

CASE REPORT

Anaphylaxis after treatment with recombinant factor VIII: investigation and therapeutic challenge

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SUMMARY

We report a 10-year-old patient with haemophilia A developing anaphylaxis to recombinant factor VIII (octocog alfa). Allergic reactions, and especially anaphylactic events, are rare in patients with haemophilia A. The nature of these reactions is not fully understood. Here, we demonstrate a type I hypersensitivity reaction using sodium dodecyl sulfate-polyacrylamide gel electrophoresis immunoblotting assay. This test revealed itself as an essential diagnostic tool, as it allowed us to choose an alternative treatment (moroctocog alfa). Its safety was later confirmed by an uneventful challenge test.

BACKGROUND

Haemophilia A (HA) is an X linked disease characterised by a coagulation factor VIII (FVIII) deficiency, which accounts for 85%–90% of patients with haemophilia.¹ FVIII substitution treatment products are used to treat HA, and this molecule can be derived from processed human plasma (immunopurified FVIII) or produced from cell lines engineered to express large amounts of FVIII (recombinant FVIII).² In mild cases, it is also possible to use products other than clotting factor, as synthetic drug desmopressin.

In contrast to haemophilia B, allergic manifestations are rare complications in patients with HA treated with FVIII products. Also, in haemophilia B, allergic reactions are implicated in a higher risk of inhibitors development, which does not happen in HA.² There are few published reports of anaphylactic reaction in patients treated with FVIII^{3–10} and the mechanisms involved in these events remain controversial. The allergic investigation is essential to identify a safe alternative treatment for these patients.

The aim of this report is to describe a rare anaphylactic reaction to recombinant FVIII (octocog alfa) in a haemophilic child and describe the allergic research that allowed us to identify a safe therapeutic option.

CASE PRESENTATION

The patient is an adolescent with mild HA (35%–40% FVIII activity; hemizygotic for the mutation: exon18; nt 5962–5964 del 3pb (GAG), del codon 1969), without evidence of atopic diseases. In the previous years, during bleeding episodes, he was treated once with immunopurified FVIII,

and several times with desmopressin, without any complication.

At the age of 10, he presented at the emergency department (ED) with a finger haematoma, demanding recombinant FVIII administration (octocog alfa, infusion of 500 U). The infusion was uneventful and he was discharged from ED. He did not receive any other treatment, nor did he suffer from a viral infection at that time.

Fifteen minutes later he developed dry cough, sore throat and dizziness, and in 25 min also had pruritus and urticaria, so he was brought back to the hospital. At observation he was haemodynamically stable (blood pressure 102/56 mm Hg; heart rate 80 bpm), without any difficulty breathing and the only alteration observed was an evanescent rash. He was treated with an oral antihistamine (hydroxyzine) with complete resolution of symptoms.

He had no known allergies. Inhibitors test by Nijmegen-Bethesda methodology was always negative and IgA deficiency was excluded.

INVESTIGATIONS

Six months later, he was submitted to a consented challenge test with octocog alfa administered at a slow rate infusion (1 mL/hour) and immediately after he developed chest tightness, nausea and vomiting. There was no haemodynamic instability and symptoms resolved with intramuscular epinephrine (1:1000, 0.01 mL/kg=0.4 mL).

Allergologic workup included prick test with three different samples of FVIII (octocog alfa 100 IU/2 mL, moroctocog alfa 1000 IU/10 mL, plasma-derived FVIII 1000/10 mL) with no cutaneous reaction. Basophil degranulation test to the previously mentioned drugs was also negative. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting assay suggested the presence of specific IgEs in patient's serum, able to react with proteins present in octocog alfa and plasma-derived FVIII sample. However, no specific IgE was detected against moroctocog alfa (figure 1). The search for inhibitors was negative (IgG antibodies).

Considering the analytical study, a challenge test with moroctocog alfa was conducted in day hospital setting without any adverse events.

OUTCOME AND FOLLOW-UP

Since the anaphylactic reaction, the patient did not need any treatment with recombinant FVIII but, if necessary moroctocog alfa, is presumably the drug



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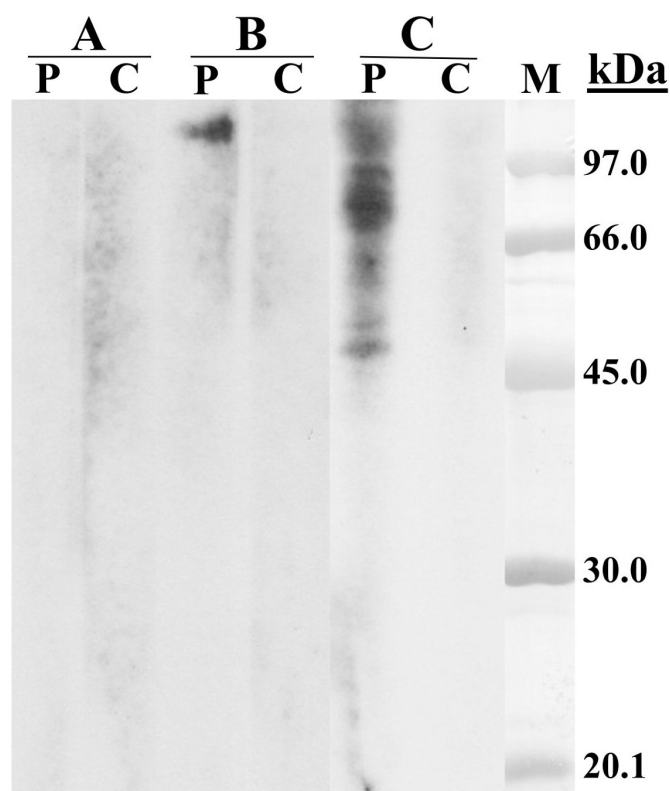


Figure 1 Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting results. (A) Moroctocog alfa. (B) Octocog alfa. (C) Plasma-derived factor VIII (FVIII) sample. Lane P: patient serum. Lane C: control serum (pool of sera from non-atopic subjects). Lane M: molecular mass standard.

of choice, as both the analytical study and the challenge test confirmed its safety.

DISCUSSION

Allergic reactions with the use of FVIII are uncommon. It is unusually coincident with the development of an inhibitor antibody which did not happen in our case. Even so, it complicates treatment to a great degree.¹

Despite its rarity, FVIII allergy can be life threatening and hamper replacement therapy. There are reports of anaphylactic reactions in patients with HA with allergy either to plasma derivative^{3–5 7–9} and recombinant FVIII concentrates.^{3–6 9} When these reactions occur it is mandatory for a clinical investigation to exclude other causes (eg, fast rate of drug administration) and to search for therapeutic alternatives. Indeed, in our case, the challenge test confirmed the diagnosis of drug allergy.

The pathophysiology of these rare allergic reactions linked to FVIII is not yet fully understood. In general, the most common allergic reactions to drugs are type I hypersensitivity reaction which is mediated by IgE. However, in HA there are few case reports that could demonstrate an FVIII-specific IgE response.^{4 7} Other authors suggest an association between IgG2 or IgG4 as the cause of the anaphylactic response.^{9 10} Pernod *et al* suggest a link between these allergic reactions and human anti-mouse anti-FVIII antibodies or albumin antibodies in patients treated with immunopurified concentrates or first/second-generation recombinant FVIII products, respectively.³ Other reports were simply unable to identify the cause of the reaction.^{5 6}

In this report, the SDS-PAGE immunoblotting assay was an essential tool for the physiopathological diagnosis. It confirmed a type I hypersensitivity reaction.

The possible link between IgG antibodies and anaphylactic reaction reported in previous cases of severe haemophilia⁹ was excluded as the inhibitors were always negative. The following step in our study was to search for safe therapeutic alternatives to octocog alfa.

As a result of all our research, we studied FVIII replacement products: two recombinant FVIII concentrates (moroctocog alfa and octocog alfa) which are produced from animal cell lines, and one plasma-derived FVIII. Both recombinant FVIII concentrates are produced from a mouse cell line and do not contain albumin in the final preparation (as in first-generation recombinant products). Previous case reports have hypothesised that albumin could be a trigger factor for anaphylactic reactions when using FVIII products.³ The immunoblotting result showed no evidence of specific IgE against anti-moroctocog alfa, so it was considered a safe alternative which avoided the need of a desensitisation procedure. The safety of moroctocog alfa treatment was confirmed by a challenge test without adverse reactions.

As an alternative therapy, fourth-generation recombinant FVIII products (eg, simoctocog alfa) could also be considered, as they are produced in human cell lines and have no added human or animal protein.² It is assumed that this protein minimises the risk of allergic reactions due to the lack of eventual contaminant proteins from non-human origin, and due to a protein structure very similar to the endogenous FVIII (if not the same).

The authors highlight the importance of reporting these rare reactions to FVIII and the study that allowed us to offer an apparent first-line therapeutic option to our patient in order to promote a better knowledge of the diagnostic and therapeutic approach for these patients.

Learning points

- ▶ Anaphylactic reactions are a side effect of factor VIII (FVIII) products.
- ▶ Although the mechanism of these adverse effects remains controversial, the anaphylactic response can be caused by a type I hypersensitivity reaction.
- ▶ Sodium dodecyl sulfate-polyacrylamide gel electrophoresis immunoblotting assay can be a helpful diagnostic tool in FVIII allergy.

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