https://doi.org/10.46344/JBINO.2025.v14i05.19

RED MEAT ALLERGY (ALPHA-GAL SYNDROME): AN EMERGING BUT UNDER RECOGNIZED CRUCIAL PUBLIC HEALTH CONCERN

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ABSTRACT

Red meat allergy, known medically as alpha-gal syndrome (AGS), is an emerging and underrecognized public health issue characterized by an IgE-mediated hypersensitivity reaction to the carbohydrate galactose-a-1,3-galactose (alpha-gal). This syndrome is triggered by the bite of certain tick species, which introduce alpha-gal into the human bloodstream, leading to the production of specific antibodies. Upon subsequent exposure such as eating red meat or products containing alpha-gal affected individuals may experience allergic reactions, which can be severe and even life-threatening. AGS is unique among food allergies in that it is triggered by a sugar molecule rather than a protein, and its symptoms typically appear three to eight hours after ingestion, distinguishing it from most other food allergies. Since its initial identification in the United States, AGS has been reported globally, reflecting the expanding range of tick vectors. Diagnosis relies on clinical history, evidence of tick exposure, and laboratory detection of alpha-gal–specific IgE antibodies, but remains challenging due to delayed symptom onset and variable presentations. Management is limited to strict avoidance of alpha-gal–containing foods and products, emergency preparedness, and prevention of further tick bites. With no cure currently available, AGS poses significant challenges for affected individuals and public health systems. This review discusses the etiology, clinical features, diagnostic complexities, and preventive strategies for AGS, emphasizing the need for increased awareness, improved diagnostic tools, and coordinated public health responses to address this growing threat.

Keywords:Alpha-gal Syndrome, Food related anaphylaxis,Publichealth, Red meat allergy, Tick-bite meat allergy

Introduction:

Tick bite meat allergy, also known as red meat allergy or mammalian meat allergy (MMA), is a form of acquired meat allergy that manifests symptoms 3 to 8 hours after consuming mammalian meat. Previously being exposed to specific tick bites causes the illness. According to the scientific community, this allergy is commonly referred to as "Alpha-gal Syndrome," and it was initially identified in the USA in 2002 by Thomas Platts-Mills (NIAID, 2017). It is currently known to occur in 17 countries across all six continents where tick bites occur (Kwak *et al*., 2018).

A food allergy known as red meat allergy or alpha-gal syndrome (AGS) is brought on by galactose-a-1,3-galactose (alpha-gal), a carbohydrate that is present in most mammals with the exception of primates. Unlike other allergies, this one usually appears hours after consuming red meat, such as lamb, beef, or hog, and manifests as a delayed hypersensitivity reaction (Wilson *et al*., 2019). AGS is becoming a more significant worldwide health issue after being discovered in the US and being reported in Australia, Europe, Africa, and Asia (Wilson *et al*.,2024). In order to assist in preventing future epidemics from turning into pandemics, this review intends to improve knowledge, preparedness, and response to this high-threat hazard ofalpha-gal syndrome. Additionally, it will promote emergency management through multisectoral collaboration.

Etiology and Pathogenesis:

All non-primate mammals' tissues contain the carbohydrate galactose-a-1,3-galactose, also known as alpha-gal, but catarrhines, a primate group that includes humans, apes, and Old-World monkeys, do not (Galili, 1993). Alpha-gal syndrome (AGS), also called alpha-gal allergy, is an IgE-mediated hypersensitivity reaction to this substance. The consumption of animal meats, like beef, pork, lamb, or venison, which contain alpha-gal, can cause severe and sometimes fatal allergic reactions in people with AGS. Additionally, some people may have adverse reactions to dairy products and some drugs that come from mammals.

The condition arises following sensitization via tick bites, which introduce alpha-gal into the human bloodstream. In the United States, the primary vector is the lone star tick (*Amblyomma* americanum). In other regions, different tick species are implicated: the paralysis tick (*Ixodesholocyclus*) in Australia, *Haemaphysalis longicornis* in Japan, and possibly *Amblyommahebraeum* in South Africa (Kwak *et al*., 2018; Mabelane, 2018). While the Centers for Disease Control and Prevention (CDC) have not excluded other tick species from contributing to AGS, alpha-gal has also been detected in the saliva of Ixodes scapularis, indicating a broader range of possible vectors.

Alpha-gal is introduced by the saliva of an infected tick, especially the lone star tick, when it bites a human. The immune system produces particular IgE antibodies against alpha-gal as a result of this exposure. These IgE antibodies attach to the molecule and cause the release of histamines and other mediators when alpha-gal-containing goods are subsequently consumed. This results in allergic reactions that range from urticaria to anaphylaxis.The majority of AGS

cases in the US are found in the South, East, and Central areas, which correspond to the lone star tick's ecological range. Although AGS can occur in people of any age, most instances that are recorded involve adults (CDC, 2023).

Epidemiology:

Alpha-gal syndrome has been reported across various continents, including North America, Europe, Australia, and parts of Asia and Africa (Wilson *et al*., 2024). It is mentioned that tick can make the human beings allergic to meat (Lauren, 2023). The prevalence of AGS correlates strongly with tick exposure, and cases have risen due to expanding tick habitats influenced by climate change and land use changes (Wright *et al*., 2022). While exact prevalence data remain limited, increasing case reports suggest AGS is an important emerging allergy with substantial morbidity.

Clinical Manifestations of Alpha-gal Syndrome (AGS):

Symptoms of alpha-gal syndrome typically appear three to six hours after the consumption of mammalian meat or dairy products, a delay that distinguishes AGS from most other food allergies. This delayed onset of anaphylaxis is a unique feature of AGS, which is also the first known food allergy triggered by a carbohydrate, rather than a protein (Alvarez, 2012). In contrast, intravenous administration of medications containing alpha-gal can provoke immediate allergic reactions.

Common symptoms of AGS include the following:

- Itchy rash or hives
- Angioedema (swelling of deeper layers of the skin)
- Nausea or vomiting
- Heartburn or indigestion
- Constipation
- Diarrhea
- Cough
- Dyspnea (shortness of breath)
- Hypotension
- Swelling of the lips, tongue, or eyelids
- Dizziness
- Stomach pain
- Loss of bladder control

Clinical presentations range from mild to severe, with anaphylaxis reported in approximately 60% of cases, necessitating immediate medical intervention (Vaz Rodrigues *et al*., 2022). Furthermore, dyspnea has been observed in about 70% of patients, posing a heightened risk for individuals with asthma (Wolver *et al.,* 2013).

Diagnosis of Alpha-gal Syndrome:

Diagnosis of alpha-gal syndrome is primarily based on a combination of medical history, physical examination, and laboratory testing. Clinicians typically inquire about the onset and nature of symptoms, any history of tick bites, and dietary habits, particularly the consumption of mammalian meat. During the physical exam, skin manifestations may be assessed, and vital signs such as blood pressure are checked.

Laboratory diagnosis involves measuring IgE antibodies specific to alpha-gal and, in some cases, IgE against particular mammalian meats. A level where alpha-gal-specific IgE comprises around 1% of the

total IgE in the body has been identified as indicative of AGS (Platts-Millset *al*., 2020). It is noteworthy that some individuals may have elevated alpha-gal IgE levels without clinical symptoms; in such cases, improvement following avoidance of red meat supports the diagnosis.

In instances of anaphylaxis, urgent hospital admission and treatmentincluding administration of epinephrineare critical. Currently, desensitization protocols for AGS are experimental, with only two documented successful cases reported (Unal *et al*., 2017).

Treatment and Prevention of Alpha-gal Syndrome:

Alpha-gal syndrome has no known cure or effective treatment. Epinephrine, antihistamines, and oral corticosteroids are used symptomatically to treat allergic reactions brought on by alpha-gal exposure. By rigorously avoiding foods and goods containing alpha-gal, people with AGS can avoid allergy episodes. It is generally advised to take the following precautions:

1. **Emergency preparedness**:Individuals with AGS should always carry epinephrine auto-injectors and antihistamines to promptly manage allergic reactions. In cases of anaphylaxis, immediate hospital admission for emergency treatment is critical. To date, only two cases of successful desensitization have been documented (Unal *et al.,* 2017).
2. **Avoiding tick bites**:Repeated tick bites can increase IgE antibody levels against alpha-gal, thereby heightening sensitivity. Conversely, avoiding further tick exposure can lead to a gradual decline in antibody levels over a recovery period ranging from 8 months to 5 years (Platts-Mills *et al*., 2020). Preventive measures include:
   - Avoiding grassy, brushy, and wooded areas where ticks are prevalent.
   - Staying on the center of hiking trails.
   - Treating clothing and gear with 0.5% permethrin or purchasing pre-treated items.
3. **Dietary and product avoidance**:People with AGS must avoid consuming mammalian meats, such as beef, pork, lamb, chevon, venison, and rabbit. Additionally, they should avoid:
   - Certain medications: including cetuximab (an anti-cancer drug), gelatin-based colloid plasma substitutes (used for hypovolemia), thyroid hormone supplements derived from cow or pig, and anti-snake venom derived from horse or sheep.
   - Some NSAIDs and analgesics that may contain traces of alpha-gal (Vaz Rodrigues *etal*., 2022).
   - Dairy products, which contain lower levels of alpha-gal compared to meat.
   - Various medical products such as heparin, gelatin capsules or gelatinous foods, pancreatic enzymes derived from pigs, vaccines containing gelatin (e.g., MMR, yellow fever), and prosthetic heart valves from cow or pig sources.

Outlook for People with Alpha-gal Syndrome:

People with alpha-gal syndrome must avoid consuming mammalian meat to prevent allergic reactions. However, they can safely eat non-mammalian meats, such as chicken, turkey, ostrich, emu, fish,

and seafood, which do not contain alpha-gal. Over time, the levels of IgE antibodies against alpha-gal tend to decrease, and some patients may eventually tolerate mammalian meats like beef, pork, and lamb without adverse reactions. However, additional tick bites can elevate or maintain high antibody levels, prolonging sensitivity (Platts-Mills *et al*., 2020).

From 2010 to 2022, over 110,000 suspected AGS cases were identified in the United States alone. As of November 2019, Australia has reported the highest rates of mammalian meat allergy and tick-induced anaphylaxis (Lawson, 2019). Alpha-gal syndrome can be confused with pork-cat syndrome, but unlike the immediate allergic response in pork-cat syndrome, AGS typically involves a delayed reaction.In 2020, the US FDA approved genetically modified pigs that do not produce alpha-gal sugars, known as GalSafe pigs. Meat from these pigs is considered safe for people with AGS and may also facilitate the production of alpha-gal–safe drugs and organs suitable for xenotransplantation (Dolgin, 2021).

A recent CDC study estimates that AGS may affect up to 450,000 people in the US, with cases rising as warmer climates favor the expansion of lone star tick populations (Lauren, 2023). Despite this, many clinicians and healthcare providers have limited awareness of the condition. In the US, more than 85% of individuals with AGS recall a prior tick bite (Molla*et al*., 2024).AGS is unique among allergies because it involves sensitization to a sugar molecule (galactose-a-1,3-galactose) rather than a protein. This sugar is present in mammalian meat but absent in apes and humans, distinguishing AGS from other food allergies.

Public Health Implications:

The rising incidence of AGS poses challenges for public health due to its atypical presentation, need for increased awareness among healthcare providers, and implications for blood transfusion safety and organ transplantation, given alpha-gal presence in these contexts (Mabelane *et al*., 2023). Surveillance and tick control programs are essential to mitigate the growing burden.

Conclusion and Recommendations:

Alpha-gal syndrome remains an important cause of allergy in the Indian subcontinent. AGS is a distinct and well-known kind of delayed food allergy brought on by sensitization to the carbohydrate galactose-a-1,3-galactose (alpha-gal), usually from tick bites. AGS, which causes allergic reactions ranging from moderate to potentially fatal anaphylaxis, is caused by a sugar molecule present in mammalian flesh and associated products, unlike most food allergies. Despite being thought of relatively uncommon, the increase in cases recorded worldwide, especially in areas where tick populations are spreading, suggests that AGS is becoming a more serious public health issue.

The diagnosis of AGS remains challenging due to its delayed symptom onset, variability in clinical presentation, and limited awareness among healthcare providers. Current management relies heavily on strict avoidance of alpha-

galcontaining foods and products, emergency preparedness, and prevention of tick bites. Despite advances such as the approval of alpha-gal–free "GalSafe" pigs and ongoing research into desensitization protocols, AGS remains incurable, requiring long-term vigilance by affected individuals.

Recommendations:

- Healthcare professionals should be trained to recognize the atypical presentation of AGS and include it in differential diagnoses for unexplained anaphylaxis, especially in tick-endemic areas.
- Governments and public health agencies should strengthen tick surveillance programs and educate the public on tick bite prevention, particularly in high-risk regions.
- More clinical trials are needed to explore immunotherapy, desensitization, and the development of alpha-gal–free pharmaceuticals to improve treatment options for AGS patients.
- Widespread availability of reliable alpha-gal–specific IgE testing is critical to facilitate early diagnosis and prevent severe allergic reactions.

Contribution of authors:

All the authors contributed during the preparation and submission of the manuscript.

Conflict of interest:

There was no conflict of interest.

Funding:

Nil

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