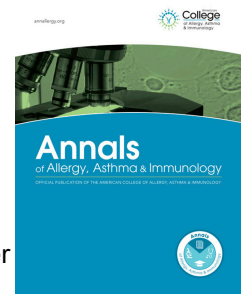


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Désirée E. Larenas-Linnemann, MD, Maria del Carmen Costa-Domínguez, MD, Peter Socrates Creticos, MD



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Challenging Clinical Case

Title:

Acute emotional stress proposed as a risk factor for anaphylaxis in patients receiving allergen immunotherapy

Authors

Désirée E. Larenas-Linnemann, MD¹

Maria del Carmen Costa-Domínguez, MD²

Peter Socrates Creticos, MD³

Affiliations:

1. Investigational Unit, Médica Sur Clinical foundation and Hospital, Mexicocity, Mexico
2. Hospital Español de México, Division of Allergy & Clinical Immunology
Mexicoity, Mexico
3. Associate Professor of Medicine, Johns Hopkins School of Medicine and Division
of Allergy & Clinical Immunology / Clinical Research Director, Creticos Research
Group

Corresponding author:

Désirée Larenas-Linnemann

Hospital Médica Sur, Torre 2, cons.602

Puente de Piedra 150, Col. Toriello Guerra, Del. Tlalpan

14050 México D.F., México

marlar1@prodigy.net.mx

Conflict of interest:

1. DLL reports personal fees from Amstrong, Astrazeneca, Boehringer Ingelheim, Chiesi, DBV Technologies, Grunenthal, GSK, MEDA, Menarini, MSD, Novartis, Pfizer, Novartis, Sanofi, Siegfried, UCB., and has received grants from Sanofi, Astrazeneca, Novartis, UCB, GSK, TEVA, Boehringer Ingelheim, Chiesi. None related to this paper.
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3. PSC declares he received research grants in the area of allergen immunotherapy from Circassia, Greer Labs, Merck, and Stallergenes within the past 5 years. He currently is a consultant to ASIT, Allakos, Allergy Therapeutics, Biomay, and Stallergenes/Greer and is an author and section editor for UpToDate on allergen immunotherapy. He has served on work groups for the NIAID and PCORI. None related to this paper.

Keywords

Allergen immunotherapy; subcutaneous immunotherapy; anaphylaxis; allergic rhinitis; asthma; epinephrine; emotional stress; immunotherapy guidelines; allergen immunotherapy, safety; neuropeptides, cytokines.

Introduction and Case Presentation

We have prepared a case that highlights the relationship between a patient's emotional state and the potential for systemic allergic reactions including anaphylaxis in a heretofore stable patient receiving maintenance subcutaneous allergen immunotherapy (SCIT) for treatment of allergic rhinoconjunctivitis (ARC) and mild persistent asthma.

Clinical history

Susy, a 12-year-old patient, **suffered from AR and moderate persistent asthma as a preschooler**. She was treated with nasal washes, intranasal corticosteroids +/- oral antihistamines and a combination controller agent [inhaled corticosteroid+long-acting β -agonist (ICS-LABA)] during winter and for some months post-asthma exacerbations. As her parents preferred a more definitive solution for her allergic condition, AIT was discussed with the patient and her family, and at 5 years-of-age she started sublingual immunotherapy (SLIT) . After two-and-a-half years SLIT was discontinued, as her family felt that she had reached a satisfactory degree of improvement. However, at age 10, her respiratory allergies recrudesced.

Re-evaluation

As a result of reoccurrence of her symptoms at age 10, she was again referred for follow-up at the Allergy Clinic. During her workup, it was noted that her symptoms were most remarkable during the ash tree pollen season (early spring), the spring grass season, during late winter, and upon cat exposure.

Medication was re-started and repeat skin prick testing [glycerinated allergen extracts (10.000 AU/mL, ALK Roundrock, U.S.; w/v 1:20, Alerquim, Mexicocity, Mexico)] revealed: (wheal/erythema) positive reactions to trees [*Fraxinus* (Ash): 5.5/25mm; *Ulmus* (Elm): 3mm; *Populus* (Poplar): 5/23mm // grasses [*Cynodon* (Bermuda): 5/17mm // weeds [*Artemisia* (Sage): 7.5/18mm; *Salsola* (Russian Thistle): 10/35mm; *Atriplex* (Orache): 7/23mm; *Helianthus* (Sunflower): 5/18mm // cat hair 7/34mm.

Clinical Impression/Course of Action

Based on her current clinical history and her resultant findings on skin testing, a decision was made to initiate subcutaneous immunotherapy (SCIT), as it was felt this would afford a more complete therapeutic response, as contrasted to her prior SLIT treatment which provided good but not sustained benefit.

She began SCIT [aqueous extracts in 10% glycerin] with 2 separate vials: *Vial A* [*Fraxinus*, *Populus*, *Cynodon*, *Artemisia* (maintenance vial with 1:200 w/v of each); *Vial B* (*Ulmus*, *Salsola*, *Helianthus*, Cat hair (maintenance vial with 1:200 w/v of each, and Cat hair (400BAU/mL)] [ALK, Roundrock, U.S. and Alerquim, Mexico City, Mexico].

Course of Immunotherapy – Buildup Phase

During build-up Susy presented several large local reactions [LLR] (wheal of 2-4cm diameter), some lasting more than 24 hours. Based on clinic policy for moderate LLRs (diameter of 3-fingers or more or 2+ fingers and lasting more than 24 hours), the patient's subsequent injection dose was not advanced until her injection reactions were within guidelines.

As such, Susy required a prolonged up-dosing that lasted almost eight months to achieve maintenance; albeit, without any systemic reactions. Of note, Susy was regular with her allergy injections. Her maintenance immunotherapy regimen was finally stabilized at 0.35-0.4ml from her respective [Vial A] and [Vial B], with good clinical response; both shots being given simultaneously in the same arm every 2-3 weeks. After a year of SCIT shots her allergy symptoms again became much better controlled, with intermittent mild-moderate asthma exacerbations two to three times a year, typically during the winter season in association with respiratory infections, and which were easily managed with a short 1-2-week course of her controller agent: ICS-LABA.

Course of Immunotherapy – Acute Emotional Distress

At 14 months of SCIT maintenance, Susy came to the clinic for her regular allergy shot. She was softly crying. The nurse completed the pre-injection questionnaire without finding any problems, but kindly told her to sit down until her crying had calmed down, before administering her SCIT injections.

Susy received her scheduled maintenance injection (0.35-0.40ml). Within 15 minutes she complained of local itching not only at the injection site, but also on the contralateral arm, where the last injections were given ~3 weeks ago. Minutes later she developed wheals bilaterally, on both of her arms, at the actual and at the previous injection site. [The injections were the third doses from vials started a month prior, without any injection-related side effects]. She was treated with an oral antihistamine [cetirizine 10mg].

While our nurse was trying to comfort and manage Susy's situation, she became quite distressed because of her father's recent hospitalization (see below). She started to cry

again and seemingly presented mild dyspnea. Her symptoms of tachypnea were considered to be secondarily to her crying and sighing.

To be on the safe side, our nurse administered 2 puffs of Salbutamol-Ipratropium bromide via a soft mist inhaler (Combivent Respimat®) to Susy, but her dyspnea and distress continued to worsen over the next 10-20 minutes. Lung auscultation revealed coarse crackles and mild wheezing during inhalation when sighing. No stridor. As she was crying we tried unsuccessfully to register her blood pressure, and only heart rate and peripheral capillary oxygen saturation (SpO₂) were accurately measured with pulse oximetry [90bpm; 92%, normal for Mexico City with an altitude of 2200 m above sea level]. She did not cooperate to blow a peak expiratory flow (PEF).

According to international guidelines on anaphylaxis, the diagnosis can be made when, after the exposure to a known allergen, at least two organ systems are involved.(1, 2) Susy clearly presented systemic signs/symptoms in one organ system [skin], as the contra-lateral arm developed a wheal. However, her signs/symptoms present in the second organ system [respiratory], could simply be due to her crying: watery rhinorrhea and dyspnea-sighing, albeit with coarse crackles and mild inspiratory wheeze, a consideration of anaphylaxis cannot be ruled-out. Nonetheless, at this point we were less certain of a possible diagnosis of anaphylaxis.

Worsening Clinical Course

In short order, Susy started to experience dizziness, a sense of general malaise and an increase in heart rate (90 to 105 bpm). [SpO₂ was maintained within normal limits]. Susy was placed in supine position, still softly crying-sighing and it was not clear if her unwell

being was due to being upset. We tried to calm her down; however, her condition did not improve.

Clinical Impression

At this point, we have one confirmed organ system involvement [Skin], and two other organ systems possibly involved [respiratory; cardiovascular] and a lack of improvement in the patient's general condition. A decision was made to administer epinephrine (1:1000, 0.30mL IM in the vastus lateralis), after which, her dyspnea and general condition improved over the next 10-15 minutes and her heart rate came down to 86 bpm. She stopped crying and recovered. Susy's clear and fast reply to epinephrine were highly suggestive of a diagnosis of anaphylaxis, when taking into consideration her "unwell being", dizziness, and respiratory distress (dyspnea + inspiratory wheezing).

Post-care

Susy left the consulting room after a further observational period of 1.5 hour on cetirizine 10mg once daily for seven days and her ICS-LABA (double dose every 12 hours for 5 days post-event).

As our national guidelines on allergen immunotherapy(3) indicate, a second generation antihistamine was prescribed, and her maintenance asthma treatment was temporarily increased.

One could argue that the dizziness she referred to might have been due to hypotension. If a patient presents with anaphylaxis with hypotension, a short course of prednisone after dismissal has been suggested by some investigators, to reduce the risk of biphasic anaphylaxis. However, the discussion on this point is still open.(4) In this particular case we

did not document clear hypotension in Susy; therefore, we refrained from adding prednisone. Her AIT was restarted almost a month later with one tenth of the dose and slowly build-up from there.

Assessment of Emotional Stress

The day of her anaphylaxis, Susy was upset because a first-degree family member had been hospitalized unexpectedly. She and her mother had planned to visit him, but being a child her visit was denied due to the risk to the child associated with a radiocontrast procedure that the father had undergone. Instead, her mother brought her to our part of the hospital grounds to get her allergy shot. Susy was sad upon arrival and softly crying. After allowing her to calm down she received her shot as she was considered stable. However, as outlined, after ~20min she felt unwell and started crying again and her clinical course of events unfolded with multiple organ involvement and evidence for possible anaphylaxis. In context, this episode could not be attributed to a specific food, drug intake, menstrual cycle, or physical exercise prior to administration of her SCIT injection.

Discussion

Clinical characteristics and Pathophysiologic Mechanisms

Stress, as an instinctive fight-and-flight reaction to enhance survival, may have a negative impact on everyday medical procedures and interventions. A clear association has been established between behavior, neuroendocrine function, and the immune response (psycho-neuro-immunology).(1)

As such, allergic diseases such as asthma, allergic rhinitis and atopic dermatitis, can exacerbate due to acute stress related to release of neuropeptides, neurotransmitters, and other stress-related substances (e.g. neuropeptides) in the central nervous system, that act either directly or indirectly on the activation of the allergic inflammatory response.(5) Corticotropin releasing hormone (CRH) and substance P can degranulate mast cells through the GR receptor and Neurokin-1, respectively, resulting in an immediate release of histamine and tryptase which act on vascular endothelial cells leading to allergic symptoms, including anaphylaxis. (5) (6)

It is generally recognized that stress activates the hypothalamic-pituitary-adrenal axis and results in release of corticotropin releasing hormone (CRH), which downstream results in anti-inflammatory responses due to a rise in systemic glucocorticosteroids. Conversely, the dual role of CRH, acting under several circumstances pro-inflammatory, was recently demonstrated. Moreover, CRH can be secreted locally in skin, lung and other tissues where this peripheral CRH can trigger mast cells directly via the CRH receptor (CRH-R) and through the release of neurotensin which then activates mast cells.(7) Mast cell-activation following stress finally results in an increased vascular permeability. Furthermore, the expression of CRH-R1 and -R2, on mast cells can be enhanced by inflammatory cytokines such as IL-1, IL-4, IL-6 and lipopolysaccharide.(8) As such, allergic inflammation augments the tissue's sensitivity to stress-induced increases in CRH concentrations. Substance P, a neuropeptide, can also enhance the expression of functional CRH-R1 on mast cells,(9) thus emphasizing the link between emotional reactions and the enhanced mast cell sensitivity to stress. Furthermore, peripheral CRH can reduce the production of the inhibitory interleukin (IL), IL-10 from T-regulatory cells.(10) Finally, investigators have speculated that CRH could even be

secreted under stress in the lungs and thus contribute to the pathophysiology of asthma.(11)

Clinical Implications

There are several examples in the literature of stress-induced increase of the allergic response in the clinical setting. Kiecolt-Glaser(12) and subsequently Heffner(13) demonstrated that upon skin-prick-testing allergic patients with and without acute stressors, the size of the wheal was greater when exposed to stress. The former author also demonstrated a longer positive delayed response (4-24 hrs post-SPT). The latter also found a larger number of positive SPT sensitizations with acute stress as a cofactor. Furthermore, Jensen-Jarolim's group recently published that elevated oxytocin and noradrenaline levels associated with the stress response can be linked to an augmented allergic reaction (14). Liu et al. studied 20 otherwise healthy college students with mild asthma and demonstrated that physiological stress related to school examinations can enhance airway inflammation in response to an antigen challenge. There was a rise in sputum eosinophil counts and eosinophil-derived neurotoxin (EDN) levels post-allergen challenge during final exams. Although no baseline differences were detected before allergen challenge conducted at mid semester and during final exams, sputum eosinophil counts rose higher and persisted longer in response to the allergen challenge during final exams ($p < 0.01$). Also, during this stress-full period baseline blood eosinophil levels were higher. Moreover, IL-5 production by cultured sputum cells was enhanced.(15) Ten years later Theoharides et al. presented a review article in this journal demonstrating how stress can contribute to the worsening of asthma through CRH, neurotensin and/or substance P-mediated mast cell activation.(11)

Review of the original cognitive response literature has clearly demonstrated that psychological factors influence the allergic response – indeed, physiologic stress has been linked to an increase of hay fever symptoms in ragweed-allergic subjects(16) and Cohen et al. even showed how guided imagery can reduce response (TAME-esterase) to nasal provocation in ragweed allergic patients.(17) On the other hand, interventions, including hypnosis and relaxation training have been shown to inhibit allergic responses to skin testing(18-20) and asthmatic responses provoked by allergic stimuli(21), respectively. The specific intervention of guided imagery has been used to promote physiological relaxation(22) and modulate cellular activity of the immune system(23, 24). This further supports our premise that the human mind is influenced by emotion and the underlying cognitive responses can influence immune responses.

Most recently, a randomized, cross-over trial in peanut-allergic adults of double-blind, placebo controlled food challenges showed a significantly reduced reaction threshold after sleep-deprivation or exercise prior to the challenges as compared to the dose of reaction threshold during the baseline challenges, (25), thus providing evidence for the effect of physical stress on the allergic reaction.

Stress and Anaphylaxis

A most intriguing case is one of a lady who had a history of 16 episodes of anaphylaxis in a 15-years span, seemingly idiopathic in origin, who reportedly presented a clinical picture compatible with anaphylaxis (diffuse pruritus, intense chest erythema, as well as eyelid,

facial, and tongue angioedema with difficulty breathing), after a placebo intradermal injection of normal saline as a first step in a planned challenge testing.(26)

Diagnosis

In this case, ideally the diagnosis would have been confirmed by blood tryptase levels, taken preferably 2 and not more than 4 hours after the event. However, in the clinical context of an emotionally upset patient, just recovering from the event, this may not always be possible. The response of our patient to the administration of epinephrine, with general status and clinical parameters returning to normal, is consistent with the diagnosis of anaphylaxis. For ethical reasons, no tryptase was taken, as it would not change our management. Furthermore, clinical staff should have an eye to the emotional wellbeing of patients, as the features of crying, fitfulness, and hyperventilation can easily mask respiratory symptoms that otherwise evolve into unrecognized and more troublesome asthma or multisystem involvement in a distraught patient.

Management

To our knowledge, this is the first case where emotional stress appears to have been a predisposing factor for our patient's anaphylactic reaction to her allergy injection. Prompt administration of epinephrine is mandatory and should not be postponed until vital signs can be taken, as this is not always possible in the context of a crying and distressed patient. To prevent this kind of events, we would recommend withholding allergy injections when a patient comes into the clinic, emotionally distressed, as we believe this clinical presentation may predispose the distraught patient to physiological changes that induce a state of

228 heightened sensitivity with the resultant clinical manifestations of a systemic allergic
229 reaction, or worse, anaphylaxis.

230

231 We are not aware of any publication of an anaphylactic reaction related to emotional stress
232 at the moment of SCIT administration and current immunotherapy guidelines do not
233 mention acute stress as a potential risk factor for adverse effects during and after SCIT
234 administration.(27-30). We would like to conclude with the recommendation to withhold a
235 SCIT injection in a patient presenting with acute emotional distress.

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