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FACTOR V AND VIII INHIBITOR IN PATIENTS WITH COMBINED FACTOR V AND VIII DEFICIENCY

HASSAN MANSOURI TORGHABEH, M.Sc.,[1] ALI AKBAR POURFATHOLLAH, Ph.D.,[1] MAHMOOD MAHMOODIAN SHOOSHTARI, Ph.D.,[2] ZAHRA REZAIE YAZDI, M.D.,[3*] AND HABIBOLLAH ESMAILI, Ph.D.[4]

From the [1]Experimental Hematology and Blood Banking Dept, Medical Sciences School, Tarbiat Modares University (T.M.U.), the [2]Iranian Blood Transfusion Organization Research Center, Tehran, the [3]Department of Internal Medicine, Mashhad Medical Sciences University, Mashhad, and the [4]Community Medicine and Public Health Department of Mashhad Medical Sciences University, Mashhad, Iran.

ABSTRACT

Patients with coagulation factor(s) deficiency who use coagulation therapy are susceptible to forming inhibitors against coagulation factor(s). In this survey we detected factor V and VIII inhibitor in ten patients with combined deficiency of factors V and VIII from north east of Iran (Khorassan province). It was revealed in our survey that eight patients had both factor V and factor VIII inhibitors and two patients had none. Because factor V and factor VIII share approximately 40% amino acid sequence homology in their A and C domains, it remains to be elucidated if it is one molecule that recognizes both factor V and VIII or whether there are two inhibitor molecules against common sites.

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Keywords: Combined factor V&VIII deficiency, Factor V inhibitor, Factor VIII inhibitor.

INTRODUCTION

Already six types of combined hereditary deficiency of coagulation factors have been reported.[1] Combined deficiency of factor V & VIII was reported in 1954 by Oeri et al.[2] This inherited disorder is a rare bleeding diathesis that has been reported in 106 cases from 62 families throughout the world until 2000.[3] Most patients are from the Mediterranean region, including Italy,[4] Iran[5] and Israel.[6] Additional families have been reported from India,[3,15] Japan,[7] North America and Europe.[4] In genetic defects of single coagulation factors, the relationship of the clinical severity with the plasma factor level is well established. However, the data available from published reports show wide variation with regard to clinical manifestations in cases of combined factor V & VIII deficiency.[8] Many mechanisms have been proposed to explain this mysterious dual deficiency. In 1980 Marlar reported an apparent deficiency of protein C inhibitor as the underlying mechanism for this disorder.[9] This intriguing model was based on the observation that 4 unrelated patients with combined deficiency of factor V & VIII had no protein C inhibitor in their blood.[10] Despite this attractive hypothesis, subsequent studies failed to confirm it in these patients.[11,12] Unfortunately, "the slaying of a beautiful hypothesis by an ugly fact" was played almost immediately.[10] Genetic linkage studies in affected families mapped the gene for combined factor V & VIII deficiency to the long arm of chromosome 18q.[13] Positional cloning studies led to the identification of Endoplasmic Reticulum Golgi Intermediate Compartment (ERGIC) as responsible mutations. It has been shown that 18 distinct ERGIC-53 mutations can cause complete loss of ERGIC-53 protein expression. Patients with combined deficiency factor of V and VIII use factor VIII preparation and Fresh Frozen Plasma (FFP) to compensate (the low level of coagulation factor V & VIII) in the circulation. Like other inherited deficiencies of coagula-

***Correspondence:** Dr. Zahra Rezaie Yazdi, Research Manager, Main building of Mashhad Medical Sciences University, Daneshgah St, Mashhad, Iran.
E-mail: Rezaieyazdi-z@mums.ac.ir

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tion factors, these patients are susceptible to formation of inhibitors.

MATERIAL AND METHODS

Our studying group comprised 10 patients with combined factor V & VIII that included 6 males and 4 females. Our patients are from 3 unrelated families from different parts of northeast of Iran (Khorassan province). Minimum and maximum age of affected patients was 3 years and 45 years old respectively with mean 24.9±13.89 SD (years). Minimum and maximum factor VIII activity was 4% and 14% respectively with mean 10.1±3.07% SD and 5% and 14% respectively for factor V with mean of 9.1±3.41% SD among 10 affected patients.

The patients, who agreed to undergo inhibitor evaluation (10/19), were invited to Ghaem hospital in Mashhad for blood sampling and filling out questionnaires. Blood samples were collected with trisodium citrate (0.109M) with a proportion of 1: 9 and then centrifuged at 2000 g for 20 minutes at 4°C to get poor platelet plasma. These samples were stored at -80° C and transported to the coagulation laboratory of the Iranian Blood Transfusion Center in Tehran for testing. Inhibitor assay for factor V inhibitor and factor VIII inhibitor was performed by one stage method (Bethesda method).[14] Pooled plasma included samples of 23 healthy men and 3 healthy women. Normal plasma was an arbitrary value of 100% activity. Factor V & VIII C deficient plasma was used as commercial deficient plasma (Diagnostica Stago, France).

RESULTS

As Table I show among 10 patients under survey, 8 patients had factor VIII inhibitor and 2 patients none.

Minimum and maximum titer for factor VIII inhibitors were 0.57(B.U.) and 6 (B.U.) with mean of 2.06±1.75(B.U.).

Among 10 patients with combined factor V & VIII deficiency, 8 patients had factor V inhibitor.

Minimum titer and maximum titer of factor V was 0.63 and 5 (B.U.) with mean of 1.77± 1.44 (B.U.). All 8 patients had both factor V and VIII inhibitors.

DISCUSSION

The populations in the area around the Mediterranean basin appear to be the main source of these rare mutations. The frequency of combined deficiency of factor V and VIII in oriental Jews and Iranian families has regularly been estimated to be 1:100,000.[6] This may be due to the high rate of consanguineous marriages in Iranian families. Among these 10 patients 2 patients were son & daughter from one family. In Khorassan province we have a population of 5,600,000 and 19 known cases of combined factor V and VIII deficiency. So its frequency is approximately 0.34:100,000. Most of our patients have mild deficiency of factor V and also mild to moderate deficiency of factor VIII.

Factor VIII and IX inhibitors have been recognized in hemophilia A & B in previous decades and there are many papers and articles in this regard but we have not found any relevant article about the formation of factor V & VIII inhibitor. This may be due to the rare number of cases and their wide distribution in the population. However 8 patients with combined deficiency of factor V & VIII who were under study had both factor V and factor VIII inhibitor. Because factor VIII has the same domain structure as factor V (A1-A2-B-A3-C1-C2) and shares nearly 40% amino acid sequence homology in its A and C domains,[8] this inhibitor molecule(s) may be one molecule that recognizes and neutralizes both factor V and factor VIII. This is the problem which remains to be elucidated and our future survey will be about it and determine which domain(s) of factors V & VIII this inhibitor

Table I. Status of factor V &VIII inhibitors in 10 patients with combined factor V & VIII deficiency from northeastern Iran.

Patient No.	Factor V	Factor VIII Inhibitor (B.U.)	Frequency Inhibitor (B.U.)	Cumulative Percent
1&2	0	0	2	20%
3	0.63	0.57	1	10%
4	0.7	0.63	1	10%
5	0.8	1.2	1	10%
6	1.3	1.3	1	10%
7	1.5	1.9	1	10%
8	1.8	2.2	1	10%
9	2.5	2.7	1	10%
10	5	6	1	10%

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can recognize.

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