

CASE REPORT

IgE-mediated anaphylactic reaction to purified and recombinant factor VIII in a patient with severe haemophilia A

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Summary. We report a 51-year-old patient with severe haemophilia A developing a severe life-threatening anaphylactic reaction to recombinant factor VIII (rFVIII). Anaphylactic reactions are a rare but well-known side effect of FVIII products. The nature of these reactions could not be clarified as previous studies failed to demonstrate a specific IgE response.

Here, we could prove a grade 3 anaphylactic reaction as an IgE-mediated response to rFVIII for the first time by Western blotting.

Keywords: allergy, bleeding disorder, IgE-mediated reaction, inhibitors, recombinant

Introduction

The mainstay of haemophilia A therapy relies on the replacement of lacking factor VIII (FVIII) by infusions of FVIII concentrates. The FVIII products used today are either plasma derived or recombinant [1]. Whereas the development of IgG isotype inhibitors is a serious and frequent complication in the management of haemophilia [2–4], the development of IgE antibodies to FVIII has not yet been reported. The IgE isotype is responsible for immediate type I reactions, resulting in a potentially life-threatening situation, if the allergen is encountered. This is the first report demonstrating a clear IgE-mediated reaction to purified and recombinant factor VIII (rFVIII).

Case report

We report a 51-year-old male patient with severe haemophilia A (<1% VIII-activity), no evidence of atopy and IgA deficiency. The patient had a history of hepatitis C, psoriasis vulgaris and haemophilic arthropathy and low-titre FVIII inhibitor (7.2 BU). For the FVIII-specific inhibitor test, the modified Nijmegen method was used [5] based on the one-

stage FVIII clotting measurement (BCS-Coagulometer [Dade Behring, Holding GmbH, 65760 Eschborn, Germany]). Genotyping revealed a 2302delC mutation corresponds with a high probability of IgG inhibitor development [6]. He had been without the necessity for factor replacement for 2 years, when he presented with bleeding into his outer abdominal muscle. Human factor VIII (hFVIII) concentrate (Haemate HS, ZLB Behring [ZLB Behring GmbH, 35002 Marburg (Lan), Germany]) had to be reinstituted. Subsequently, he developed a large iliopsoas haematoma. However, after periodic substitution with a purified FVIII product, the patient increasingly developed pruritus and urticaria. These symptoms were responsive to prophylactic intravenous (i.v.) antihistamines and corticosteroids. In an attempt to eliminate these unwanted symptoms, it was decided to change treatment to a recombinant form of FVIII (Advate® Baxter [Baxter GmbH, 85716 Unterschleißheim, Germany]). However, the application of 1000 U led to a massive (WHO grade 3) anaphylactic reaction including generalized erythema, conjunctivitis, rhinorrhoea, bronchospasm and initially treatment-resistant hypotension. The symptoms resolved after appropriate emergency treatment.

Allergologic testing was performed including prick and intracutaneous testing of the purified and recombinant product eliciting positive reactions. The intracutaneous testing was positive with an urticarial reaction to purified (1:100 dilution of i.v. preparation) and recombinant (1:1000 dilution of i.v. preparation) FVIII. Furthermore, Western blotting

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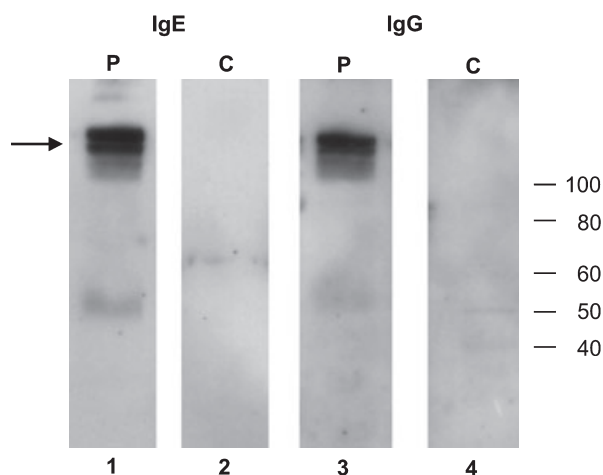


Fig. 1. Western blotting: presence of IgE (lane 1) and IgG (lane 3) antibodies against recombinant FVIII (Advate®) in the serum of the patient, but not in control serum (lane 2, lane 4).

revealed the presence of IgE and IgG antibodies to the recombinant form of FVIII used (Fig. 1).

The laboratory investigations showed a total IgE of 66.6 kU L^{-1} and a latex CAP class 2 (Fa Pharmacia – Upjohn) (0.95 kU L^{-1}).

Discussion

Based on the medical history and the test results, an FVIII-specific allergy was diagnosed. Anaphylactic reactions are a rare but well-known side effect of FVIII products [2]. Adverse reactions have also been frequently observed after porcine FVIII [7]. The nature of these reactions could not be clarified as previous studies failed to demonstrate an FVIII-specific IgE response. Furthermore, despite the fact that in up to 30% of haemophiliacs the development of FVIII inhibitor IgG antibodies can be detected, an Ig class-switch to an IgE response to FVIII has not yet been reported.

In 1998, two cases of IgE-mediated anaphylactic reactions to factor IX were published [8]. Both cases showed positive skin prick testing and Radio-allergen-sorbent-test (RAST)-reactions. Western blotting was not performed. Shopnick *et al.* reported an anaphylactic reaction following the infusion of a recombinant form of FVIII concentrate. However, the paper did not demonstrate an IgE response to FVIII. In our case, we could demonstrate an IgE as well as an IgG antibody response to the rFVIII by Western blotting.

Recently, it has been suggested that the lack of von Willebrand factor may enhance the immunogenicity of rFVIII products as it may interfere with the recognition of antigenic epitopes in the purified FVIII products [9,10]. This may, in part, explain the

markedly enhanced anaphylactic reaction after the administration of the recombinant product.

Alternative therapeutic options are the application of recombinant, activated factor VII (rFVIIa) [11,12]. To our knowledge, this is the first report on a proven IgE-mediated anaphylactic reaction to hFVIII representing a new potentially life-threatening adverse effect of FVIII replacement therapy.

Declaration of sources and funding

None.

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