Galactose-alpha-1,3-galactose syndrome

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ABSTRACT

The galactose-alpha-1,3-galactose (alpha-Gal) syndrome is a newly recognized and unique form of food allergy, characterized by delayed reactions to mammalian meats. This form of allergy occurs in individuals who become sensitized to alpha-Gal, a carbohydrate that is present on most mammalian tissues. Sensitization occurs after exposure to multiple arthropod bites, most commonly the lone star tick. Cases of the alpha-Gal syndrome are primarily found in the southeastern United States, which overlaps with the known geographic distribution of the lone star tick. Patients present with a history of delayed symptom onset, ~2–6 hours after ingestion of mammalian meat. As with other immunoglobulin E (IgE) mediated food allergic reactions, alpha-Gal reaction symptoms may include skin, respiratory, gastrointestinal, or cardiovascular systems, and severity may range from mild reactions to severe anaphylaxis. The diagnosis is based on the detection of alpha-Gal specific IgE (sIgE) as well as the total IgE value because some cases include patients with low total IgE levels but a high percentage of alpha-Gal sIgE to total serum IgE levels. Percutaneous testing with commercial meat skin-prick testing extracts is not a reliable tool for diagnosis. Prick-prick skin testing to fresh cooked meat may be considered, whereas intradermal testing to fresh meat is primarily reserved for research purposes. The mainstay of treatment involves avoidance of mammalian meat and medications that express the same carbohydrate antigen. With a small portion of patients, other meat-containing products should also be avoided if symptoms persist with mammalian meat avoidance alone. Prolonged avoidance of mammalian meat as well as avoidance of further tick bites can decrease alpha-Gal sIgE over time, and some patients are able to reintroduce mammalian meat into their diet.

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The galactose-α-1,3-galactose (α-Gal) syndrome is characterized by delayed anaphylaxis to mammalian meat and develops in individuals who have become sensitized or developed specific immunoglobulin E (sIgE) to α-Gal after exposure to multiple tick bites. The most common arthropod involved is the lone star tick *Amblyomma americanum* (Fig. 1).[1] The allergy was noted to be present in the southeastern portion of the United States, in the same distribution of Rocky Mountain spotted fever. Most immunoglobulin E (IgE) mediated food allergies are to proteins in foods; however, α-Gal sIgE is directed at a carbohydrate.[3] The α-Gal syndrome is caused by an IgE antibody against Galα1-3Galβ1-(3)4GlcNAc-R (α-Gal), a carbohydrate that is present in glycoprotein from arthropod saliva and tissues of mammals.[4] This same carbohydrate is expressed on the monoclonal antibody cetuximab, which was discovered through examination of patients who had preexisting sIgE to cetuximab before treatment that subsequently developed into allergic reactions after treatment with the monoclonal antibody.[5] Clinical suspicion after this observation ultimately led to the detection of α-Gal syndrome.

Van Nunen *et al.*[6] first reported, in 2007, the relationship between arthropod bites and development of mammalian meat allergy. This association was confirmed by Commins *et al.*[6] in 2009 with the discovery of the α-1,3-galactosyltransferase (*GalT*) gene, which is the epitope thought to be responsible for mammalian meat allergy. Humans have an inactivated *GalT* gene, which results in the production of antibody to *GalT*, with recognition of the α-Gal antigen. Humans do not synthesize α-Gal and all sources of α-Gal exposures are from nonprimate sources.[5] Arthropods, specifically ticks, can generate α-Gal with functional *GalT*s.

There are two mechanisms postulated to explain the production of human anti–α-Gal IgE after tick bites: (1) the interaction between α-Gal on tick salivary protein and antigen presenting cells (APC) and B lymphocytes leads to IgE-mediated acquired protective immunity, which results in elevated α-Gal IgE, and (2) tick saliva contains factors that can induce class recombination of B cells to make α-Gal IgE, IgM, and IgG antibodies.[3] High serum levels of anti–α-Gal IgE can lead to delayed anaphylaxis with red meat consumption, immediate anaphylaxis to tick bites, certain medications, and xenotransplantation.

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Figure 1. *Lone star tick. Ref. 2.*

Risk factors for the development of α-Gal syndrome include genetic predisposition, immune mechanisms that lead to a strong IgE response to α-Gal after tick bites, geographic location, activity that increases exposure to ticks, cat ownership, infection with pet-associated endoparasites, and age. Reactions may also be augmented also by alcohol consumption, physical exercise, and certain medications.[4]

CLINICAL PICTURE

A patient-reported history of prolonged itching at the site of tick bites may be a predictor of α-Gal sensitization.[5] The α-Gal reactions have been reported to most mammalian meats, including beef, lamb, pork, goat, whale, and seal, even in adults who have been asymptomatic for decades with ingestion of meat. Reaction symptoms may start 2–6 hours after ingestion of meat. Common symptoms can range from localized urticaria or angioedema to severe anaphylaxis.[7,8] Other common symptoms include pruritus, shortness of breath, cough, wheezing, abdominal pain, nausea, diarrhea, or vomiting.[5] Delayed gastrointestinal symptoms can occur without cutaneous involvement or respiratory symptoms and may make the diagnosis more difficult to make. Less common symptoms associated with α-Gal syndrome include arthritis and chronic urticaria.[6] The clinical history should suggest a diagnosis of α-Gal–related red meat allergy, but the diagnosis should also be considered in patients who present with otherwise unclear triggers for anaphylaxis.

DIAGNOSIS

Although the clinical history should suggest a diagnosis of α-Gal–related mammalian meat allergy, the diagnosis should also be considered in patients with an unidentified trigger of anaphylaxis. Further testing can then be solicited to evaluate for α-Gal syndrome. An α-Gal sIgE level of ≥2 IU/mL or an α-Gal sIgE value of >1–2% of the total serum IgE value is consistent with a diagnosis of α-Gal syndrome.[5,9] Both sIgE to α-Gal and total IgE levels are measured in some patients because the total IgE value may be low, while the sIgE to α-Gal may be a high percentage of the total IgE value. A diagnosis is also confirmed by observing cessation of symptoms and allergic reactions with the patient's dietary elimination of mammalian meat.[9]

Although most cases are seen in adulthood and late childhood, we have seen pediatric patients present with similar features to the adult patients.[5,10] In contrast to most food allergy, for both adult and pediatric patients, skin-prick testing by using both commercial meat extracts and fresh meat is not a reliable method for evaluation of α-Gal syndrome.[5,8–10] Skin-prick testing was seen to produce small reactions (2–5 mm) in many pediatric and adult patients. Some papers have stated that intradermal testing by using commercial extracts may yield more predictive prick results that are not limited by sensitivity as with standard prick testing; intradermal testing with commercial extracts, however, is not the standard of care in clinical practice.[1,8] With fresh food extracts to mammalian meat, the results are not validated, and, with numerous available food preparations in fresh meats, testing is difficult to standardize.[8] In a research setting, intradermal testing to fresh meat is a reliable way of testing, however, is less likely to be used, especially in pediatric patients.[8,10] Intradermal testing, as with all food allergens, has a higher risk of reaction in testing for α-Gal syndrome and should be carefully considered before attempting. Serum sIgE testing remains the mainstay of evaluation for α-Gal syndrome.[5]

TREATMENT

Patients with α-Gal syndrome should be instructed to avoid mammalian meat, organs, and sausage casings as well as medications such as cetuximab, infliximab, and gelatin-based colloid plasma substitute.[5,11] Cetuximab and, to a lesser extent, infliximab also express the oligosaccharide and can elicit allergic reactions in patients with α-Gal syndrome. In discussions with patients, it must also be communicated that additional exposure to tick bites can maintain or lead to increased serum levels of α-Gal sIgE. With mammalian meat avoidance, the sIgE level to α-Gal will decrease over time in most patients, some to negative levels after <0.1 IU/mL. Some individuals have been able to reintroduce mammalian meat into their diets.[5,10] Counseling should also be discussed for proper tick avoidance measures, such as protective clothing and insect repellant.[4] Desensitization to meat for a limited number of patients with α-Gal syndrome has been successful in a research setting but is not recommended in clinical practice at this time.[8] Due to the delayed onset of reaction, incremental dose oral food challenges are not feasible for α-Gal syndrome.[10,12] When meat challenges with beef or pork were attempted in patients with α-Gal syndrome, the onset of symptoms ranged from 3 to 7 hours, consistent with the delayed onset of symptoms reported.[6]

In select patients with α-Gal syndrome, avoidance of mammalian meat products alone is not sufficient to prevent reactions. Avoidance of additional meat-containing products, such as those that contain gelatin, as well as milk products may be necessary.[5] These include traditional milk-containing or gelatin-containing food products but also collagen and lard. In addition, this population may need to be careful of gelatin-containing vaccines such as yellow fever; measles, mumps, and rubella; and live zoster vaccine; as well as bovine or porcine heart valves; supplementation with pancreatic enzymes; and treatment with antivenoms.[5] There is speculation as well that α-Gal sensitization may carry an increased risk of coronary atherosclerosis, although the evidence is not definitive.[5]

CLINICAL PEARLS

- The onset of α-Gal syndrome is typically during late childhood or early adulthood, and is related to previous lone star tick bites.
- The α-Gal related allergic symptoms are delayed, with onset 2–6 hours after ingestion of mammalian meat; this differs from typical IgE-mediated food-allergic reactions to protein allergens, which typically occur within minutes to an hour of exposure.
- Adults are more likely to have anaphylaxis, whereas children may have recurrent episodes of urticaria or angioedema as well.
- The IgE response is to a carbohydrate moiety rather than a protein antigen, as with traditional food allergies.
- The mainstay of management of α-Gal syndrome is avoidance of mammalian meat; a minority of patients also need to avoid dairy and gelatin, and other mammalian-derived products.
- IgE levels to α-Gal decrease over time with avoidance of tick bites but will increase with subsequent tick bites.

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