CASE REPORT

Detection of Serum Histamine-Releasing Factors in a Patient With Idiopathic Anaphylaxis and Multiple Drug Allergy Syndrome

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Abstract

We describe the case of a 30-year-old woman who reported several episodes of anaphylaxis with angioedema and relapsing urticaria. Some events were related to nonsteroidal anti-inflammatory drug intake and one episode followed alcohol ingestion, but in most cases no triggers could be identified. Specific immunoglobulin E determination was negative for food and drug allergens, C3 and C4 were in the normal range, C1 inhibitor was slightly reduced and serum tryptase was undetectable. In vivo autologous serum skin test and in vitro basophil histamine release assay were positive indicating the presence of circulating histamine-releasing factors. When oral tolerance tests were performed, only doxycycline was tolerated whereas levofloxacin, clarithromycin, nimesulide and tramadol caused mild urticaria. Premedication with cetirizine allowed the patient to tolerate levofloxacin, clarithromycin and nimesulide. The demonstration of circulating histamine-releasing factors in a patient with idiopathic anaphylaxis and multiple drug allergy syndrome provides a new mechanistic insight and might open the way to new therapeutic approaches.

Key words: Autologous serum skin test. Chronic urticaria. Histamine-releasing factors. Idiopathic anaphylaxis. Multiple drug allergy syndrome.

Resumen

Describimos el caso de una mujer de 30 años con varios episodios de anafilaxia con angioedema y urticaria recidivante. Algunos episodios se relacionaron con la administración de NSAID y un episodio con la ingesta de alcohol, pero en la gran mayoría de casos no pudo ser identificado el factor desencadenante. La determinación de immunoglobulina E específica fue negativa para alérgenos alimentarios y drogas, C3 y C4 estaban dentro de los valores normales, el C1 inhibidor estaba levemente disminuido y la triptasa sérica indetectable. Tanto el test del suero autólogo in vivo como el test de liberación de histamina in vitro fueron positivos indicando la presencia de factores de liberación de histamina circulantes. Efectuado el test de tolerancia oral, sólo la doxiciclina fue bien tolerada mientras la levofloxacina, la claritromicina, el nimesulide y el tramadol causaron una leve urticaria. La premedicación con cetirizina permitió a la paciente tolerar la levofloxacina, la claritromicina y el nimesulide. La demostración de factores de liberación de histamina circulantes en nuestra paciente con anafilaxia idiopática y síndrome de alergia múltiple a drogas conduce a un nuevo mecanismo intrínseco abriendo la vía para una nueva línea terapéutica.

Palabras clave: Test cutáneo con suero autólogo. Urticaria crónica. Factores de liberación de histamina. Anafilaxia idiopática. Síndrome de alergia múltiple a drogas.

Introduction

Idiopathic anaphylaxis is a life-threatening condition characterized by recurrent episodes of anaphylaxis triggered by unknown stimuli [1-3]. Although clinical and functional differences have been found among patients with idiopathic anaphylaxis [4], the pathomechanism remains elusive and treatment is only symptomatic. Several mechanisms have been proposed to explain idiopathic anaphylaxis, including occult systemic mastocytosis, an increased releasability of basophils and mast-cells, the release of histamine-releasing factors from lymphocytes, sensitivity to endogenous and exogenous hormones and intake of certain drugs, such as ß-blocking agents, angiotensin-converting enzyme inhibitors and even cyclo-oxygenase inhibitors [5]. However, once an occult systemic mastocytosis has been excluded, no definite mechanism has been identified as underlying cause of idiopathic anaphylaxis. In recent years, it has been demonstrated that 30-50% of patients with chronic urticaria have circulating histamine-releasing autoantibodies directed either against the α subunit of the high affinity immunoglobulin (Ig) E receptor (FcεRIα) or against IgE [6-8]. The presence of these histamine-releasing autoantibodies can be demonstrated in vivo by intradermal injection of autologous serum (autologous serum skin test [ASST]) and in vitro by measurement of histamine release from basophils stimulated with patients' sera (basophil histamine release assay [BHRA]) [9,10].

It has been suggested that histamine-releasing autoantibodies may be involved in idiopathic anaphylaxis, but definitive proof of this is still lacking. Here we describe a patient with recurrent episodes of anaphylaxis triggered by drugs or by unknown stimuli, who had a positive ASST and BHRA.

Case Description

A 30-year-old woman came to our clinic because she reported several episodes of anaphylaxis with angioedema occurring from the age of 16 and she was looking for antibiotics and antiinflammatory drugs that she could tolerate. In her family history there were no allergic disorders or episodes of angioedema. She had smoked five cigarettes per day since the age of 20 and she had been taking oral contraceptives for the last five years. The first episode of anaphylaxis with angioedema occurred when she was 16, after having eaten pasta and fish and after having taken an acetylsalicylic acid tablet. Hospitalization in intensive care and treatment with epinephrine, H_1 antihistamines and steroids was followed by a prompt recovery. She reported 15 further episodes of generalized anaphylaxis with angioedema up until the age of 28, at least two of which required hospitalization in an intensive care unit. One episode of anaphylaxis occurred after alcohol intake; and in all the other cases, no relationship was reported with food or drug intake, exercise or insect bite. In addition, the patient reported frequent but transient urticarial rashes that she could easily control with H_1 antihistamines. In some cases the urticarial rashes followed ingestion of acetaminophen or pyrazolones, but most frequently no triggering factors could be identified. In the last two years the patient avoided any drug intake except for oral contraceptives and she experienced only recurrent mild urticaria. Skin prick tests for inhalant and food allergens were performed when she was 26 and were negative. An additive-free diet was tried before the patient came to our clinic, but had no effect whatsoever on the urticaria. The search for specific IgE antibodies for inhalant, food, drug and hymenoptera venoms was performed by UniCAP RAST (Phadia, Uppsala, Sweden) and was slightly positive for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (0.56 and 0.61 kU_A/L, respectively, with negative values below 0.35 kU_A/L) and for yellow jacket (0.48 kU_A/L). Total IgE level was 158 kU/L (normal values < 100 kU/L). Common laboratory investigations were normal, including a hemocytometric test, renal and liver function tests and serum electrophoresis. Functional C1 esterase inhibitor, measured by the reagent kit of Immuno (Vienna, Austria) was slightly below the normal range (60% with normal values ranging between 70 and 120%). Antigenic C1 inhibitor was assayed by radial immunodiffusion (Dade Behring, Monburg, Germany) and was also slightly reduced (60% with normal range between 70 and 120%). Serum levels of the complement fractions C3 and C4 were determined by radial immunodiffusion (Dade Behring) and were normal, although C4 was at the lower limit of the normal range. Serum tryptase was measured by a commercially available enzyme immunoassay (Phadia, Uppsala, Sweden) and was undetectable (<1 µg/L). ASST was performed by intradermal injection of 0.05 mL of sterile fresh autologous serum in the volar aspect of the forearm, according to the technique of Sabroe et al [9]. The test gave an unequivocal positive response (at 30 minutes a 4 × 3 mm weal and 25 × 25 mm flare). Intradermal injection of saline solution (0.9% wt/vol sodium chloride) was used as a negative control (no weal and no flare at 30 minutes) and skin prick test with 10 mg/mL histamine was used as a positive control (4 × 3 mm weal and 20 × 25 mm flare). BHRA was performed as described [10], using basophils from a normal nonatopic donor with a total IgE level of 8 kU/L. Histamine concentration in the cell supernatant was measured by an automated fluorometric technique and results were expressed as percentage net histamine release [11]. Histamine release induced by control sera from 20 normal subjects was below 5%, and this value was used as cut-off, also taking into consideration our previous experience [10]. Histamine release induced by the patient's serum was 7%, indicating the presence of circulating histamine-releasing factors.

In the search for antibiotics and antiinflammatory drugs that she could tolerate, the patient agreed to undergo oral elective tolerance tests, which were performed using a single blind design. Briefly, after administration of placebo, doubling doses of the challenged drug were administered at 30 minute intervals until a therapeutically active dose was reached. Among the antibiotics administered (levofloxacin, clarithromycin and doxycycline), only doxycycline was tolerated. Conversely, a mild urticarial rash was observed after levofloxacin and chlarithromycin intake. Similarly, ingestion of nimesulide and tramadol was followed by mild urticaria, with tramadol also inducing nausea and vomiting. The urticarial reactions observed were mild, but the patient was seriously concerned about the possibility of taking antibiotics and antiinflammatory

drugs when needed. Therefore, we decided to repeat the oral tolerance tests after premedication with cetirizine 10 mg one tablet, which was taken in all cases the night before the test. After premedication with cetirizine, the patient could tolerate levofloxacin, chlarithromycin and nimesulide.

Discussion

The patient described suffered from recurrent episodes of anaphylaxis with angioedema, relapsing urticaria and hypersensitivity reactions to NSAIDs. Some events were related to drug intake and one episode followed alcohol ingestion, but in most cases no trigger of anaphylaxis and urticaria could be clearly identified. When the patient was symptom-free, serum tryptase was undetectable and this allowed an occult mastocytosis to be excluded as the underlying cause of anaphylaxis. Idiopathic capillary leak syndrome was also excluded on the basis of clinical picture and absence of a monoclonal gammopathy at serum electrophoresis. C1 inhibitor was slightly reduced to an extent that was not consistent with hereditary or acquired angioedema but rather suggested chronic consumption because of chronic but modest complement activation, perhaps by histamine-releasing autoantibodies. In patients with chronic urticaria, histamine-releasing autoantibodies have been shown to fix complement, which in turn enhances histamine release [12]. However, in our patient an important involvement of the complement system could be ruled out because C4 levels were still in the normal range. This is at variance with the usual findings in patients with congenital or acquired C1 inhibitor deficiency in which C4 concentrations are markedly reduced. Furthermore, liver disease could not explain the modest reduction in C1 esterase level because liver function tests were normal.

The most interesting finding to emerge from the in vivo and in vitro investigations was ASST and BHRA positivity, which indicated the presence of circulating histamine-releasing factors, probably anti-FcεRIα or anti-IgE autoantibodies. A routine in vitro assay able to detect circulating and functionally active anti-FcεRIα and/or anti-IgE autoantibodies is still lacking. ASST is considered as an in vivo screening test for histamine-releasing autoantibodies directed against the high affinity IgE receptor or against IgE [9]. BHRA is considered as a confirmatory test showing the presence of functionally active histamine-releasing autoantibodies [13].

Two episodes of anaphylaxis in our patient were related to acetylsalicylic acid and alcohol intake, but we suppose that these were only precipitating factors and that the underlying and most important pathomechanism was the presence of histamine-releasing factors. It is known that many patients with chronic urticaria experience disease exacerbation following NSAID ingestion [14]. This phenomenon has also been described in patients whose chronic urticaria is clearly autoimmune, ie characterized by positive ASST and presence of circulating histamine-releasing autoantibodies [15]. On the other hand, a positive ASST has been observed in most patients with multiple intolerances to NSAIDs but with no chronic urticaria and approximately in one third of the patients with intolerance to a single NSAID [16]. In addition, most patients with multiple drug allergy syndrome and more than one third of subjects with a history of hypersensitivity to a single antibacterial drug have a positive ASST [17]. It has been hypothesized that offending drugs may enhance or facilitate the activity of circulating histamine-releasing factors (or autoantibodies) leading to acute urticaria episodes, whereas such factors alone might not be sufficiently efficient to do this. The same phenomenon might have occurred in our patient.

Food additives (eg sulphites or benzoates) were unlikely to have played a role in eliciting anaphylactic and urticarial reactions, since in most cases our patient reported no relation between food, alcohol beverage or drug intake and anaphylaxis. Furthermore, an additive-free diet was tried before the patient came to our clinic, but had no effect on recurrence of urticaria. It is noteworthy that an extensive investigation carried out by a Spanish group failed to show any role for food additives in chronic urticaria [18]. After 1110 oral provocation tests in patients with chronic urticaria, the authors found that only 0.63% provocation tests resulted in urticaria exacerbation and none was repeated after re-provocation. Regarding the possible role of alcohol, only one episode of anaphylaxis occurred after alcohol intake. We suppose that alcohol was involved as an occasional precipitating factor, but was certainly not responsible for the numerous episodes of anaphylaxis and recurrent urticaria. It is well documented that alcohol may cause urticarial and anaphylactoid reactions which are not IgE-mediated and may facilitate reactions to food and/or additives [19,20].

From a practical point of view, it is interesting to note that our patient who had a marked propensity to react to chemically unrelated drugs, such as nimesulide, tramadol, levofloxacin and chlarithromycin, was able to tolerate these drugs when premedicated with cetirizine. Therefore, the patient was given the possibility of taking nimesulide and two antibiotics (levofloxacin and clarithromycin) with concomitant H_1 antihistamine therapy. On the basis of these findings, we suggest that when reactions are mild and not life-threatening, it is worth exploring the possibility of giving selected drugs with concomitant H_1 antihistamine medication in patients with multiple drug allergy syndrome.

As yet, the presence of circulating histamine-releasing factors has not been systematically evaluated in patients presenting with idiopathic anaphylaxis, and we suggest that this investigation should be undertaken. Immunosuppressive drugs like ciclosporin, are very effective in most patients with chronic urticaria [21], and the demonstration of an autoreactive mechanism might indeed open the way to new therapeutic approaches also applicable to idiopathic anaphylaxis.

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