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# Alpha-Gal Allergy: a new threat to Appalachia

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## ABSTRACT

Alpha-gal allergy, or mammalian meat allergy, is described as the development of IgE antibodies to the oligosaccharide galactose-a-1,3-galactose following a bite from the tick species Amblyomma americanum (Lone Star tick) or Dermacentor variabilis (Wood tick). Dermatologic or gastrointestinal symptoms are usually delayed by four to six hours after exposure, making the diagnosis difficult. Due to the use of mammalian proteins in many common medications, surgical equipment, and prosthesis, unexpected reactions can occur. In the United States, this pathology is predominately seen in the southeast but has been associated with other tick species on every continent except Antarctica. As the habitat for Amblyomma and Dermacentor continues to move further north due to changing patterns in deer population and weather, the incidence of alpha-gal syndrome has increased in the states outside its normal southeastern locale, especially in people with occupations and hobbies that require time outdoors in wooded areas.

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## INTRODUCTION

Alpha-gal allergy (AGA), also known as mammalian meat allergy, is a newly recognized pathology in which affected individuals can experience both new dermatologic (urticaria and angioedema) and gastrointestinal (nausea, diarrhea, and indigestion) symptoms due to antibodies against an oligosaccharide made by non-primate mammals. As symptoms follow a history of tick exposure, those with outdoor occupations and hobbies in wooded areas tend to be most at risk. The problem with the familiarity of this disease is multifactorial and includes recency of diagnosis, regionality, and delay in symptoms from exposure. Five cases of allergic reactions to dietary meat were initially discussed in the 1989 Georgia Allergy Society conference,[1,2] but the pathophysiology was officially described in 2009 by Van Nunen.[1,3,4] Cetuximab, a monoclonal antibody created in murine SP2/0 cells[1,2,5] designed to treat unresectable metastatic colorectal cancer and head and neck squamous cell cancer,[1-3,5,6-9] aided its discovery in the intervening twenty years. Immediate anaphylactic reactions to cetuximab were seen during investigational trials as early as 2004.[2] These reactions were largely confined to the southeastern United States (US),[2] where they were seen 20 times as often as the remainder of the nation.[1,6] In 2008, Chung discovered 20% of healthy controls from Tennessee had antibodies to portions of cetuximab, which in 2011 were confirmed to be related to the oligosaccharide alpha-gal.[6]

In addition to the southeastern US, AGA is seen from other tick species on every other continent except Antarctica (Table 1). The regionality of AGA in the US is primarily related to the distribution of Amblyomma americanum (Figure 1: Texas Lonestar tick) and, to a lesser extent, Dermacentor variabilis (Figure 2: Wood tick).[2,7,10-12] The deer population, on which the Lonestar tick feeds, is a primary factor restricting the range of this pathology, but this is changing. An overabundance of host species due to changing leash laws and hunting patterns has allowed this tick is spread to the upper Midwest and the east coast.[3,10] Changes in sub-freezing temperatures, humidity, and


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**Tick Species Associated with Alpha Gal Allergy**

*Table #1*

| Continent | Tick |
|---|---|
| Africa | *Amblyomma hebraeum** |
| Asia | *Haemaphysalis longicornis* |
| Australia | *Ixodes holocyclus* |
| Europe | *Ixodes ricinus* |
| North America | *Ambylomma americanum* (Lone Star tick) |
| | *Dermacentor variabillis* (Wood Tick) |
| | NOT *Ixodes scapularis* (Deer tick) |
| South America | *Ambylomma sculptum* |
| * suspected | |

**TABLE 1.** Tick species on each continent that have been implicated in causing Alpha Gal Allergy.

ground temperature alter the questing and molting phases of the tick lifecycle, furthering the northward spread.[3,13]

## CASE

An 18-year-old Caucasian male with a history of seasonal allergies intermittently treated with cetirizine and a medication allergy to both amoxicillin and sulfa presented to the emergency department (ED) after two episodes of urticaria and pruritus over a one-month period. The initial episode began at midnight with urticaria on the trunk and arms, severe external pruritus, and mild pharyngeal pruritus. Within an hour, the urticaria resolved with diphenhydramine. He denied dyspnea, nausea, or swelling. The second episode occurred after midnight with a more severe ""burning"" urticaria on the trunk and extremities. He also experienced angioedema of the face and hands, a cough, pharyngeal pruritus, mild dyspnea, chest tightness, and abdominal cramping with diarrhea. These symptoms were refractory to diphenhydramine at home. In the ED, he was treated with Solu-Medrol, famotidine, intravenous fluids, and more diphenhydramine. Symptoms resolved in about an hour. While no lab work was ordered, chest radiograph and electrocardiogram were unremarkable.

Exam and vitals in the office four days later were unremarkable. A complete blood count, complete chemistry profile, and erythrocyte sedimentation rate were also normal. He denied new chemical, food, or environmental exposures. For his symptomatic days, he could only remember eating at Burger King® the evening of the most recent episode.

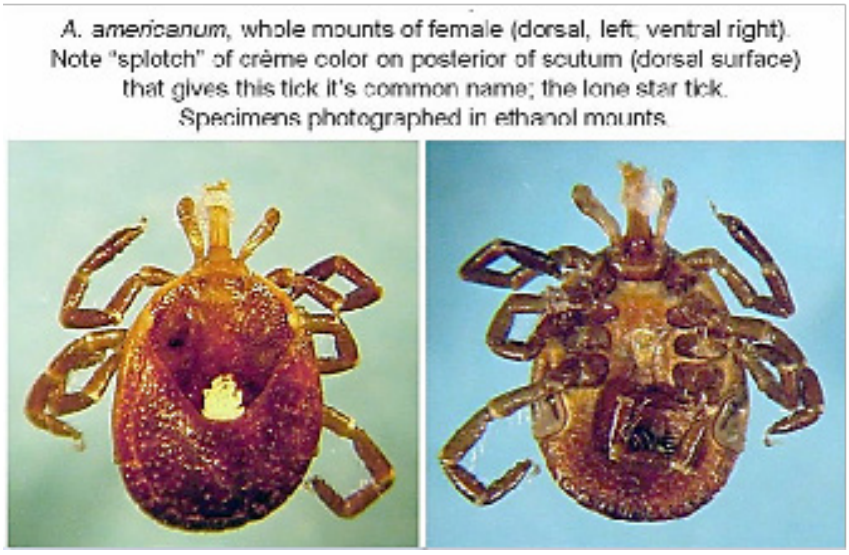


**FIGURE 1:** Amblyomma americanum (Texas Lonestar tick). Photos courtesy of James Joy, Digital Museum of Medical and Veterinary Acarology.

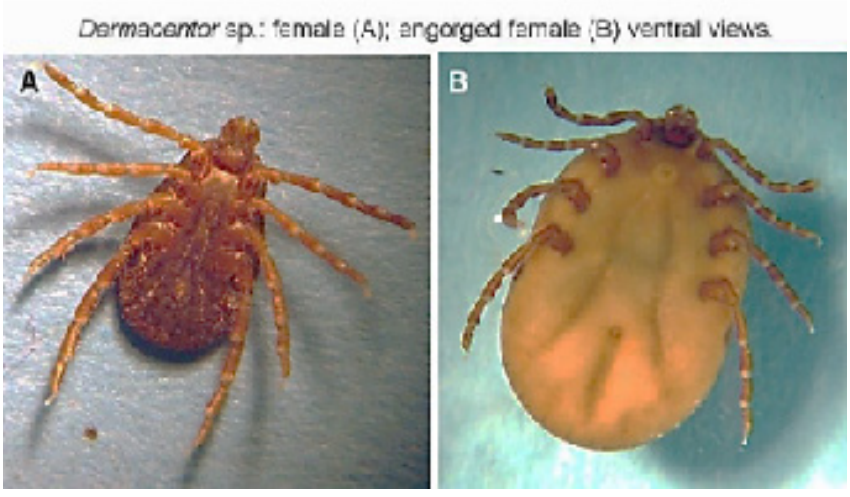


**FIGURE 2:** Dermacentor variabillis (Wood tick). Photos courtesy of James Joy, Digital Museum of Medical and Veterinary Acarology.


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Recent activities included hunting, fishing, and mowing lawns, which were associated with poison ivy, chiggers, and "pulling off a lot of ticks." Daily cetirizine was initiated, and he was given an EpiPen with instructions regarding its use. Due to worsening symptoms, he was scheduled to see allergy/immunology.

In the month preceding his allergist appointment, he noted mild urticaria and "gagging" that occasionally led to emesis with cheese or milk consumption. These symptoms were not severe enough to require the use of his Epi-Pen. He did recall eating a hamburger without a severe reaction. The allergist ordered labs, and the patient was sent home with strict dietary instructions to avoid eating mammalian meats, limit milk and cheese, and monitor any reactions. The importance of tick avoidance measures was also discussed. Daily cetirizine and as-needed Epi-Pen were continued. Labs returned confirming AGA: complete blood count was normal, a tryptase level of 6.0 (normal 2.2 to 13.2), and a total IgE of 226.0 with an alpha-gal IgE of 46.9 (normal < 0.10). Since the diagnosis, he has been able to reintroduce small amounts of cheese, but larger amounts have caused some gastrointestinal pain. He continues hunting and fishing but now uses insect repellent and is diligent about tick inspections after being outside.

## DISCUSSION

### Pathophysiology

Alpha-gal is a carbohydrate oligosaccharide, galactose-alpha-1,3-galactose, created by the alpha-1-3-galactosyltransferase gene.[2,3] This gene is truncated in humans and catarrhine primates (Old World monkeys and apes) and produces a functionally inactive enzyme.[2,3,7,11,14,15] Therefore, alpha-gal is seen as foreign to these species. Production in other mammals allows IgM/IgG sensitization across the gut from dietary consumption of meat and milk[3,6,14] as it survives heating, although freeze-drying and homogenization may diminish its presence.[2,11] Alpha-gal IgM/IgG across the gut biome is thought to serve as a protective barrier to some strains of E. coli, Klebsiella, and Salmonella, as well as helminths, who share a commonality of surface epitopes with alpha-gal. [3,6,11,14]

Despite this initial sensitization common to all humans, the development of a secondary hypersensitivity reaction is necessary to develop AGS. This occurs through the introduction of alpha-gal directly into the bloodstream through the prolonged feeding of a tick. In order for a tick to feed, it must disrupt the physical barrier of the epidermis, enter the dermis, and inhibit pro-inflammatory cytokines to overcome immunologic and hemostatic defenses.[3] Interestingly, ticks also lack the enzyme to make alpha-gal, but through immunolocalization it is known to reside in their salivary secretory vesicles. Multiple theories have been postulated as to how alpha-gal is found in a species unable to construct it. Residual remains from a previous blood meal on non-primates are unlikely as alpha-gal has been seen in ticks naïve to those species.[3,6,10] Coinfection with another organism, such as a rickettsial species, is possible but is still unproven.[2,3,6] Cleavage of type B blood is possible as it differs from alpha-gal epitopes by one fructose residue.[3,8,10,16]

Regardless, alpha-gal from tick saliva is required to trigger and augment AGA.3 A dual allergen exposure hypothesis requires both type 1 and type 2 hypersensitization (Figure 3).16 Alpha gal-specific IgE from a type 1 hypersensitivity reaction seems necessary for AGA to occur,[1,3,4,6,10,17,18] evidenced by increased levels of IgE after exposure that decreased over time with avoidance.[4] These antibodies, produced in B lymphocyte memory cells, convert from producing alpha-gal specific IgM/IgG after sensitization from the tick bite.[1,3] After this conversion, symptomatic reactions occur as alpha-gal is absorbed from the gut and presented by basophils to the memory cells. These in turn, stimulate mast cells,[1,2,19] whose numbers increase after subsequent infestations.3 The delay in symptom onset likely relates to the absorptive process as basophils typically elicit a reaction within 20 minutes.[1-3,6,19] This multi-hour delay represents absorbing digested lipids as chylomicrons, repackaging, and transit delays.[1,2] Factors affecting gut permeability and intestinal perfusion also affect symptom delay.[3] Absorption is increased by alcohol consumption,[1-3,6,16] high alpha-gal load (i.e., internal organs), and exercise.[1,3,16] Fatty foods and non-steroidal anti-inflammatory


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**Potential Medical Complications Related to Alpha Gal Allergy**

*Table 2*

| | |
|---|---|
| ***Effects on Health*** | |
| Cardiovascular Disease | Increased atheromatous burden |
| Kounis Syndrome | Ischemic chest pain from allergic or immunologic causes |
| ***Inactive Compounds in Medications**** | |
| Gelatin | Found as an inactive component in gelcaps, hemostatic agents, plasma expanders, suppositories, and vaccines |
| Glycerin | Found as an inactive component in some prparations of acetominophen, anti-seizure medication, OTC cold & GI preparations, prenatal vitamins, progesterone, and vitamin supplements |
| Lactic Acid | |
| Steric Acid | Found as an inactive component in some preparations of acetominophen, magnesium, opioids, and vitamin supplements |
| ***Medications**** | |
| Albumen | some is of Bovine origin |
| Antivenom | Equine and Ovine origin |
| Cetuximab | Murine origin |
| Collagen | Bovine and Equine origin |
| Hemostatic Agents | recombinent proteins from baby hamster kidney cell origin |
| Heparin | Porcine intestinal and Bovinr lung origin |
| Pancreatic Enzymes | Porcine pacrease origin |
| ***Surgical Issues*** | |
| Biologic Mesh | |
| Biologic Suture | Catgut |
| Heart Valves | Bovine and porcine |

**TABLE 2.** Medical conditions affected by Alpha Gal Allergy and commonly used medical products derived from animals.

medications slow the response.[1,3,11,16]

## Diagnosis

Delayed absorption is the primary impediment to the quick diagnosis of AGA. Studies show correct diagnoses occur in less than 10% of encounters.[20] A suspicion for a meat allergy aids a good history which included: a previous history of asymptomatic meat consumption, dermatologic symptoms 2-6 hours after eating meat, absence of symptoms in a meat-restricted diet, and a history of tick exposure.[1,2,6] Diagnostic testing confirms historical information with a positive serum alpha-gal IgE ratio of >/= 2 IU/mL or a ratio > 2% (normal </= 1%) of the total serum IgE.3,11 False positives can occur in parasitized patients,5 but levels tend to correlate with clinical disease.11 Other tests are intradermal skin prick tests using milk, beef, or pork with turkey, chicken, or fish control,[1-3] as well as basophil activation tests using cetuximab.[11] However, these tests should be used in conjunction with IgE levels due to highly variable sensitivity.[3] Tryptase levels demonstrate an allergic reaction has occurred.[17] The gold standard of an oral food challenge, either with a 150-gram pork load or incremental increases every 15 minutes, is not recommended because of the delay in symptoms.

## Treatment/Prognosis

There is no definitive cure for AGA. The treatment cornerstone is avoidance of red meat,[1,6,9,11,16] although evidence is insufficient to recommend avoiding dairy products.[1] Patients should also avoid further tick or other ectoparasites (chigger)[1,18] bites by wearing proper clothing, utilizing protective sprays, and suppressing host-seeking ticks.[1,17] Evidence suggests avoidance of further tick bites may decrease alpha-gal IgE and symptoms over time, but symptoms can return with new exposures.[3,6,11]


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Equally important in the treatment of AGA is identifying potential patient risks, including medical risks (Table 2) and treating reactions. Thorough medical record documentation, a written action plan, and medical alert bracelets may be helpful.[6,11] Plans should include early identification and management of symptoms. Should symptoms occur, histamine blockers, steroids, albuterol, epinephrine, oxygen, intravenous fluids, or simply observation/supportive care may all be included depending on severity.[6,11] Patients should be educated about the rarity of AGA as they may experience hardship and frustration when medical providers lack sufficient knowledge regarding this process. Furthermore, patients must feel empowered for self-advocacy to drive their medical care if needed.[18]

## CONCLUSION

AGA is a relatively new, incompletely explored pathology. Delay in symptomatology following mammalian meat consumption makes diagnosis difficult and requires clinician suspicion to diagnose quickly. As behavioral and environmental factors are allowing its spread outside of the typically confined area in the southeastern US, providers unfamiliar with the pathology are encountering it. Physician awareness is essential to help patients manage the associated dietary and medical issues.


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