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Brief Communication

FIRST SURVEY OF FACTOR IX INHIBITOR IN NORTHEASTERN IRAN

Hemophilia is one of the most common, and is the most severe, inherited bleeding disorders. In 1952, Bigss and Aggeler recognized and described the two currently accepted types of the hemophilia, i.e. type A, or classical hemophilia and type B or Christmas disease.[1] This disease is classified as severe, intermediate and mild types according to plasma levels of the deficient coagulation factor.[2]

Modern control of hemophilia began in the 1970s with the introduction of plasma concentrates.[3] Nowadays with improvement of screening tests for donors, improvement of recombinant methods and introductions of tests such as PCR, risk factors for infection transition by coagulation factors have decreased but a new and major problem that has risen is inhibitor formation.[4] The Inhibitor in most cases of hemophilia B is IgG with IgG1 subclass;[5] this means that injected coagulation factor will be destroyed and neutralized without having any activity.[6,7]

The patients with inhibitor need more coagulation factors and control of bleeding episodes in these patients in comparison with hemophilia B without inhibitor is more difficult.

Although factor IX inhibitor is less common than factor VIII inhibitor,[8,9] it is more dangerous, because factor IX inhibitor may cause anaphylactic shock and death.[10] Due to absence of any study on this field for patients in northeastern Iran, we decided to investigate inhibitor status in these patients.

Forty-eight patients with hemophilia B participated in this study. Their mean age was 21.35 ± 11.8 SD years and minimum and maximum age of patients were 4 and 53 years old respectively. The patient population included 22 patients (45.9%) with severe, 18 patients (37.5%) with medium and 8 patients (16.6%) with mild hemophilia B. There are about 66 patients with hemophilia B in various cities of northeastern Iran (Khorassan province) that were invited for blood sampling and answering questionnaires of whom 48 patients responded.

After mixing blood samples with trisodium citrate 3.2 gr/dL (0.109 M) with a proportion of 1:9, blood samples were centrifuged with 2000 g for 15 minutes to gain Poor Platelet Plasma (PPP). Then we conducted a primary test $APTT_{mix}$ on mixture of equal volume of patient's plasma and pooled plasma (1:1). Pooled plasma included samples of 15 healthy men. In this test, most samples of patients who had inhibitor, were 8-10 s longer than control. Then incubation mixtures were prepared for all samples including 0.2 mL pooled plasma and 0.2 mL patient plasma and after 2 hours incubation in 37° C, Bethesda assay was evaluated according to references.[11-14] Factor IX deficient plasma was prepared commercially from (Diagnostica Stago, France). Reference interval for inhibitor was calculated less than 0.5 Bethesda Unit (BU).

Our obtained results showed that among 48 patients with hemophilia B, 3 patients (6.3%) had factor IX inhibitor. Minimum and maximum titer of inhibitor were 0.8 and 1.8(BU) respectively with mean of 1.38 ± 0.46 SD (BU).

Table I showed among 22 patients with severe hemophilia B, 2 patients (66.6%) had factor IX inhibitor, between 18 patients with medium hemophilia B no patient had inhibitor and among 8 patients with mild hemophilia B, 1 patient (33.3%) had factor IX inhibitor.

Factor IX inhibitor was detected in 3 patients (6.3%) of the population under survey. Although factor IX inhibitor has been documented in many articles so far, this is the first evaluation for inhibitor assay for patients with hemophilia B in northeast of Iran. Other similar researches have reported frequencies of factor IX inhibitor between 2%-12% in severe hemophilia B and to a less extent in medium and mild hemophilia B. Minimum and maximum titer of inhibitor were 0.8 and 1.8(BU) with mean 1.38 ± 0.46 SD. None of our patients under survey had been evaluated for factor IX inhibitor so far, while evaluation of inhibitor formation is recommended every 4-6 months for each patient with or without history of inhibitor. Our obtained result about the percent of factor IX inhibitor was in agreement with the estimation of inhibitor in other countries and people. Also we could show

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Table I. Results of inhibitor assay according to severity of hemophilia B.

Severity of hemophilia		RESULT		Total
		Negative	Positive	
Severe	Count	20	2	22
	%Within severity	90.9%	9.1%	100.0%
Medium	Count	18		18
	%Within severity	100.0%		100.0%
Mild	Count	7	1	8
	%Within severity	87.5%	12.5%	100.0%
Total	Count	45	3	48
	%Within severity	93.8%	6.3%	100.0%

that patients with severe hemophilia B are more susceptible to inhibitor formation, that is also in agreement with other similar articles in this field. All of our three patients with factor IX inhibitor had low titers of factor IX inhibitor that may be due to less common use of coagulation therapy in these patients.

Due to the importance and serious danger of high titers of factor IX inhibitor, it is recommended that all patients with hemophilia B be evaluated for factor IX inhibitor every 6 months at least.

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