Allergic reaction in a cohort of hemophilia A patients using plasma-derived factor VIII concentrate is rare and not necessarily triggered by factor VIII

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INTRODUCTION

In contrast to hemophilia B, allergic manifestations are rare complications in hemophilia A patients treated with factor (F) VIII concentrates. Nevertheless, it can be serious and hamper the hemophilia treatment in these cases. The objective of this study was to evaluate the incidence of allergic reaction in a cohort of hemophilia A patients treated only with plasma-derived FVIII (pdFVIII) concentrates.

METHOD

Patients presenting with allergic symptoms after administration of pdFVIII concentrates were prospectively assessed for the occurrence of allergic reactions in subsequent infusions and evaluated for the presence of neutralizing antibodies against FVIII (inhibitors) and the anti-FVIII immunoglobulins subclasses.

Detection of neutralizing antibodies against FVIII:

Inhibitors were determined by Bethesda-Nijmegen modification assay.

ELISA for detection of binding subclasses antibodies:

Anti-FVIII immunoglobulins were detected by ELISA method, according to standard procedures, using antihuman-Ig specific for subclasses IgG1, IgG4 and IgE (Southern Biothechnology Inc., USA). The plates were coated with a pdFVIII, Octavi SD Optimum® (Octapharma, France), or a full-length recombinant FVIII concentrate (rFVIII), Advate® (Baxter, Switzerland). Plasma samples were diluted between 1:10 and 1:1,280. Samples from 20 healthy individuals were used to validate the test.

RESULTS

Three out of 322 hemophilia A patients (0.9%) presented with allergic reaction after exposure to plasma derived products (pdFVIII or aPCC) during the past fifteen years in our center. The clinical and laboratory finding are on the table 1.

Patient 1

The first case was a 46 years-old man, with severe hemophilia A (FVIII < 1 IU/dL), without history of inhibitor, and no evidence of atopic diseases. During the previous 5 years, he presented sporadic allergic reactions with the use of several different pdFVIII concentrates. In the investigation no deficiency of IgA was detected, while elevated serum level of IgE was observed. During the treatment of a joint bleed event with pdFVIII concentrate, (Octavi SD Optimum®, Octapharma, France) he developed a severe allergic reaction, with urticaria, laryngeal edema, and bronchospasm. Anti-pdFVIII IgG4 was detected in the samples collected at the same day of the allergic reaction with peak titer after 15 days. Interestingly, anti-pdFVIII IgE was also detected in the same samples. However, no IgE was observed when ELISA plates were coated with rFVIII, and low titer of IgG4 was detected in these analyses, although inhibitor remained negative during the whole period (Fig. 1A).

Patient 2

The second case was a 35 years-old man, with severe hemophilia A (FVIII < 1 IU/dL). Ten years before, he developed allergic reactions to pdFVIII concentrate, characterized by fever and chills. In that occasion inhibitor was detected for the first time, with peak titer of 160 BU. No evidence of IgA deficiency or clinical manifestations of atopic diseases were observed, despite high level of serum IgE. Plasma samples were collected when he presented allergic symptoms after he received aPCC for the treatment of a hemathrosis. The analyses in those two occasions showed that anti-FVIII IgG1 and IgG4 were observed when the ELISA plates were coated with both pdFVIII and rFVIII (Fig. 1B). Anti-FVIII IgE was negative in these analyses.

Patient 3

The third one was a 5 years-old boy with moderate hemophilia A (FVIII 4.6 IU/dL), with history of atopy, manifested as allergic rhinitis and asthma, with high serum level of IgE. One year before, during the treatment of a mild hematoma with pdFVIII, he developed urticarial reaction associated with bronchospasm, fever and facial angioedema. These allergic manifestations disappeared after switching to recombinant FVIII concentrate. Inhibitor was never detected and IgA deficiency was excluded. Plasma samples were collected 48 hours after a severe allergic reaction with the use of plasma-derived product and four months later. No anti-FVIII immunoglobulin was detected in the samples first collected, and only low titer of anti-pdFVIII IgG1 was observed in the samples collected four months after the reaction (Fig. 1C).

Figure 1.

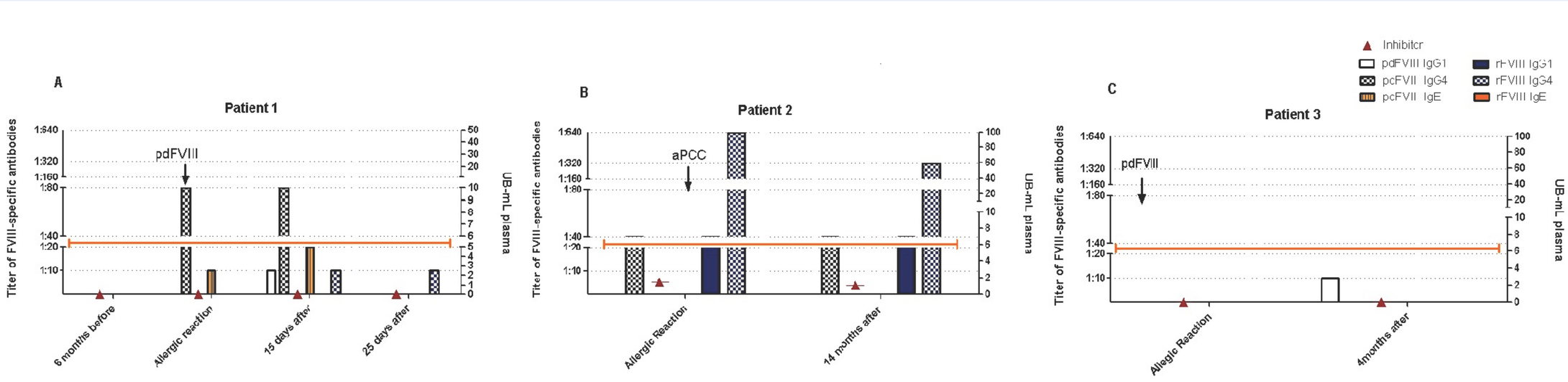

Table 1. Clinical and laboratory findings of three cases with allergic reaction to pdFVIII concentrates

	Patient 1	Patient 2	Patient 3
Age at enrollment	46y	35y	5y
Race	Black	Caucasian	Black
Diagnosis	Severe HA	Severe HA	Moderate HA
FVIII genotype	ND	p.Q1659Stop	ND
Inhibitor history	No	High-responding	No
Comorbidities	HCV and chronic arthropathy	HCV and chronic arthropathy	None
Type of products related to allergic reactions	Several pdFVIII	Several pdFVIII and aPCC	Several pdFVIII
Atopic history	No	No	Yes
Family allergy history	No	No	Yes
Serum IgE level, IU/mL	1,430 (NR < 100 IU/mL)	6,430 (NR < 100 IU/mL)	3,560 (NR < 90 IU/mL)
IgA deficiency	No	No	No

HA, hemophilia A; ND, not determined; HCV, hepatitis C virus; pdFVIII, plasma-derived factor VIII concentrate; aPCC, activated prothrombin complex concentrate; NR, normal range according to the age.

DISCUSSION

Allergic reactions with the use of FVIII-containing products are not frequently observed. In the past fifteen years we followed more than three hundred hemophilia A patients, that had received only pdFVIII products during this period. In this cohort we observed an occurrence of allergic reactions in 0.9% of these patients.The use of rFVIII products can be an alternative for most of the cases in whom the allergic manifestation is related to other proteins present in plasma-derived products. However, in the case of FVIII driven allergic reaction the use of rFVIII products will not be the best choice, and in fact, this can intensify the reaction. Kadar et al. 2007, described a case report with anaphylactic reaction after the administration of rFVIII, and proved for the first time that it was mediated by anti-FVIII IgE.

CONCLUSION

In our cohort of hemophilia A patient the incidence of allergic reaction to pdFVIII products was lower than 1%. The in vitro evaluation performed in samples from the three patients with these events, was not able to demonstrate that the allergic manifestation was directed to FVIII. Thus, apart from the limitations when inhibitor is present, the use of rFVIII concentrate can be a choice for this kind of complication.

REFERENCE

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