Inhibitors of Hemophilia A in Children Less Than 15 Years Attending Children Welfare Hospital in Baghdad

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Abstract:

Background: Inhibitor formation is a major complication of hemophilia treatment that interferes with clinical response to factor infusion and results in significant morbidity. It is estimated to occur in up to (15–25%) of hemophilia A patients treated with factor VIII.

Aim of the study: The objective of this study is to assess factors associated with inhibitor development in patients less than15 year old with hemophilia A in children welfare teaching hospital in medical city/ Baghdad.

Patients and methods: A retrospective descriptive study that had been performed by reviewing patients files & interviewed with those who visited the hemophilia ward in children welfare teaching hospital ,medical city , Baghdad , from the 1st of August 2008 to the 1st of September 2012. Detection of inhibitors was done by mixing study for the (258) patients with hemophilia A less than 15 year old & then Bethesda assay for those with not corrected mixing study. Then data were collected from patients with positive test for inhibitors according to a pre-constructed forma which contained clinical, laboratory finding & treatment regimens.

Results: it was found that, from (285) hemophilia A treated patients less than 15 year old only (27 ,10.47%) patients had inhibitors, from these; the majority (26) patients (96.3%) of them had severe hemophilia A while one patient (3.7%) had moderate hemophilia A. Twenty two patients (81.5%) were high responders while three patients (11.1%) were low responders. the majority (22 ,81.5%) of our studied patients received blood and blood products transfusion before they developed inhibitor.

Conclusion: Understanding the environmental (modifiable) risk factors responsible for increased risk of inhibitor development is essential to identify patient's risk profile and to allow tailoring of treatment on an individual basis (thus reducing inhibitor formation risk and obtaining optimal benefit).

Recommendations: The avoidance/minimization of intense FVIII exposure (possibly through early prophylaxis, and furthermore, delayed surgical procedure when possible) during the first year of life. Further research is necessary to establish the efficacy of such an approach and to ascertain further measures that may be implemented to reduce the likelihood of inhibitor development in the high-risk patients.

***Key words*:** Inhibitors, Bethsida Test, Factor 8, Recombinant Activated Factor 7, Mixing Studu.

Introduction:

The hemophilia's are a group of related bleeding disorders that most commonly are inherited. Hemophilia A and B are X-linked recessive diseases. They exhibit a range of clinical severity that correlates well with assayed factor levels. Severe disease is defined as < (1%) factor activity, whereas 1 to (5% and >5%) of normal are defined as moderate and mild disease, respectively [1, 2]. Hemophilia occurs in

approximately 1:5,000 males, with (85%) having factor VIII deficiency and (10-15%) having factor IX deficiency. Hemophilia shows no apparent racial predilection, appearing in all ethnic groups [3].

A common complication of hemophilia is the development of an inhibitor which usually occurs shortly after replacement therapy has been initiated. The inhibitors are antibodies (primarily IgG) polyclonal alloantibodies directed against the specific deficient factor which neutralize clotting factor activity [4].

Inhibitor formation is estimated to occur in up to (15–25%) of hemophilia A patients treated with factor VIII [4]. Inhibitor antibody formation is a T cell-dependent immune response directed against infused factor VIII [5].

People with inhibitors find that their normal treatment does not work. They face uncontrolled bleeding, pain, and joint damage more frequently because treatment with factor concentrates is ineffective. Inhibitors are a significant concern for people living with hemophilia, and treating them is one of the biggest challenges in hemophilia care today, Inhibitors occur more frequently in patients with severe forms of hemophilia and are rarer in people with moderate or mild hemophilia. The vast majority of patients who develop an inhibitor do so within the first 50-75 exposure days, with a maximum risk around the 10-20th exposure [6].

Patients with inhibitors have more difficulty in achieving hemostasis and tend to have more musculoskeletal complications; in this setting, the bleeding frequency may increase due to the presence of acute and chronic synovitis [7].

An inhibitor is suspected when the patient's bleed is not promptly controlled with the usual dose of clotting factor concentrate; or when the treatment seems less and less effective and bleeding becomes more and more difficult to control.

In about one-third of patients with factor VIII inhibitors, the inhibitor disappears spontaneously (this is called a transient inhibitor). Among those with persistent inhibitors, (60-80%) can be eliminated using immune tolerance induction. In the remaining (20-40%) of cases, immune tolerance induction fails and inhibitors persist throughout the patient's life [6].

Aim of the study:

The objective of this study is to assess the factors associated with inhibitor development in patients less than15 year old with hemophilia A in children welfare teaching hospital in medical city/ Baghdad.

Patients and methods:

A retrospective descriptive study that had been performed by reviewing patient's files and interviewed with hemophilic patients who visited the hemophilia ward in children welfare teaching hospital, medical city, Baghdad, from the 1st of August 2008 to the 1st of September 2012. Detection of inhibitors was done by mixing study for the (258) patients with hemophilia A less than 15 year old and then Bethesda inhibitor assay for those with not corrected mixing study. Data were collected from patients with positive test for inhibitors according to a pre-constructed forma which contained clinical, laboratory finding and treatment regimens.

Results:

The total number of patients with hemophilia A (age less than 15 years) included in the study was (258) patients, (166) patients had severe hemophilia, (64) patients had moderate type and (28) patients had mild hemophilia (figure 1).

In this study; it was found that (27) patients (10 %) had inhibitors (figure 2).

Regarding the severity of hemophilia A, in this studied sample it was found that the majority (96.3%) of patients with inhibitors had severe hemophilia A while (3.7%) had moderate hemophilia A (table 1).

Table 2 shows the duration between first time factor VIII infusion and inhibitor development. It was found that (14.8%) of the patients developed inhibitor in less than one year duration, (14.8%) developed inhibitor between (1-2) years duration and (70.4%) developed inhibitor in more than 2 years durations.

According to Bethesda test it was found that (81.5%) of patients were high responder, (11.1%) were low responders (table 3).

An exposure day is a 24-hours period during which a dose of concentrate has been administrated, irrespective of size and frequency) [8]. Regarding number of exposure days to factor VIII before development of inhibitors; it was found that the majority (59.3%) of the studied sample had less than 50 exposure days while (40.7%) had 50 or more exposure days to factor VIII (table 4).

In relation to family history of inhibitors it was found that (33.3%) of the studied patients had positive family history of inhibitors and (66.7%) had negative family history of inhibitors (table 5).

In this study; it was found that the majority (81.5%) of studied patients received blood and blood products transfusion before they developed inhibitor, (68.2%) received blood and cryoprecipitate, (13.6%) received cryoprecipitate only, (9.1%) received blood transfusion only (4.5%) received fresh frozen plasma and cryoprecipitate and (4.5%) received all while (18.5%) didn't receive blood or blood products transfusion (table 6).

Discussion:

Inhibitor formation is a major complication of hemophilia treatment that interferes with clinical response to factor infusion and results in significant morbidity. It is estimated to occur in up to (15–25%) of hemophilia A patients treated with factor VIII.

Regarding the severity of hemophilia in this studied sample , it was found that the majority (96.3%) of patients with inhibitors had severe hemophilia A, while (3.7%) had moderate hemophilia A, this result is comparable to study done by Mahasandana [9] they had nine cases with inhibitors (eight of them had severe hemophilia and one moderate hemophilia A).

In this study (15.6%) of patients with severe hemophilia A were developed inhibitors to factor VIII. In a study done by Lusher JM [10] in USA, it was found that (25-50%) of children with severe hemophilia A, developed inhibitors to factor VIII. The discrepancy between these two results probably related to the sample size, regularity of attendance of the patient for treatment, and availability of the factor VIII.

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In Netherland, a study done by Gouw SC et al [11]. They found that the median duration between the first exposure to factor VIII and inhibitor development was 6 months.

It was found that (81.5%) were high responder, (11.1%) were low responder and in (7.4%) Bethesda test was not done because the patient did not attend the haemophilia ward, the result was comparable to a study in Spain in which (81.8%) of patients with inhibitors were high responders and (18.2%) were low responders [12], but differ from that mentioned by YEE T. T. et al [13] whom did a study in London, where (48%) of patients were high responders and (52%) patients were low responders. Also it's differ from the result of a study done in Germany by Scharrer I et al [14]; were they found that the majority of those with inhibitors were low responders. The discrepancy between these results is a matter of further studies.

Concerning family history of inhibitors, it was found that (66.7%) of patients did not have inhibitors in their families and (33.3%) had positive family history of inhibitors, this is comparable to a study done by Gouw SC et al [11]. in which there was negative family history of inhibitors in (85%) and positive in (15%).

This study revealed that 22 patients (81.5%) had received blood and blood products transfusion before they developed inhibitors, and 5(18.5%) didn't receive blood and blood products, this result agree with a Ragni M. V. et al study in USA [15] in which (80%) of patients with inhibitors were have history of blood or blood product receiving, also a study done in Germany by Ehrenforth S et al [16], which confirmed that inhibitor formation is associated with blood products exposure.

Conclusion:

Understanding the environmental (modifiable) risk factors responsible for increased risk of inhibitor development is essential to identify patient's risk profile and to allow tailoring of treatment on an individual basis (thus reducing inhibitor formation risk and obtaining optimal benefit).

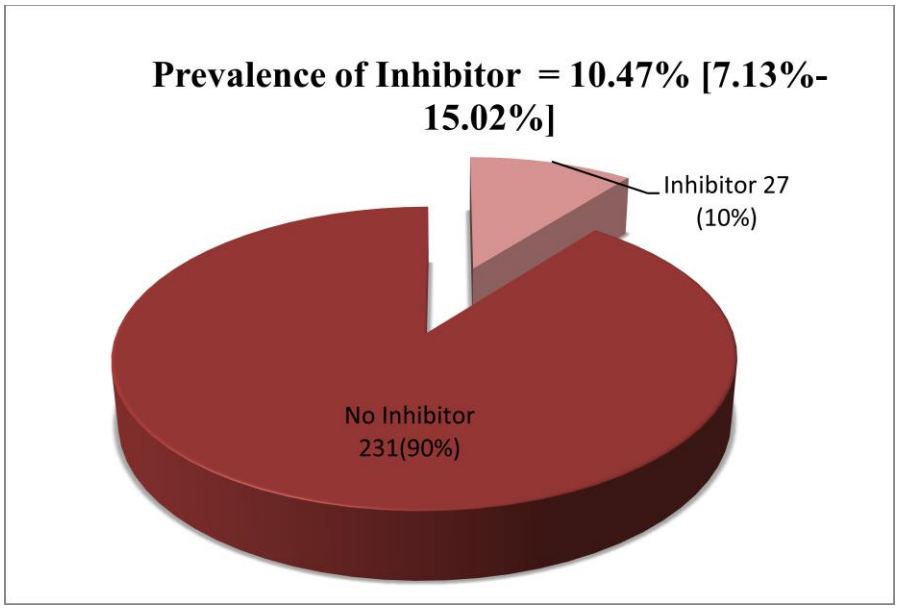

Figure (2): Prevalence of inhibitor among hemophilia A patients.

Table (1): Distribution of study sample according to severity.

Severity of Hemophilia A	N	(%)
severe	26	(96.3)
moderate	1	(3.7)
Total	27	(100.0)

Table (2): Duration between first time factor VIII infusion and inhibitor development.

Durations	Total=27	100%
< one year	4	14.8
1-2 year	4	14.8
> 2 year	19	70.4
Total	27	100.0

Table (3): Distribution of study sample according to Bethesda test.

Bethesda Test	N	(%)
High Responders	22	(81.5)
Low Responders	3	(11.1)
Total*	25	(100.0)

***In two patients, Bethesda test was not done.

Table (4): Distribution of study sample according to family history of factor VIII inhibitors.

Family History of Inhibitor	N	(%)
Yes	9	(33.3)
No	18	(66.7)
Total	27	(100.0)

Table (5): Distribution and descriptive statistics of study sample according to blood and blood products transfusion.

	Variables	No.	%
1.	No history of transfusion	5	(18.5)
2.	Positive history of transfusion	22	(81.5)
	*Blood	2	(9.1)
	*Cryoprecipitate	3	(13.6)
	*Blood & Cryoprecipitate	15	(68.2)
	*FFP & Cryoprecipitate	1	(4.5)
	*All types	1	(4.5)

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