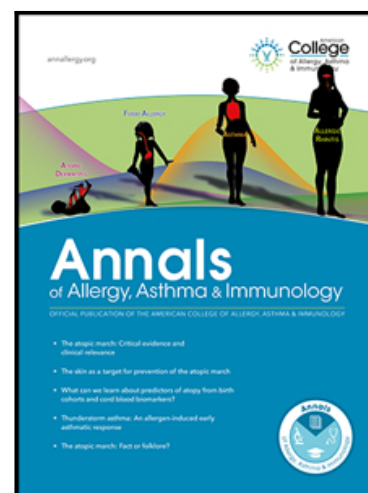


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Idiopathic Anaphylaxis and Undiagnosed Anorexia Nervosa

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Dr. Shaker has a family member who is CEO of Altrix Medical and is a member of the Joint Task Force on Allergy Practice Parameters (AAAAI/ACAAI)

Drs. Kennedy, Capucilli, and Ms. Yuan have no conflicts of interest to declare.

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This report describes an association between anorexia nervosa and idiopathic anaphylaxis.

While eating disorders affect 0.6% of the population¹, and idiopathic anaphylaxis occurs in approximately 1 in 10,000 individuals² an association between anorexia nervosa and mast cell dysfunction has not previously been described. Features of anorexia nervosa include restriction of eating and energy intake, intense fear of gaining weight, and distorted perception of body weight and shape.¹ We describe a fourteen-year-old girl with a history of well controlled hypothyroidism who developed sudden lip and eyelid edema, abdominal pain, stool urgency, lethargy, diarrhea, vomiting, throat tightness, and presyncope. Her symptoms began 30 minutes after she finished eating vegetables from a Ruby Tuesday's salad bar in Philadelphia. On arrival to the emergency department after ambulance transport, she had a blood pressure of 110/60 with bradycardia of 50 bpm and greater than 5 second capillary refill, along with cool distal extremities. Treatment included 0.3mg of intramuscular epinephrine x 8 and subsequent intravenous epinephrine infusion, intravenous fluid resuscitation, nebulized albuterol, intravenous corticosteroids, and diphenhydramine. Antecedent events included travel and a recent upper respiratory tract infection for which ibuprofen had been used seven hours before symptom onset. Foods consumed prior to the event were lettuce, spinach, pepper, onion, tomato, cilantro, cucumber, carrot, ranch dressing, pumpernickel croutons, parmesan cheese, onion, artichoke, oranges, grapes, ham, and pasta; however, the patient was previously and subsequently tolerant of each of these foods. Prior to dinner the patient had used Zicam (*Galphimia glauca* 4x, *Luffa operculata* 4x, *Sabadilla* 4x) and ibuprofen, but subsequently tolerated Zicam, aspirin, and ibuprofen. Acute serum tryptase at the time of the event was 32.5 ng/mL (with convalescent tryptase after event measuring 3.2 ng/ml). Specific IgE testing was negative to shrimp, crab, sesame, galactose-alpha-1,3-galactose and latex, with negative skin testing four weeks later to shrimp, lobster, scallop, egg, milk, soy, wheat, peanut, almond, walnut, cashew, sesame, lettuce, onion, and latex. Past medical history was

negative for symptomatic rhinitis, asthma, or food allergy, with prick skin testing positive only to Timothy grass (8mm wheal) and negative to dust mites, cat, dog, tree pollens, weed pollens, and molds.

Persistent bradycardia, hypokalemia (potassium 3.0 mmol/L), and hypocalcemia (calcium 7.5 mg/d) during the initial hospitalization prompted disclosure of further history which revealed a restrictive eating pattern that had been previously unreported. The patient reported cutting out fats and carbohydrates, restricting meals with frequent body checking, and a recent 20 lb weight loss, dropping from the 50th to the 3rd percentile, as well as secondary amenorrhea. Following recovery from the anaphylactic event, the patient underwent gradual nutritional restoration using an inpatient, standardized eating disorder protocol with a starting caloric intake of 1400 kcal/day, increasing to 3800 kcal per day. After extensive investigation failed to identify a cause for the patient's anaphylactic event, she was diagnosed with idiopathic anaphylaxis. Several months after her initial presentation the patient experienced a second anaphylactic event with abdominal discomfort, diarrhea, and mild swelling of lips and tongue, which resolved promptly with intramuscular epinephrine. Again, potential culprits were scrutinized (no recent exercise, ibuprofen use, bee sting, or menses), and no specific trigger or cofactor was identified, with subsequent tolerance of all foods eaten before the episode.

Anorexia nervosa is a psychological and potentially life-threatening illness involving restricted energy intake and body dysmorphism that can affect virtually any organ system, leading to growth impairment, myocardial dysfunction, amenorrhea, electrolyte disturbance, respiratory impairment, and cognitive dysfunction. Latzer and colleagues reported a case of urticaria and angioedema induced by bingeing and purging in a 16-year old patient during an admission for anorexia nervosa and postulated a form of inducible urticaria.³ However despite some anecdotal experience of subjectively reported food and medication allergies in patients with the condition, there is scant literature describing associations of allergic responses.

Although the association with undiagnosed anorexia nervosa may be coincidental, it is of interest that autophagy had been associated with both anorexia nervosa and mast cell degranulation. Autophagy (literally “self-eating”) is a lysosomal catabolic pathway that removes aging protein and damaged organelles. It is an evolutionarily conserved process common to all eukaryotes, induced during starvation to conserve and recycle cellular resources. Autophagy is a multi-step process involving the consumption of organelles by a phagophore to form an autophagosome, which subsequently fuses with a lysosome to form an autolysosome. It is involved in critical processes of development such as aging, and its dysregulation has been implicated in cancer and neurodegenerative diseases. Food restriction is one of the best-known inducers of autophagy.⁴ Notably, cells unable to undergo autophagy show impairment of mast cell degranulation⁵. Ushio and colleagues⁶ evaluated autophagy in bone-marrow derived mast cells (BMMCs) from mice lacking autophagy-related gene *Atg7*, an essential enzyme for autophagy induction. The authors found that *Atg7*^{-/-} cells demonstrated severe impairment in mast cell degranulation, but not cytokine production or cross linking of FcεRI. Furthermore, passive cutaneous anaphylaxis reactions were severely impaired in mast cell-deficient mice reconstituted with *Atg7*^{-/-} BMMCs compared with *Atg7*^{+/+} BMMCs. Conversely, Choi et al. reported that *Atg7*^{-/-} was associated with eosinophilic inflammation, mast cell infiltration, and PGD₂ dysregulation in a murine model of chronic rhinosinusitis.⁷

While anorexia nervosa induces cellular metabolic changes including autophagy in humans, and autophagy impairment leads to the inhibition of both mast cell degranulation and passive anaphylaxis in a murine model, clinical correlates of these relationships have not been well described. Of course any mechanistic relationship between autophagy and anorexia is conjecture. Other physiologic changes caused by anorexia nervosa could also contribute to anaphylaxis. In a murine model of anorexia nervosa, chronic food restriction led to increased colonic permeability,⁸ which could increase the likelihood of a primary IgE-mediated food allergy (of note, NSAIDs may also disrupt the gastrointestinal mucosal

barrier⁹). Additional mechanisms through which anorexia nervosa could increase risk for severe anaphylaxis include bradycardia, alterations in splanchnic circulation, frequent purging, fasting, and electrolyte imbalance. Anorexia may be yet another cofactor which increases the severity of anaphylaxis, similar to exercise, acute infection, emotional stress, disruption of routine, or premenstrual status.¹⁰

To our knowledge, this is the first association of idiopathic anaphylaxis and anorexia nervosa. A possible mechanism for this association is anorexia nervosa-induced autophagy, but this explanation remains speculative. Further study of the incidence of anaphylaxis in the setting untreated anorexia nervosa could be of interest to determine if a relationship exists between these conditions.

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