Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Praca oryginalna/Original research article

Elevated factor VIII activity and venous thromboembolism in patients referred to the Iranian Blood Transfusion Organization: A case control study

Seyed Mohammad Reza Tabatabaei [1], *Seyed Mehdi Sajjadi* [2], *Minoo Ahmadi Nejad* [1], *Farzaneh Tavasoli* [1], *Azita Azarkeivan* [1,*]

[1] *Iranian Blood Transfusion Organization Research Center, Tehran, Iran*
[2] *Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Birjand University of Medical Sciences, Birjand, Iran*

ARTICLE INFO

Article history:
Received: 16.07.2015
Accepted: 22.01.2016
Available online: 02.02.2016

Keywords:
- Elevated factor VIII
- Venous thromboembolism
- Iranian population

ABSTRACT

Objective: A high plasma level of factor eight (FVIII) is a risk factor for venous thromboembolism (VTE). Since, there was no report about the association of elevated FVIII and VTE in Iranian population, the incidence of elevated FVIII and its association to VTE was evaluated. **Materials and methods:** 152 consecutive idiopathic VTE patients referred to the Iranian Blood Transfusion Organization (IBTO) and 130 healthy matched blood donors were studied. At least one confirmed idiopathic deep vein thrombosis (DVT) or pulmonary embolism (PE) was found among all cases. The blood samples were collected at least 3 months after DVT/PE diagnosis. The normal reference range was determined by using the Control samples of the donors. FVIII levels were measured using PTT based one-staged assay. **Results:** The FVIII levels in the cases and controls were 157.3 ± 53.4 and 111.8 ± 29.7, respectively. In cases, the lowest and the highest levels of FVIII were 66 IU/dl and 364 IU/dl, while they were 42 IU/dl and 195 IU/dl for the controls.

There was no relation between gender, age and FVIII level in either group. The normal reference range for the controls was 52–171 IU/dl. Considering the cut-off point as 180 IU/dl, the elevated values were seen in 28.9% of the case group vs. 3.1% of the control group. **Conclusion:** Elevated factor VIII is likely to be a risk factor for VTE. Moreover, a new normal reference range for the Iranian population was defined.

* *Corresponding author at:* Iranian Blood Transfusion Organization Research Center, Tehran, IRAN (ISLAMIC REPUBLIC OF). Tel.: +98 9121490645; fax: +98 2188060717.
E-mail address: azitaazarkeivan@yahoo.com (A. Azarkeivan).

http://dx.doi.org/10.1016/j.achaem.2016.01.001

Introduction

Today, thrombosis in conjunction with complicating embolic events is considered to be the most important cause of diseases and mortality in developed countries [1]. A wide variety of acquired and inherited factors may lead to thrombosis [2]. Elevated factor VIII (FVIII) levels is considered a main risk factor for arterial disease and venous thromboembolism (VTE) [2–13]. In the general population, persistently elevated levels of coagulation FVIII above 150 U/dL are a recognized risk factor for VTE events [14], which is probably due to (1) the increased rate of thrombin generation in the external pathway of coagulation and (2) enhanced platelet aggregation seen in the presence of elevated levels of FVIII [15–17].

The evaluation of bleeding risk as a result of hereditary or acquired FVIII deficiency is the major reason for FVIII levels measurement. Moreover, determination of FVIII levels would help physicians to make better decisions for patients' first-degree relatives [12]. To the best of our knowledge, there has been no study on the association of elevated FVIII and VTE in the Iranian population along with a normal reference range. Thus, in this study, the prevalence of elevated FVIII levels and its association with venous thrombosis in thrombotic patients referred to the coagulation laboratory of the Iranian Blood Transfusion Organization (IBTO) were investigated.

Materials and methods

In this case–control study, 152 consecutive idiopathic VTE patients and 130 age-, sex-, and ethnicity-matched healthy blood donors were enrolled.

All cases showed at least one confirmed idiopathic DVT or pulmonary embolism (PE), using diagnostic methods such as venography and spiral CT scan. For cases, blood samples were drawn at least three months after diagnosis of DVT or PE, which appears to be a long enough period to avoid acute-phase response caused by the thrombotic phenomenon. Plasma from healthy blood donors was applied to determine the normal reference range. All individuals were informed about the study and the samples were collected with their agreement. Since one-stage assays are the most common methods used to analyze clinical plasma samples [18], factor VIII levels were measured by using a one-stage assay – the PTT-based Diagonistica Stago on the STA compact automated coagulation factor analyser. Blood samples taken from the antecubital vein were collected into tubes containing 0.129 M trisodium citrate as an anticoagulant. In order to prepare platelet poor plasma, within 30 min of blood collection, the samples were centrifuged at 4 °C, 2500 × g for 20 min. Then the plasma was stored at −70 °C. They were thawed for 5 min in a 37 °C water bath to perform assays.

So as to compare the proportion of subjects above and below the upper cut-off value of 180 IU/dl, Fisher's exact test was used. The mean FVIII levels in the two groups were compared by the use of a Student's t-test. All statistical analysis was performed by SPSS software version 20 and $p < 0.05$ was considered as statistically significant.

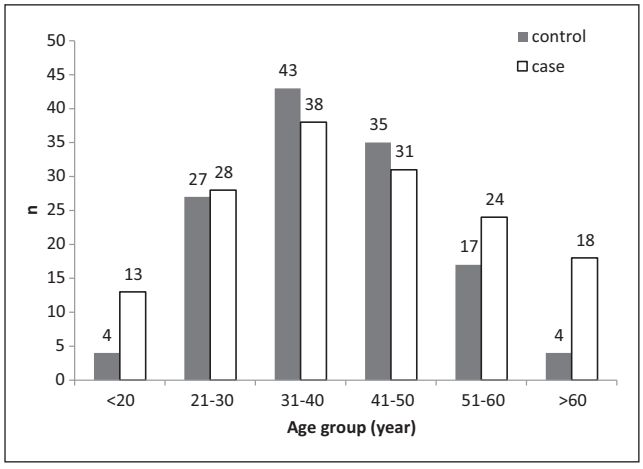

Fig. 1 – Comparison of age in the study and control groups

Results

We studied 152 patients with idiopathic VTE and 130 healthy blood donors as the control group. Cases consisted of 84 (55.3%) males and 68 (44.7%) females, while the control group consisted of 75 (57.7%) males and 55 (42.3%) females. The mean age in the cases and the controls were 40.7 ± 13.6 years and 39.6 ± 11.1 years, respectively. A family history was ascertained in 33 (21.7%) of the 152 patients. FVIII levels were 157.3 ± 53.4 and 111.8 ± 29.7 for cases and controls, respectively. In the case group, the lowest and highest levels were 66 IU/dl and 364 IU/dl, while they were 42 IU/dl and 195 IU/dl for controls.

A Chi-square test showed significant difference between the elevated levels of FVIII in the two groups ($p \leq 0.001$). There were no relationships between gender, age and FVIII levels in the study population. In the age group over 60 years, the incidence of thrombosis was higher than the other age groups; however, the increase was not statistically significant. Fig. 1 shows the comparison of the case and control groups by age. Accordingly, the normal reference range for healthy subjects was 52–171 IU/dl.

Considering 180 IU/dl as a cut-off point, FVIII levels were notably greater in the cases than the control subjects with an OR of 9.41 (95% CI: 3.47, 25.48). That is, elevated values were seen in 28.9% of the cases and in just 3.1% of the controls (Table I).

Discussion

There are several reports referring to elevated FVIII levels as a thromboembolism risk factor [2–5, 7–12, 19, 20]. The upside

Table I – Normal and elevated FVIII levels in the study and control groups based on 180 IU/dl as the cut-off point

Factor level	Normal FVIII	Elevated FVIII	Total
Case	108 (71.1%)	44 (28.9%)	152 (100%)
Control	126 (96.9%)	4 (3.1%)	130 (100%)
Total	234	48	282

of this study, as with some other research [12, 21], is the consecutive idiopathic patients being investigated. The high incidence of elevated FVIII is seen in patients with first-time DVT (25%). In addition, 11% of healthy subjects in the control group were observed with FVIII levels of more than 150 IU/dl [22].

As the blood samples were collected at least 3 months after any VTE event in the cases, the effect of many transient risk factors for temporarily increased FVIII levels had already been eliminated. A new normal range has been introduced for the Iranian population in this study. Furthermore, new lower and upper limits were determined in our patients (66–364 IU/dl) and healthy subjects (42–195 IU/dl).

There are significant differences in the cut-off values between this study (180 IU/dl) and that of Wells'2005 study (270 IU/dl) [12]. However, the incidence rates of elevated FVIII levels in both studies are not significantly different (20% vs. 28% respectively).

In the present study, elevated FVIII levels were determined for 23.8% of males and 35.3% of females, however, the difference was not statistically significant, so it could not be concluded that females are at a higher risk of thrombotic events than males. Finally, advancing age was considered as a risk factor for thrombosis. As with gender, however, it was not statistically significant. Nonetheless, in order to increase the chance of identifying more high-risk cases, it would be useful to define a specific cut-off value for patients aged over 60.

It is clear that more clinical and laboratory studies are needed to evaluate the effects of FVIII levels on thrombotic tendency and any factors that may influence this trend.

Authors' contributions/Wkład autorów

SMRT – study design, literature search, manuscript preparation. FT – data collection. MAN – statistical analysis. SMS – manuscript preparation, literature search. AA – study design, data interpretation, funds collection.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

We express our thanks to the Research Center of Blood Transfusion, High Institute for Education and Research on Transfusion Medicine in Iran for giving us the opportunity to collect samples and also for their financial support.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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