1). The risk of death due to cardiovascular disease in factor V Leiden carriers who smoked (RR 0.7; 95% CI, 0.2-3.1) was approximately similar to that in non-smoking carriers (RR 0.9; 95% CI, 0.4-2.0). One subject, a 94-year old woman, died from the complications of venous thrombotic disease at the age of 97 and did not carry the factor V mutation.

Discussion

We have assessed the impact of factor V Leiden, the most common genetic risk factor for venous thrombosis, on mortality in two study designs. A cross-sectional comparison of the prevalence of factor V Leiden in the young and the elderly did not indicate a major effect of the factor V Leiden mutation on population mortality. A 10-year follow-up study among elderly subjects confirmed these results. Furthermore, heterozygosity of factor V Leiden was not associated with an increased risk of common specific causes of death in old age.

Previous studies showed that the deleterious effect of the factor V Leiden mutation is enhanced by non-genetic factors. The deleterious effect of the mutation on the risk of venous thrombosis was found to be more pronounced among elderly individuals (7). Nevertheless, the mortality of elderly subjects in our study was not influenced by the factor V mutation. Another previously suggested modulating factor is smoking. Factor V Leiden was reported to be associated with the risk of myocardial infarction in women younger than 45 years of age who smoked, whereas among non-smoking carriers the risk was not increased (6). This association was attributed to the low prevalence of atherosclerosis in young women and assumed to be absent in the general population. We did not detect any increased all-cause or cardiovascular disease mortality among elderly factor V Leiden carriers who smoked.

The women in the cohort studied were born between 1887 and 1901 and oral contraceptives were not available during their reproductive period. Should the reported interaction between the factor V mutation and the use of oral contraceptives (10) confer an increased mortality, this would not have affected the mortality in the generation studied. By similar reasoning, it cannot be excluded that the mortality of women with the factor V Leiden mutation from subsequent generations might be higher.

It may be argued that our study did not have sufficient power to detect small increases in mortality risk among factor V Leiden carriers. However, combined with data from previous studies it seems unlikely that heterozygosity for factor V Leiden contributes to mortality in the general population. First, factor V Leiden is not an important risk factor for arterial thrombosis in the general population (2, 4, 5). Second, although the mutation is associated with a considerable risk of deep vein thrombosis (1, 2), the increase in risk of its lethal complication, ie. pulmonary embolism, is limited (11-14). Third, parents of subjects with factor V Leiden did not suffer increased all-cause or cause-specific mortality (15). Finally, heterozygosity for factor V Leiden is compatible with extremely old age (16, 17).

Since our study indicates that factor V Leiden carriers in general are not subject to increased mortality, long-term prophylactic anti-coagulant therapy, which induces the risk of fatal haemorrhage (18), should not be considered solely on the basis of factor V Leiden status.

Table 1  All-cause and cause-specific 10-year mortality risks of factor V Leiden carriers compared with non-carriers in subjects aged 85 years and over

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>N</th>
<th>Mortality risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>250</td>
<td>0.9 (0.5-1.7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>63</td>
<td>0.3 (0.0-2.4)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>83</td>
<td>1.7 (0.7-4.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>97</td>
<td>1.7 (0.8-3.7)</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>62</td>
<td>2.2 (0.9-5.5)</td>
</tr>
<tr>
<td>All-cause</td>
<td>587</td>
<td>1.0 (0.7-1.5)</td>
</tr>
</tbody>
</table>

Mortality risks were estimated with a Cox proportional hazard model and adjusted for gender and age at baseline.
Acknowledgements

We wish to thank Annie Jie and Simone Droog for excellent technical assistance, the Red Cross Blood Bank Leidsenhage, especially Marjo Dirven, for collecting the control population, and the Central Bureau of Statistics for generously making available the mortality statistics and database linking. This study was supported by grant 94.047 from the Netherlands Heart Foundation and grant AG06354 from the US National Institutes of Health.

References


Received May 8, 1998 Accepted June 23, 1998