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α-Gal Syndrome: Busting Paradigms in Food Allergy

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Abstract

α-Gal syndrome, also known as red or mammalian meat allergy, results from immunoglobulin E–mediated hypersensitivity responses to the carbohydrate galactose-α-1,3-galactose (α-gal). Patients with α-gal syndrome experience immediate onset of allergic symptoms following the injection of pharmaceutical products containing α-gal. However, it typically takes 2 hours or more after dietary α-gal ingestion before patients with α-gal syndrome experience immunoglobulin E–mediated hypersensitivity responses. The case report by Heffes-Doon and colleagues highlights the lack of official guidelines on when and how to reintroduce mammalian meat products into the diet when there is clear laboratory evidence of declining α-gal immunoglobulin E levels.

Keywords

Food allergies; Allergy and immunology; Alpha-gal syndrome

Commentary

α-Gal syndrome (AGS), also known as red or mammalian meat allergy, describes the symptoms associated with immunoglobulin (Ig) E–mediated hypersensitivity responses to the carbohydrate galactose-α-1,3-galactose (α-gal). Platyrrhine monkeys and all nonprimate mammals possess functional galactosyltransferase enzymes and can glycosylate endogenous lipids and proteins with this sugar (1). In contrast, all other primates, including humans, lack functional galactosyltransferase enzymes and α-gal moieties. Thus, humans make immunologic responses to α-gal. In fact, α-gal–specific immunoglobulin (Ig) M, IgA, and IgG antibodies are detectable in human blood. Commensal microbes, primarily in the gut, contain α-gal and serve as a source of α-gal antigen that primes α-gal–specific immune responses in humans (2). Immunity against α-gal has been associated with protective immunity against plasmodium, the infectious agent that causes malaria (2). Investigations are ongoing into designing influenza and COVID-19 vaccines to induce α-gal–specific

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antibodies, because this may enhance the immunogenicity and efficacy of these vaccines (3). Immunoglobulin G antibodies against α-gal have also been implicated in acute rejection of organ xenotransplants, including valves derived from pigs and cows (1).

The link between α-gal–specific IgE and allergic reactions to α-gal was first reported in 2008 (4). In the southeastern United States, a higher frequency of patients than predicted from clinical trials experienced immediate hypersensitivity reactions with the first infusion of cetuximab, a chemotherapeutic biologic monoclonal antibody. Cetuximab was synthesized in a mammalian Chinese hamster ovary (CHO) cell line, which glycosylated the monoclonal antibody with α-gal. In 2009, researchers led by Commins in the United States and Van Nunen in Australia published the first case series of delayed onset, IgE-mediated, hypersensitivity responses to ingested mammalian meat in persons with circulating α-gal IgE (3). Following this, multiple patient cohorts have been described in the United States, South and Latin America, Europe, Asia, and Africa (5).

Patients with AGS experience immediate onset of allergic symptoms following the injection of pharmaceutical products containing α-gal. These pharmaceuticals include biologics such as cetuximab, gelatin expanders, gelatin-containing vaccines, equine and sheep-derived antivenom treatments, and heparin contaminated with α-gal. Indeed, *in vitro* experiments suggest that α-gal glycolipids and glycoproteins can activate basophils sensitized with α-gal specific IgE in the same time frame as conventional food-protein allergens (1, 6). However, it frequently takes 2 hours or more after dietary α-gal ingestion for patients with AGS to experience classic, IgE-mediated, hypersensitivity responses. Studies suggest that glycosylating proteins with α-gal moieties slow both transit of α-gal glycoproteins across intestinal epithelial surfaces and intracellular glycoprotein digestion (1). Ingested α-gal glycolipids must be absorbed, digested, and packaged into lipid particles such as chylomicrons before systemic trafficking (1). In addition, metabolic profiling has revealed differences in lipid and fatty acid metabolism between persons with and without AGS (7). Thus, delayed allergic responses to ingested α-gal are currently attributed to the slow transit and metabolic processing of α-gal glycolipids and glycoproteins (1).

This delay in allergic symptom onset in AGS stands apart from the allergic effector phase of conventional food protein allergies. Typically, allergic patients who consume their food-protein allergen develop symptoms associated with mast cell and basophil (allergic effector cell) degranulation within minutes of consuming the food (3). Similar to conventional food-protein allergy, alcohol, exercise, underlying infection, and simultaneous consumption of nonsteroidal anti-inflammatory drugs may act as accelerants that decrease the threshold for allergic effector cell degranulation in AGS (3). This increases the likelihood and speed in allergic symptom appearance in patients with AGS after consuming α-gal. Most patients with AGS report cutaneous symptoms (hives and itching) in conjunction with gastrointestinal symptoms (gastroesophageal reflux, abdominal bloating and cramping, and diarrhea). However, approximately 20% of patients with AGS describe only gastrointestinal symptoms after consuming α-gal in mammalian meat (5). In the southeastern United States, AGS is a leading driver of anaphylaxis among adults and an emerging trigger for a diarrhea-predominant irritable bowel syndrome–like illness (8).

Allergic sensitization to α-gal (induction of α-gal–specific IgE) is associated with exposure to hard-bodied ticks (9). This contrasts with food-protein allergy, in which development of food protein–specific IgE requires previous exposure to the food itself through an epithelial barrier (1). Multiple tick species are associated with the development of α-gal IgE and AGS (3). In the United States, the culprit tick is *Amblyomma americanum*, also known as the lone star tick. The geographic distribution of *A americanum* ticks in the United States mirrors the geographic distribution of cases of AGS (10). As a result, most of reported AGS cases in the United States come from the southeast (11) where *A americanum* ticks are common. In a case-control study, Kersh and colleagues found that patients with AGS were 11 times more likely than controls to recall finding ticks on their bodies, twice as likely to live near wooded forest, and nearly 6 times more likely to report spending more than 17 hours outside (9). Saliva from ticks associated with AGS contains proteins glycosylated with α-gal. Moreover, the levels of detectable salivary α-gal increase the longer a tick feeds on a mammalian host (12). Altogether, there is strong circumstantial evidence that implicates tick bites as the driving factor for α-gal–specific IgE development. How tick bites might alter immune responses to promote α-gal IgE production are under active investigation (1).

α-Gal syndrome can resolve spontaneously. In most patients, resolution is associated with the ability to consume dairy products and a decline in α-gal–specific IgE levels over time, especially with avoidance of additional tick bites (13). However, as Heffes-Doon and colleagues highlight in their case report, there are no official guidelines on when and how to reintroduce mammalian meat and other products into the diet when there is clear laboratory evidence of declining α-gal IgE levels. No consensus guidelines exist about the appropriate α-gal–specific IgE level or proportion of total IgE levels to use to determine when oral α-gal challenge is appropriate. Expert opinion suggests that if the α-gal–specific IgE level is less than 2 kU/L or less than 2% of total IgE, it may be reasonable to conduct an oral mammalian meat challenge (14). However, the appropriate α-gal–specific IgE level to guide mammalian meat reintroduction may vary with the population studied. For example, in a South African patient cohort, an α-gal–specific IgE level of 5.5 kU/L or greater was associated with a 95% probability of mammalian meat allergy (15). Heffes-Doon and colleagues provide one approach to mammalian meat reintroduction grounded in shared decision making, namely periodic tracking of α-gal IgE levels and offering an in-office oral challenge with 100 grams of mammalian meat with an α-gal IgE level greater than 2 kU/L in a patient who maintained the ability to consume dairy products. Other strategies for mammalian meat reintroduction include gradual reintroduction in the home setting when α-gal–specific IgE levels are less than 2 kU/L or less than 2% of total IgE (3, 14). However, the report rightly highlights a gap in the clinical care of patients with AGS, namely the need for consensus guidelines on mammalian meat introduction in patients with declining α-gal IgE.

Our understanding of allergic sensitization to food-protein allergens continues to expand, with increasing focus on the skin as an organ that facilitates allergic sensitization to foods. Allergic sensitization to α-gal associated with cutaneous tick infestation provides a new angle to dissect the skin's role as a sensitizing organ in food allergy. It is unusual for a carbohydrate to serve as the primary driver of food allergy as in AGS. Continued interrogation of the allergic sensitization phase in AGS, reasons behind the delay in

symptom onset, and the factors that promote disease resolution will widen our paradigms for understanding and managing food allergy.

References

1. Carson AS, Gardner A, Iweala OI. Where's the beef? understanding allergic responses to red meat in alpha-gal syndrome. J Immunol. 2022;208:267–77. doi:10.4049/jimmunol.2100712 [PubMed: 35017216]
2. Yilmaz B, Portugal S, Tran TM, et al. Gut microbiota elicits a protective immune response against malaria transmission. Cell. 2014;159:1277–89. doi:10.1016/j.cell.2014.10.053 [PubMed: 25480293]
3. Macdougall JD, Thomas KO, Iweala OI. The meat of the matter: understanding and managing alpha-gal syndrome. Immunotargets Ther. 2022;11:37–54. doi:10.2147/ITT.S276872 [PubMed: 36134173]
4. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med. 2008;358:1109–17. doi:10.1056/NEJMoa074943 [PubMed: 18337601]
5. Levin M, Apostolovic D, Biedermann T, et al. Galactose α-1,3-galactose phenotypes: lessons from various patient populations. Ann Allergy Asthma Immunol. 2019;122:598–602. doi:10.1016/j.anai.2019.03.021 [PubMed: 30922956]
6. Iweala OI, Choudhary SK, Addison CT, et al. Glycolipid-mediated basophil activation in alpha-gal allergy. J Allergy Clin Immunol. 2020;146:450–2. doi:10.1016/j.jaci.2020.02.006 [PubMed: 32088306]
7. Steinke JW, Pochan SL, James HR, et al. Altered metabolic profile in patients with IgE to galactose-alpha-1,3-galactose following in vivo food challenge. J Allergy Clin Immunol. 2016;138:1465–7.e8. doi:10.1016/j.jaci.2016.05.021 [PubMed: 27448448]
8. Croglio MP, Commins SP, McGill SK. Isolated gastrointestinal alpha-gal meat allergy is a cause for gastrointestinal distress without anaphylaxis. Gastroenterology. 2021;160:2178–80.e1. doi:10.1053/j.gastro.2021.01.218 [PubMed: 33524403]
9. Kersh GJ, Salzer J, Jones ES, et al. Tick bite as a risk factor for alpha-gal-specific immunoglobulin E antibodies and development of alpha-gal syndrome. Ann Allergy Asthma Immunol. 2023;130:472–8. doi:10.1016/j.anai.2022.11.021 [PubMed: 36574585]
10. Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. J Allergy Clin Immunol. 2011;127:1286–93.e6. doi:10.1016/j.jaci.2011.02.019 [PubMed: 21453959]
11. Binder AM, Commins SP, Altrich ML, et al. Diagnostic testing for galactose-alpha-1,3-galactose, United States, 2010 to 2018. Ann Allergy Asthma Immunol. 2021;126:411–6.e1. doi:10.1016/j.anai.2020.12.019 [PubMed: 33422649]
12. Crispell G, Commins SP, Archer-Hartman SA, et al. Discovery of alpha-gal-containing antigens in North American tick species believed to induce red meat allergy. Front Immunol. 2019;10:1056. doi:10.3389/fimmu.2019.01056 [PubMed: 31156631]
13. Kim MS, Straesser MD, Keshavarz B, et al. IgE to galactose-α-1,3-galactose wanes over time in patients who avoid tick bites. J Allergy Clin Immunol Pract. 2020;8:364–7.e2. doi:10.1016/j.jaip.2019.08.045 [PubMed: 31520841]
14. Commins SP. Diagnosis & management of alpha-gal syndrome: lessons from 2,500 patients. Expert Rev Clin Immunol. 2020;16:667–77. doi:10.1080/1744666X.2020.1782745 [PubMed: 32571129]
15. Mabelane T, Basera W, Botha M, et al. Predictive values of alpha-gal IgE levels and alpha-gal IgE: total IgE ratio and oral food challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. Pediatr Allergy Immunol. 2018;29:841–9. doi:10.1111/pai.12969 [PubMed: 30144162]

Key Points

- α-Gal syndrome is an allergic hypersensitivity response to galactose-α-1,3-galactose (α-gal), a carbohydrate attached to fats and proteins in mammalian meat.
- In the United States, lone star tick bites are commonly associated with its development, and most patients experience delayed cutaneous and gastrointestinal symptoms after eating mammal meat.
- Spontaneous resolution of α-gal syndrome is more likely in those who avoid additional tick bites and experience a decline in α-gal–specific IgE levels over time.
- There are no standardized guidelines on when and how to reintroduce mammalian meat into the diet as α-gal–specific IgE levels decline.

Case Report

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