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Food allergies are a rapidly growing medical and public health problem. Recent studies estimate an incidence of 5% in children younger than 5 years old and 4% in adults. In severe cases, subjects can experience anaphylaxis and even death if exposed to a food to which they are sensitive. There is no known cure. Rather, doctors recommend that the sufferer avoid exposure to the allergen. The mechanism of disease is thought to be immunologic.

A number of drugs can be used during an acute food allergy attack, but only one—intramuscular injection of epinephrine—immediately resolves all of the symptoms associated with the episode. Tellingly, epinephrine is a neurotransmitter/hormone of the autonomic nervous system (ANS) that augments sympathetic function. Emerging data in the literature supports a neuro-immune connection, particularly in light of how the ANS innervates and regulates lymphoid tissues and other constituents of the immune system. It is possible that food allergy syndrome (and perhaps all cases of anaphylaxis) may require both an allergic sensitivity and an underlying inability to generate an adequate sympathetic response (or an underlying parasympathetic/vagal dominance).1

To test this hypothesis, we performed extensive autonomic testing on a 5-year-old subject with a history of virally-triggered asthma and severe tree nut allergy.

The subject’s heart rate was measured during deep breathing. During inhalation, activation of lung stretch receptors normally suppresses
vagal activity, promoting tachycardia. The subject’s heart rate during inhalation was 104 beats per minute, which is normal for a 5-year-old. During exhalation, unloading of lung stretch receptors reverses vagal suppression, typically reducing heart rate by 20 to 30 beats per minute (bpm). The subject’s heart rate declined to 54 bpm, suggesting sympathetic under-activity. Heart rate response to CO2 retention and release did not alter heart rate variability, suggesting central autonomic dysfunction, possibly at the brain stem level. Large fiber autonomic neuropathy was ruled out through additional testing. Skin sympathetic response (SSR) tests were performed limb-to-limb to localize the autonomic dysfunction. Delayed sympathetic function was observed only between the upper limbs, suggesting a possible defect somewhere along the cervico-thoracic sympathetic arc.

The findings appear consistent with the subject’s history of asthma (characterized by expiratory wheeze and bronchospastic cough) and food allergy syndrome (anaphylaxis, angioedema, gastrointestinal cramping, hypotension, and bronchospasm). In the case of asthma, an allergic response to a viral antigen (characterized by degranulation, release of substance P, and activation of other cascading pathways) activates the autonomic afferent fibers, which are biased towards vagal dominance in this subject. During exhalation, insufficient sympathetic counter-response to vagal resurgence (associated with unloading of lung stretch receptors) results in expiratory wheeze (bronchoconstriction) and asthmatic cough (bronchospasm). In the case of food allergy syndrome, an allergic response to tree nut antigen (characterized by degranulation, release of vasoactive intestinal peptide, and activation of other pathways) triggers autonomic afferents.

Given the subject’s underlying vagal bias, the subject exhibits symptoms consistent with vagal overload including angioedema, bronchoconstriction, hypotension, and gastro-intestinal cramping. These are all hallmarks of anaphylaxis. The underlying autonomic dysfunction
effectively turns a routine immunologic response to an antigen into a catastrophic, maladaptive response. Historically, epinephrine was the treatment of choice for acute asthma attacks given its elevation of sympathetic response. Today, selective sympathomimetic drugs (beta2 agonists) are used for the treatment of acute asthma. Epinephrine remains the treatment of choice for food allergies, and beta2 agonists can be used to treat the respiratory component of food allergy attacks.

Vagal motor tone exerts parasympathetic innervation to all organs from the cervical region to the transverse colon (with the one exception of the adrenal glands). This varied control includes parasympathetic control of the heart (rate), GI system (peristalsis), vascular (sweating and microvascular permeability such as swelling). Neurotransmitters associated with parasympathetic nerves include acetylcholine, vasoactive intestinal peptide, neuropeptide Y, nitric oxide, enkephalin and somatostatin. However, acetylcholine is the predominant neurotransmitter released from large diameter post-ganglionic cells and acts primarily on the M3 receptors, resulting in increased glandular secretion from the mucous/serous glands of the sinonasal membranes. Overstimulation of these foci triggers many of the cholinergic side effects.

Sympathetic input originates in the intermediolateral column of the upper thoracic segments of the spinal cord. The preganglionic fibers travel through the anterior thoracic roots via the stellate ganglion to the superior cervical ganglion where they first synapse. Postsynaptic fibers then travel via the carotid plexus where it bifurcates, innervating various cranial, cervical, and thoracic end-organs. Sympathetic nerve stimulation induces vasoconstriction, but has only a minor effect on mucous secretion. Neurotransmitters associated with sympathetic nerves include mainly norepinephrine or neuropeptide Y, both potent vasoconstrictors.

Sympathetic receptors are classified as alpha or beta. In general,
alpha agonists act on the resistance and capacitance blood vessels to decrease blood flow and airway resistance, while beta2 agonists are vasodilators. Since there is a marked alpha predominance in respiratory pathway blood vessels, vasoconstriction generally prevails. Thus, disruption or diminution of the sympathetic supply to the respiratory system will result in vasodilatation and increased airway resistance, as is seen in severe food allergies and anaphylaxis. Interestingly, there exist case reports of subclinical injury to the cervical spine region sympathetic pathway, resulting in vagally-mediated rhinitis and swelling in humans. These reported cases were also associated with adrenergic hyperactivity.

In the case of our 5-year-old subject, the origin of the subject’s sympathetic under-responsiveness remains to be explored. Possible defect locations include end-organs, afferent fibers, brain stem, hypothalamus, spinal cord, and efferent fibers. Since the autonomic dysfunction appears regional, a genetic or cellular defect seems less likely, although secondary systemic consequences to the autonomic nervous system from chronic use of beta-agonists and steroids should be considered. There is a classic allergic reaction characterized by hyperreactivity of the respiratory and GI mucosa with type I hypersensitivity and provocative exposure leading to eosinophilia, plasma cells, and degranulated mast cells. The authors speculate that a vasomotor adjunct with an imbalance in ANS input results in the vasomotor, cardiovascular, and inflammatory anaphylaxis responses. The disease is characterized by the classic mismatch of parasympathetic over sympathetic drive of swelling, flushing, smooth muscle spasms, arterial spasm, and diarrhea.

Further autonomic testing will be performed to better elucidate the nature of the subject’s autonomic dysfunction. Magnetic resonance imaging on the brain and spine will be performed to rule out structural causes of autonomic circuit disruption (e.g. sympathetic lag due to
ependymal stretching from syrinx).

The potential role of autonomic dysfunction in food allergy syndrome and allergic anaphylaxis among the broader population remains to be investigated.

References

1 The sympathetic and parasympathetic nervous systems work in opposition. Sympathetic activity promotes alertness, bronchodilation, hypertension, and tachycardia, while suppressing gastrointestinal motility and erectile function. Parasympathetic activity promotes sleep, bronchoconstriction, hypotension, bradycardia, gastrointestinal motility, and erectile function. Bronchospasm, abdominal cramping, and angioedema are examples of manifestations of vagal bias.


