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Full Length Article

Association of factor V activity with risk of venous thromboembolism and atherothrombotic cardiovascular events: A retrospective population-based cohort study

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ABSTRACT

Introduction: Factor V (FV) deficiency is a rare inherited coagulation disorder associated with bleeding tendency. As a result, it has been postulated that decreased FV activity may confer protection against venous thromboembolism and atherothrombotic cardiovascular events.

Materials and methods: Using the electronic database of the largest health care provider in Israel, we identified all adult individuals who were tested for FV activity between January 2004 and June 2017. Subjects with liver cirrhosis or FV Leiden mutation were excluded. FV activity was classified into three predefined categories; FV activity > 50%, FV activity 30–50%, and FV activity ≤30%. Patients were followed from January 2004 to June 2017 for new atherothrombotic cardiovascular events (composite of myocardial infarction, stroke, and TIA) and venous thromboembolism (VTE).

Results: Overall 2021 individuals were included; 83.2% had FV activity > 50%, 9.6% FV activity 30–50%, and 7.2% had FV activity ≤30%. Compared to individuals with FV activity > 50% the adjusted HR for atherothrombotic cardiovascular events was 1.10 (95% CI, 0.63–1.90) in those with FV activity 30–50%, and 0.95 (0.49–1.8) in those with FV activity ≤30%. None of the patients with FV activity 30–50% had VTE during follow-up; therefore those with FV activity ≤50% were classified into one group. VTE incidence was lower in those with FV activity ≤50% compared to those with FV > 50% activity; adjusted HR = 0.28 (0.09–0.91).

Conclusion: This study suggests that decreased FV activity might be associated with decreased incidence of VTE. No significant association appears to exist between FV activity and atherothrombotic cardiovascular events.

1. Introduction

Factor V (FV) deficiency is a rare coagulation disorder, inherited as an autosomal recessive disease. The estimated prevalence of FV deficiency in general population is approximately 1 per million for the homozygous form [1]. FV deficiency is more prevalent in Mediterranean countries, Middle Eastern Jews and Iranians [2, 3]. At least 100 mutations in the F5 gene have been found to cause FV deficiency. FV deficiency results from mutations in both copies of the F5 gene, although some people with a mutation in a single copy of the gene have mild bleeding problems [1]. In Israel, the prevalence of FV deficiency is expected to be especially high, due to housing a multitude of predisposed ethnicities and the high rates of parental consanguinity within parts of the Israeli community [1]. Decreased FV activity and FV deficiency may be either symptomatic, presenting as bleeding from various sites, including brain, mucosa, muscles, joints and the genitourinary tract, or asymptomatic, with prolongation of PT and PTT being a possible manifestation [3–5].

FV is an integral part of the coagulation cascade, which its end-product, the thrombus, plays a key role in the etiology of venous thromboembolism (VTE) and atherothrombotic cardiovascular events [6, 7]. Hence, it has been postulated that an underlying benefit, in the

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form of protection from VTE and atherothrombotic cardiovascular events may be associated with reduced FV activity. In the medical literature, such association has never been established. It should be noted, however, that most publications cited case reports and small series of cases [8–10].

We hypothesized that decreased FV activity is associated with reduced arterial and venous thromboembolic events. We presumed that the Clalit Health Services (CHS) database, which is a population-based database, will provide a suitable platform to help clarify the issue.

2. Material and methods

2.1. Data source

This study is based on data from the computerized database of Clalit Health Services (CHS) which provides inclusive health care for more than half of the Israeli population. Health care coverage in Israel is mandatory and is provided by four groups akin to not-for-profit health maintenance organizations (HMO). All members of the different HMOs have a similar health insurance plan and similar access to health services. The electronic medical record (EMR) database of CHS includes data from multiple sources: records of primary care physicians, community specialty clinics, hospitalizations, laboratories and pharmacies. Diagnoses are captured in the chronic disease registry of the CHS by diagnosis-specific algorithms, employing International Classification of Diseases Ninth revision (ICD-9) code reading, text reading, laboratory test results and disease-specific drug usage. A number of high quality, population-based studies have been conducted based on the data retrieved from CHS database [11, 12].

2.2. Study population and outcomes

CHS laboratory computerized database was retrospectively searched for all FV activity tests performed between 1 January 2004 and 30 June 2017 in adult individuals who at start of follow-up were 18 years or older. Due to the fact that reduced FV activity being mostly congenital, we assumed that FV activity at the time of testing reflects its activity in the period prior. Therefore, we were able to set the beginning of follow-up for all patients at a similar point in time, which is 1 January 2004. Individuals were retrospectively followed from 1 January 2004 until the outcome event, death, and loss to follow-up, or 30 June 2017, whichever came first. The association of FV activity was assessed with 2 outcomes: (1) atherothrombotic cardiovascular events, defined as composite of myocardial infarction (MI), stroke, and transient ischemic attack (TIA), and (2) venous thromboembolism (VTE), defined as composite of deep vein thrombosis (DVT) and pulmonary embolism (PE). The type and the date of occurrence of each study outcome, during follow-up, were ascertained through the electronic medical records (EMR) database of the CHS by means of ICD-9 codes reading. The study was approved by a centralized institutional review board committee.

2.3. Study variables

In addition to the FV activity test results, the following data were retrieved from the computerized database of the CHS: demographic variables, presence of risk factors, selected chronic medical conditions at baseline, and antithrombotic medications use.

Demographic variables included age and sex. Comorbid conditions and risk factors included hypertension, diabetes mellitus, hyperlipidemia, smoking, congestive heart failure (CHF), and history of stroke, ischemic heart disease (IHD), atrial fibrillation, chronic obstructive pulmonary disease (COPD), and malignancy. Antithrombotic medication use was assessed for each antiplatelet and anticoagulant drug (i.e., vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors).

2.4. Factor V, PT and PTT assays

Factor V activity in the subject plasma is determined by performing a modified Prothrombin time test. The assay is done using a commercial kit with factor V deficient plasma (HemosIL, USA). Patient plasma is diluted and added to plasma deficient in FV. Correction of the clotting time of the deficient plasma is proportional to the concentration (% activity) of that factor in the patient plasma, interpolated from a calibration curve. The calibration curve is established in each lab by conducting multiple PT-measuring reactions between calibration plasma with varying amounts of FV and factor-deficient plasma. The value that is determined as abnormal is 29%. The same kit is used throughout our entire HMO and is used for at least 10 years. The assay accuracy and reproducibility is tested every 6 months by an external audit throughout the entire HMO.

The assay for PTT is SynthASil (HemosIL, USA) and the assay for PT is RecombiPlasTin 2G (HemosIL, USA). Calibration is done using standardized calibration plasma (HemosIL, USA) with control samples (Low, Medium, High – HemosIL, USA). The same assay and standard operating procedure for PT and PTT is used across the HMO laboratories.

2.5. Statistical methods

Continuous variables were summarized with mean ± standard deviation, and categorical variables were presented as numbers and proportions. FV activity was classified into 3 predefined categories: (1) FV activity ≤30%, (2) FV activity 30% to 50%, and (3) FV activity > 50%. Comparisons of baseline characteristics between the 3 categories of FV activity were performed using the chi-square test for categorical variables and using analysis of variance for continuous variables (ANOVA). Post hoc comparisons between groups were performed using Bonferroni correction. Age-adjusted survival function curves were used to plot the distribution of time to reach atherothrombotic cardiovascular events and VTE by FV activity category. Cox proportional hazard regression models were used to assess the crude and the adjusted association between FV activity and the study outcomes and to estimate the hazard rations (HRs) along with 95% confidence interval (95% CI) using FV activity > 50% as the reference category. Two approaches were used to model the multivariable Cox proportional hazard regression analysis: (1) fully adjusted model-1 that included all variables in Table 1 (age, sex, anticoagulants, antiplatelet, atrial fibrillation, malignancy, diabetes, COPD, hypertension, IHD, stroke, CHF, hyperlipidemia, and smoking), (2) fully adjusted model-2 in which only variables with significant association in the univariate analysis were included in the multivariable Cox proportional hazard model using the forward selection.

We performed two additional sensitivity analyses to assess the association between FV activity and the study outcomes: (1) FV activity was classified into quintiles according to its distribution in the study population, and highest quintile was used as reference category; (2) the association was assessed using FV activity as continuous variable.

All statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM, New York, NY). For all analyses, $p < .05$ for the 2-tailed test was considered to be statistically significant.

3. Results

Between January 2004 and June 2017 (the study period) ~3,760,000 adults subjects were registered in the CHS computerized database. A total of 2809 FV activity tests were performed during the study period in 2174 individuals (88% had only 1 test and 8.0% had 2 tests). The lowest test result was arbitrarily used in individuals who had more than one FV activity test. We excluded 139 patients with liver cirrhosis and 14 patients with FV Leiden mutation. Overall, 2021 individuals were included in this study, of them 1456 (72%) were tested