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Letter

A probable case report of stress-induced anaphylaxis

Anaphylaxis is an acute, potentially life-threatening, systemic allergic reaction that results from the release of mast cell– and basophil-derived mediators.[1] Its cause can be immunologic (immunoglobulin [Ig] E- or IgG-mediated and immune complex complement-related), nonimmunologic, or idiopathic when there is no identifiable precipitating event or agent.[1]

Some cases of "somatoform" idiopathic anaphylaxis have been reported, but such cases are defined by no response to any therapeutic intervention.[2] We present a case of recurrent "idiopathic" anaphylaxis apparently precipitated by emotional stress.

A 33-year-old white woman was referred to the Allergy Clinic of the Athens "Laiko" Hospital for recurrent episodes of life-threatening systemic anaphylaxis. The patient had had 16 episodes of anaphylaxis during 1976 to 1991, and her clinical manifestations were diffuse pruritus, intense skin erythema, as well as facial and tongue angioedema with difficulty breathing. Other symptoms included hoarseness, wheezing, shortness of breath, colicky abdominal pain, nausea, vomiting, low blood pressure, and diffuse myalgias and polyarthralgias that would start 24 hours after each episode had subsided and lasted for 4 to 5 days.

None of the episodes could be attributed to a specific food, drug, chemical substance, insect bite, time of the day, or activity. Interestingly, all episodes occurred in the periovulatory phase (12^{th}–15^{th} day) of her menstrual cycle, which was described as regular at 28-day intervals. Her obstetric/gynecologic history included 11 pregnancies between 1978 and 1989. Only 2 of them were full term, and the rest were interrupted electively. The patient had also received more than 2 courses of parenteral progesterone for the treatment of post-abortion oligomenorrhea. Her medical history included no atopic or allergic symptoms.

During previous attacks, laboratory tests included total complement, C1 esterase inhibitor, Complement fragments C3a and C5a, as well as immunoglobulins IgG, IgM, IgA, and IgE. All values were normal except for C3a, which was slightly low at 87 (N, 97–155). C1 esterase inhibitors are involved in angioedema, whereas complement fragment C3a and C5a are known mast cell triggers that could have been involved in the anaphylactic event. IgE levels were measured because certain hyper-IgE syndromes have been associated with idiopathic anaphylaxis. Skin prick tests were also negative. IgE-mediated variants and anaphylactoid reactions associated with mastocytosis, carcinoid, and pheochromocytoma were excluded through normal 24 urine methylhistamine, 5-hydroxyindoloacetic acid, and vanillyl mandelic acid, respectively. Eventually, the diagnosis of idiopathic anaphylaxis was made.

Suspicion for hormone (estrogen or progesterone) hypersensitivity was raised, because all of the episodes had occurred during the periovulatory phase of her menstrual cycle. Therefore, progesterone testing was recommended, and 6 minutes after the first intradermal progesterone injection, the patient developed symptoms of systemic anaphylaxis, including diffuse pruritus, intense chest erythema, as well as eyelid, facial, and tongue angioedema with difficulty breathing. She was immediately treated with epinephrine, antihistamines, and intravenous normal saline, after which she became stable 5 hours later. Blood histamine was not elevated, as has been reported recently.[3] Tryptase was not measured because of the unavailability of the test in the hospital at that time. Further evaluation of estrogen sensitization was decided, but first a placebo intradermal injection of normal saline was administered the following day. Within 14 minutes, systemic anaphylaxis occurred, with signs and symptoms much more severe than those observed with the progesterone testing, and the patient required more intensive treatment. The treatment of this episode included intravenous normal saline. A second placebo provocation was entertained but the patient refused.

Careful reevaluation of her case and interview of the patient's husband revealed that after 9 unwanted pregnancies, the patient was under severe stress during the periovulatory phase of her menstrual period for the possibility of a new unwanted pregnancy. Her anxiety was added to the family's preoccupation with her "life-threatening anaphylaxis problem." Therefore, even a "mild itch" was perceived by the patient and her family as impending anaphylaxis, and they were very quickly overwhelmed with panic. The result was often a full-blown anaphylactic episode.

Stress-induced anaphylaxis was entertained and led to a therapeutic strategy toward eliminating stress. Specifically, consultation was offered to the couple concerning available contraceptive methods. She was also prescribed benzodiazepines for a short period, and she was supported with psychotherapy. Moreover, the family was urged to modify their behavior so that whenever the patient expressed fears of an impending "allergic" reaction, she was addressed calmly by her family. As a result, the episodes became milder and less frequent until eventually they subsided completely over the next few months.

Stress is known to activate the hypothalamic-pituitary-adrenal axis through the release of corticotropin-releasing hormone (CRH). We have shown that CRH secreted under stress stimulates mast cell degranulation through activation of CRH receptor-1 (CRHR-1).[4] This effect is augmented by other neuropeptides also released by stress, such as substance P (SP) and neurotensin (NT).[5] In fact, both NT[6] and SP[7] induce the expression of functional CRHR-1. Moreover, we have shown that CRH induces the expression of high-affinity IgE receptor (FcεRI) and augments allergic stimulation of human mast cells.[8]

This patient's periovulatory episodes (12^{th}–15^{th} day) are in line with data reporting that acute asthma attacks in women are more frequent during the preovulatory phase.[9] A possible explanation for

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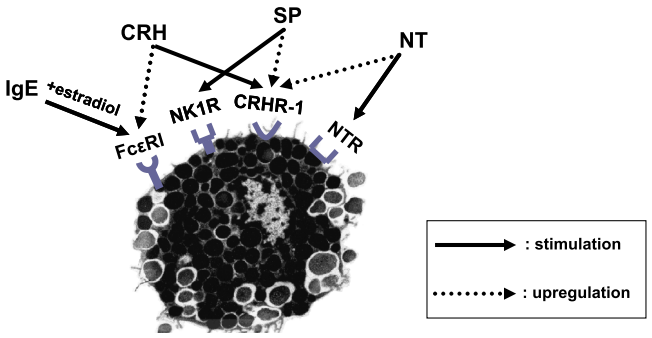

Figure 1. An illustration using a photomicrograph of an activated mast cell to show how neuropeptides secreted under stress stimulate mast cells directly through their specific receptors or indirectly through increased expression of certain receptors. CRH, NT, and SP, as well as IgE, can stimulate mast cells independently (*solid arrows*). In addition, CRH induces the expression of FcεRI, whereas NT and SP induce the expression of CRHR-1 (*dotted arrows*). Estrogen augments at least the effect of IgE. The photomicrograph was taken with a Phillips 300 transmission electron microscope, approximately 3,000 diameters magnified; solid granules are intact; granules containing gray material have secreted their content from the mast cell degranulation). CRH, corticotropin-releasing hormone; CRHR-1, CRH receptor-1; FcεRI, high-affinity IgE receptor; NKR-1, neurokinin receptor-1; NT, neurotensin; NTR, NT receptor; SP, substance P.

this could be the hormonal equilibrium of the preovulatory and periovulatory phases, during which estradiol levels peak and progesterone levels are low, thus favoring the development of an anaphylactic episode. Specifically, estradiol has been shown to enhance IgE-mediated mast cell activation.[10] We had also shown that estradiol augments carbachol-induced mast cell activation in rats.[11] We had previously reported a case of stress-induced exacerbation of urticaria pigmentosa associated with high serum CRH and increased CRHR-1 on lesional skin mast cells.[12]

Even though a number of cases of "somatoform" idiopathic anaphylaxis have been reported, "somatoform idiopathic anaphylaxis (IA) is characterized by no response to the therapeutic regimen for IA."[2] In contrast, our patient promptly responded to antihistamines and corticosteroids, which by definition excludes this case from being somatoform IA.

The mechanism by which susceptible individuals develop stress-induced anaphylaxis may therefore be caused by unique interactions among CRH, SP, and NT on mast cells (Fig 1).[13]

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