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Mysterious Allergy Caused by Tick Bite: Alpha-Gal Syndrome

Kene Isırmasının Neden Olduğu Gizemli Alerji: Alpha-Gal Sendromu

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ABSTRACT

Alpha-Gal syndrome (AGS) manifests as an intricate allergic response characterised by the formation of specific immunoglobulin E (IgE) antibodies targeting a carbohydrate termed galactose-α-1.3-galactose (α-Gal). Alpha-Gal antigens, which play a role in AGS, have been detected in the salivary glands and saliva of various tick species, especially *Amblyomma americanum*. Identifying these antigens in tick saliva underlines the potential role of tick bites in sensitising individuals to α-Gal and contributes to the complex immunological processes associated with AGS. When people with α-Gal allergy eat beef, pork, lamb, or the flesh of other mammals, they experience an allergic reaction that causes various symptoms, including rash, nausea, vomiting, and diarrhoea. In some cases, AGS can be life-threatening requiring emergency medical attention. Moreover, these reactions do not occur only due to red meat; intake of medical drugs, vaccines, and antidotes containing α-Gal epitopes can also trigger allergies. The fact that the symptoms causing IgE antibodies are directed against a carbohydrate moiety the unusual delay between food consumption and the onset of symptoms, and the differences in the reactions shown by α-Gal allergy make α-Gal syndrome an unprecedented allergic disease and distinguish it from other food allergies. Interestingly, α-Gal antigens involved in the development of AGS have been discovered in salivary secretions of different tick species in several continents. However, the underlying causes of α-Gal-specific IgE production and immune responses to tick bites are not fully understood. This complex system is crucial for identifying and developing new therapies for the disease. This article reviews the evolution of α-Gal, the current understanding of AGS and its relationship to tick species.

Keywords: Tick, red meat, Alpha-Gal, Alpha-Gal syndrome, allergy, IgE

ÖZ

Alpha-Gal sendromu (AGS), primat olmayan memelilerin hücrelerinde ve dokularında bulunan, galaktoz-α-1,3-galaktoz (α-Gal) olarak bilinen bir karbonhidrata karşı spesifik immünoglobulin E (IgE) antikorları geliştiğinde ortaya çıkan karmaşık bir alerjik reaksiyondur. AGS'nin gelişiminde rol oynayan α-Gal antijenleri, başta *Amblyomma americanum* olmak üzere çeşitli kene türlerinin tükürük bezlerinde ve tükürüklerinde tespit edilmiştir. Kene tükürüğünde bu antijenlerin tanımlanması, kene ısırıklarının bireyleri α-Gal'e karşı duyarlı hale getirmedeki potansiyel rolünün altını çizmekte ve AGS ile ilişkili karmaşık immünolojik süreçlere katkıda bulunmaktadır. Alpha-Gal alerjisi olan kişiler sığır eti, domuz eti, kuzu eti veya diğer memelilerin etini yediğinde döküntü, mide bulantısı, kusma ve ishal gibi çeşitli semptomlara neden olan alerjik reaksiyonla karşılaşırlar. Bazı olgularda AGS, acil tıbbi müdahale gerektirecek şekilde hayatı tehdit edici olabilir. Üstelik bu reaksiyonlar sadece kırmızı ete bağlı olarak ortaya çıkmaz; α-Gal epitopları içeren tıbbi ilaçların, aşıların ve panzehirlerin alımı da alerjileri tetikleyebilir. Semptomlara neden olan IgE antikorlarının bir karbonhidrat parçasına karşı yönlendirilmiş olması, gıda tüketimi ile semptomların başlangıcı arasındaki olağan dışı gecikme ve α-Gal alerjisinin gösterdiği reaksiyonlardaki farklılıklar, α-Gal sendromunu benzeri görülmemiş bir alerjik hastalık haline getirmekte ve diğer gıda alerjilerinden ayırmaktadır. İlginç bir şekilde, AGS gelişiminde rol oynayan α-Gal antijenleri çeşitli kıtalarda farklı kene türlerinin tükürük salgılarında keşfedilmiştir. Bununla birlikte, α-Gal'e özgü IgE üretiminin ve kene ısırıklarına karşı bağışıklık tepkilerinin altında yatan nedenler tam olarak anlaşılamamıştır. Bu karmaşık sistem, hastalığa yönelik yeni tedavilerin tanımlanması ve geliştirilmesi için çok önemlidir. Bu derleme α-Gal'in evrim sürecini, AGS'nin mevcut anlayışını ve bunun kene türleriyle ilişkisini gözden geçirmektedir.

Anahtar Kelimeler: Kene, kırmızı et, Alpha-Gal, Alpha-Gal sendromu, alerji, IgE

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Türkiye PARAZİTOLOJİ Dergisi

INTRODUCTION

Ticks are obligate ectoparasites and must feed on blood to complete their development at all life cycle stages (larva, nymph, adult). Ticks, as significant vectors of viruses, bacteria, and protozoan pathogens, hold paramount global public health importance (1). It is currently recognised as the second most important vector of infectious diseases in humans globally after mosquitoes. Their role in disease transmission is multifaceted, involving the transmission of various pathogens, including bacteria, viruses, protozoa, and helminths. The growing recognition of ticks as vectors underscores the imperative for comprehensive research initiatives to better understand their ecology, host interactions, and the diverse array of pathogens they harbour, with implications for global public health strategies and disease prevention (2).

The hematophagy nature and host specificity of ixodid ticks may influence their capacity to acquire, maintain and transmit various pathogens and thus contribute to tick bite-associated conditions, including Alpha-Gal syndrome (AGS), tick paralysis and babesiosis (2). While feeding on their hosts, ticks secrete a multi-component saliva that modulates host immune responses and contributes to the establishment of tick-borne viral, protozoal and bacterial pathogens in the host (3-8). In the United States of America (USA), a surveillance study by the Centers for Disease Control and Prevention between 2004 and 2016 revealed that ticks were responsible for 77% of reported cases of vector-borne diseases. (4,9). Recent research predicts an increase in tick-borne diseases, including AGS, due to the geographical expansion of several tick species (10,11).

Alpha-Gal syndrome, also called α-Gal allergy, red meat allergy or mammalian meat allergy, develops when the immune system reacts to the carbohydrate α-Gal, leading to hypersensitivity reactions (10,12). Alpha-Gal is found in most mammals, including farm animals, but is absent in humans and some primates (13). Individuals with AGS develop hypersensitivity to α-Gal and manifest as a delayed allergic reaction to mammalian meat and products containing α-Gal (e.g., dairy products, gelatin-containing colloids and pharmaceuticals) (10,14-16). Unlike traditional food allergies, allergic reactions in AGS appear late and are multifaceted. Reactions typically begin a few hours after consuming mammalian meat or other animal-based food products (Figure 1) (13). Symptoms range from severe anaphylaxis to angioedema, diarrhoea, shortness of breath, urticaria, vomiting and itching (13,17,18). The AGS first reported when specific IgE antibodies targeting α-Gal were identified in patients who developed an allergic reaction to the cancer treatment drug cetuximab and then were subsequently identified in people with hypersensitivity to mammalian meat and products (15,17).

In 2009, Australian researchers were the first to describe the relationship between AGS and tick bites. Subsequently, US researchers studying patients with anaphylactic reactions to cetuximab, a cancer drug, established that the *Amblyomma americanum* tick, the so-called "Lone Star Tick", was linked to the allergy (19,20). Since then, AGS has been reported in several world

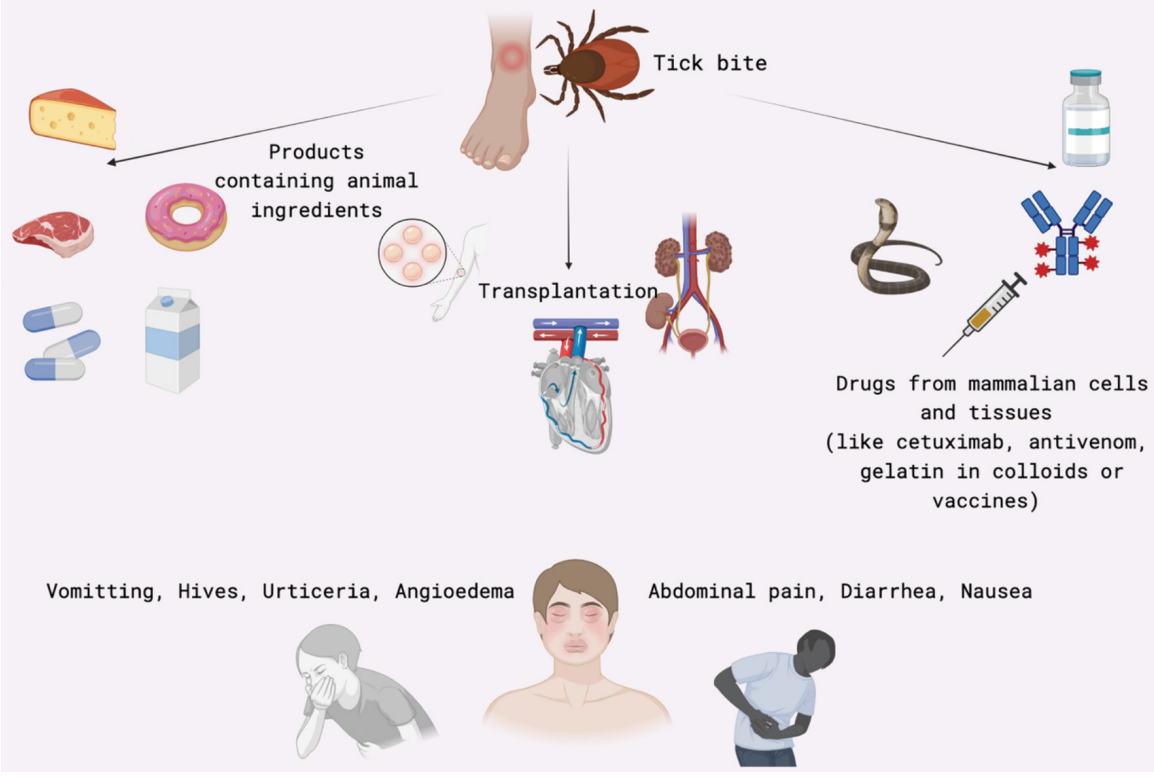

Figure 1. Tick bites are AGS's most common and important cause. Drugs derived from mammalian tissues (e.g., cetuximab, antivenoms, gelatine in some medical suspensions and vaccines) can trigger this allergy. Because of the tendency of AGS to cause a severe allergic reaction, organ transplants from animals to humans are unsuccessful. Consumption of mammalian meat or offal, dairy products, dairy products used in desserts, etc., may cause an allergic reaction

AGS: Alpha-Gal syndrome

regions, including the USA, Europe, Australia, Japan, and South Africa (21-24). In the USA, tick bites from *A. americanum* are thought to be the primary cause of AGS. However, the clustering of cases in areas outside the range of this tick suggests that other tick species or vectors may also contribute to α-Gal susceptibility (15,25,26). Globally, other tick species that cause AGS include *I. ricinus*, *I. holocyclus* and *H. longicornis* (20,27).

Although the processes that cause sensitisation to α-Gal in humans have not been fully resolved, it is thought to be linked to the α-Gal antigen present in the saliva of some tick species (25,26). Several recent studies have shown a strong association between AGS and tick bites (19,28). This phenomenon has been observed in diverse geographical locations, indicating its ubiquity. Additionally, it has been noted that patients who actively avoid recurrent tick exposures often experience a decline in blood levels of α-Gal IgE. However, the pace and extent of this decrease exhibit variability among individual patients, highlighting the intricate and potentially distinctive nature of the relationship between tick bites and the immunological response associated with AGS (19). The amount of meat consumed and the presence of cofactors (alcohol, activity, use of spices, menstrual cycles) affect the delay before the reaction and the subsequent clinical signs. Still, there may not be a correlation between the severity of the response and the IgE titre specific to α-Gal (29). Specific to AGS, recent tick bites sensitise patients to previously tolerated exposures and even lower the reactivity threshold (30).

Allergen avoidance is one of the main steps in the management of AGS (31). Although AGS is similar to other food allergies, mammalian-derived products are more difficult to avoid due to inadequate labelling and common ingredients such as "natural" sweeteners in many foods. For <10% of patients, the allergen avoidance diet also includes the elimination of gelatine as well as dairy products and derivatives (32). Furthermore, numerous pharmaceuticals are derived from mammalian sources, and specific tissues from mammals are incorporated into medical devices. Items like heart valves, plasma expanders containing gelatin, and pancreatic enzymes are potential sources of exposure to α-Gal (33,34). Due to the ubiquity of mammalian-derived products in food and healthcare, avoiding allergens can present particular challenges for patients with AGS (32).

Alpha-Gal Epitope and Generation of Human Anti-α-Gal Response

The *α-1.3-galactosyltransferase* gene (*α1.3 GT* or *GGTA1*), which has distinctive evolutionary features, has played a crucial role in the evolutionary process of mammalian species. This gene arose early in mammalian evolution and is absent from other vertebrate taxa. Its activity can be observed in various mammalian lineages, including marsupials, non-primate placental mammals, prosimians, and new world monkeys. The *α-1.3-GT* gene encodes the α-1.3-GT enzyme, synthesising a carbohydrate antigen recognised as the "α-Gal epitope". The unique distribution and functionality of the *α-1.3 GT* gene across various mammalian taxa underscore its evolutionary significance and potential implications for understanding immunological responses to the α-Gal epitope in the context of AGS. The α-Gal epitope is abundant in glycolipids and glycoproteins in cell membranes (35). The gene for the enzyme α-1.3-galactosyltransferase, which is necessary for α-Gal synthesis, was inactivated due to a frameshift mutation in the ancestors of old world monkeys (Cercopithecids) and great apes. Hence, α-Gal expression is lacking in humans and old world primates, rendering this molecular construct highly immunogenic in these species. As a result of this gene inactivation, these species lack α-Gal epitopes and naturally produce an antibody known as "anti-α-Gal antibody", which binds specifically to α-Gal epitopes and is most prevalent in humans. It is estimated that approximately 1% of circulating antibodies in healthy individuals are against α-Gal. Approximately 1% of healthy individuals' circulating antibodies are considered anti-α-Gal. When these antibodies interact with the α-Gal epitope found in mammalian organs (e.g., porcine organs), they can activate the complement system, which could result in hyperacute reactions during the transplantation (35).

Studies examining anti-α-Gal antibody classes have revealed several immunoglobulin types in human serum, including IgG, IgM, and IgA. Of note, the IgA isotype is the predominant class in human secretions, including saliva, tears, respiratory and intestinal secretions, colostrum, milk, bile, and vaginal fluid. The predominance of anti-α-Gal IgA antibodies in these secretions highlights their importance as a major component of total secretory immunoglobulins (36).

The structural similarity between the chemical composition of the α-Gal antigenic determinant and the blood group B antigen is striking. Both antigens share the configuration of two terminal galactoses connected by an α-1.3 bond. The hallmark of the blood group B antigen is the presence of a fucose molecule linked to one of the terminal galactoses via an α-1.2-glycosidic bond. This chemical parallelism underscores potential immunological cross-reactivity and further investigates the intricate relationship between anti-α-Gal antibodies and blood group B antigens, contributing to our understanding of immune responses and possible implications in health and disease (37). Galili et al. (37) findings, demonstrating the capacity of specific anti-α-Gal IgG antibodies to recognise blood group B antigens, underscore the intricate interplay between anti-α-Gal immune responses and blood group specificity. McMorrow et al. (38) research revealed a noteworthy correlation wherein individuals expressing the blood group B antigen (encompassing blood groups B and AB) exhibited reduced levels of α-Gal IgG antibody reactivity compared to those not expressing the B antigen (including blood groups O and A) (37-39). This correlation adds a layer of complexity to the understanding of immune responses to α-Gal, suggesting potential interactions with blood group determinants that warrant further exploration and elucidation. Beyond the association with B antigen, the antibody response to α-Gal exhibits significant interindividual variability and contributes to the complexity of the immune response (37-39).

Reports indicate a discernible pattern showing a strong correlation between the IgE and IgG antibody responses to α-Gal. This finding underscores the complex and interconnected relationship between various classes of immunoglobulins in the context of α-Gal immunity. Furthermore, it is worth noting that individuals with α-Gal allergy and IgE antibodies against α-Gal demonstrate significantly higher levels of anti-α-Gal IgG1 antibodies compared to healthy individuals (40,41). IgE antibodies to α-Gal are associated with allergic reactions to mammalian meat, mammalian-derived products, and α-Gal-containing drugs. However, generating an antibody response against α-Gal may benefit the organisms that produce this response. Anti-α-Gal IgM and IgG antibodies have been correlated with diminished susceptibility to *Plasmodium*

infection, the etiological agent of malaria. In areas where malaria is endemic, IgM antibody responses to α-Gal have been shown to prevent malaria infection caused by *P. falciparum* (42,43). A study demonstrated an inverse association between high titers of anti-α-Gal IgM antibodies and malaria parasite transmission (43,44). In neonates, anti-α-Gal IgG antibodies exhibit low levels for the first six months of life, followed by a gradual rise over 2-4 years until reaching adult equivalence (44). Therefore, it has been suggested that the higher risk of malaria in young children than in adults is because their immune systems have not yet produced enough natural antibodies that recognise the α-Gal carbohydrate structure. In contrast, those with high levels of these antibodies have been found to have a lower risk of contracting malaria (45). Anti-α-Gal antibodies target *Plasmodium* sporozoites and promote the death of sporozoites on the skin by blocking the sporozoites' ability to migrate from the skin to the liver. However, if erythrocytes enter the bloodstream after the parasite's mosquito bite, these antibodies do not alleviate the severity of the disease (46).

Numerous research papers have addressed the practicalities of developing anti-α-Gal antibodies in humans, highlighting their potential to induce immunogenic responses against parasites with α-Gal epitopes, such as *Trypanosoma* and *Leishmania* species (47,48). In Chagas (48) and leishmaniasis (49), anti-α-Gal antibodies protect against parasite infections. In a study in which anti-α-Gal antibodies were raised in a mouse model in which the *α-1.3 GT* gene was silenced (GGTA1- KO or α -1.3 GTKO), it was observed that the severity of *Leishmania* infection decreased (49,50). The presence of the α-Gal epitope on *Leishmania* parasites suggests it could be a vaccine candidate for blocking human cutaneous and visceral leishmaniasis (50). In addition, α-Gal antibodies have also been reported to provide protection against malaria infection, promote the healing of burn wounds and tissue repair, increase the immunogenicity of HIV and cancer vaccinations, and exhibit lytic activity against *T. cruzi* parasites (50).

Alpha-Gal expression extends beyond ticks and mammalian tissues to include various bacteria such as *Escherichia*, *Klebsiella* and *Salmonella*. Many bacteria are integral to the human intestinal microbiome. This broad distribution suggests that producing anti-α-Gal antibodies could potentially serve as a mechanism to resist microbial proliferation or mitigate the adverse effects of pathogen colonisation within the human body. The interplay between α-Gal and the gut microbiome raises intriguing questions about the immunomodulatory functions of anti-α-Gal antibodies and their role in shaping host-microbe interactions in the intricate ecosystem of the human body. Further research is essential to elucidate the complexities of these relationships and their implications for human health and immune homeostasis (51,52). Glycans play an essential role in the interaction between hosts and pathogens (53,54). The view that bacteria in the gut microbiome act as a stimulus for the continuous production of anti-α-Gal antibodies is supported by the fact that some *E. coli* and *Klebsiella* strains have been obtained from human faecal samples (51). The possible protective function of anti-α-Gal antibodies might have a broader scope, containing not only against vector-borne pathogens but also infections caused by non-vector-borne pathogens such as *Mycobacterium* spp., which are accountable for different types of tuberculosis and mycobacteriosis. In fact, anti-α-Gal antibodies may reduce mycobacteria's ability to bind to galactose-containing antigens, thus preventing their entry into host cells (51).

Additionally, they may also be effective against mycobacterium-induced inflammation. Notably, all pathogens associated with these diseases exhibit the α-Gal epitope on their surfaces (55). This broader spectrum of pathogenic targets suggests that the immune response elicited by anti-α-Gal antibodies could play a role in conferring resistance or mitigating the severity of infections caused by diverse pathogens, shedding light on the intricate interactions between α-Gal epitopes and the immune system's defence against a range of infectious agents. Studies conducted on this subject matter have indicated that the presence of anti-α-Gal immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies in the human body can effectively protect against a wide range of pathogens that possess α-Gal antigens on their outer surfaces (50,56). An experimental study on α-Gal knockout mice effectively validated the emergence of IgM antibodies targeting *E. coli* O86:B7, an important bacterium in the human intestinal tract exhibiting α-Gal expression. Significantly, these antibodies exhibited a noteworthy defensive effect in the mice, protecting them against malaria transmission (43)

The ability of anti-α-Gal IgA antibodies derived from human colostrum to effectively hinder the attachment of *Neisseria meningitidis* to human buccal cells has been observed, as these antibodies have displayed a remarkable propensity to bind to a diverse range of Gram-negative commensal bacteria (57). These findings propose a potential protective role of secreted anti-α-Gal IgA antibodies on mucosal surfaces, suggesting a broader impact beyond their role in allergic responses. Studies conducted on Türkiye's have demonstrated that the presence of gut microbiota in bacteria expressing high levels of α-Gal can effectively shield against clinical aspergillosis and impede the formation of lung granulomas. Interestingly, the oral administration of *E. coli* O86:B7, can significantly diminish the incidence of granulomas in the lungs. This protective mechanism serves as a safeguard for Türkiye's, effectively preventing the onset of acute aspergillosis. These multifaceted interactions underscore the potential immunomodulatory functions of α-Gal epitopes in diverse biological contexts (46).

Allergy Understanding Differentiated by AGS

Alpha-Gal syndrome, recognised as a novel food allergy syndrome, is distinguished by intense allergic responses after ingesting certain red meat types, namely beef, lamb, or pork. In contrast to the typical pattern in which allergic reactions to food are primarily directed against protein epitopes and occur immediately after ingesting the allergens, allergic reactions to red meat are specifically directed against the carbohydrate epitope α-Gal. Noteworthy is the distinctive temporal aspect of these reactions, with manifestations occurring several hours after the allergen intake. This unusual feature sets AGS apart from conventional food allergies and underscores the need for comprehensive understanding and tailored management strategies (58). Unlike protein antigens, α-Gal stands out as one of the two carbohydrates implicated in life-threatening allergic reactions, exhibiting a remarkable resistance to denaturation even at elevated temperatures (58,59). Recent studies have drawn more attention to proteins glycosylated by α-Gal and thus become responsible for red meat allergic reactions. Researchers have identified transmembrane proteins in pork, which they have

named AP-N and ACE-1. These proteins are the major IgE-binding molecules in pig kidneys. AP-N and ACE-1 proteins were involved in the primary mechanism of red meat allergy. The symptoms have been observed to cause a shorter delay (<2 hours) and more consistent reactions, especially after the consumption of pork kidneys, where these proteins are abundant (13,58).

Since the elucidation of α-Gal in 2007, numerous investigations have been undertaken to elucidate this emerging food allergy (14,60,61). Typically, food allergies are categorised into two main types: IgE-mediated and cell-mediated; the latter is also called non-IgE-mediated. IgE-mediated allergies manifest with rapid onset of clinical symptoms occurring within 30 minutes following exposure to the antigen (62,63). In the case of α-Gal syndrome, reactions tend to be severe, occasionally resulting in fatality. Moreover, the onset of clinical symptoms associated with AGS may vary, ranging from 2 to 10 hours post-exposure, depending on factors such as the antigen's route, source, and nature (17,32,64).

Delayed responses following eating red meat have been seen in individuals with α-Gal syndrome, marking a distinct clinical characteristic. It is unclear exactly how people with this disease experience a delayed sensitivity to red meat. Still, several processes are considered involved, including meat's digestion, absorption, transportation, and subsequent presentation to the host immune system. Studies also describe the effect of age and atopy on AGS. In German, Italian and Spanish patients, investigations reported no correlation between age and sensitisation to α-Gal (64,65).

A cohort of researchers presented findings indicating that the elderly population was more likely to acquire α-Gal sensitisation. These individuals were documented to exhibit a diverse assortment of clinical manifestations, encompassing urticaria, angioedema, pruritus, and systemic anaphylaxis. Before the onset of this syndrome, specific individuals reported experiencing additional symptoms such as nausea, indigestion, diarrhoea and abdominal discomfort (66,67). However, none of the above symptoms have been reported to occur in some patients after exposure to α-Gal, emphasising the unusual nature of AGS. Differences in the host's lipid or fatty acid metabolism, one of the most important of these extraordinary circumstances, may delay the detection of α-Gal in the bloodstream and the onset of AGS symptoms (22,68).

Investigating the influence of allergen dose on AGS patients, a study observed a correlation between meat source and the incidence of delayed anaphylactic reactions to α-Gal (69,70). Beef consumption elicited the highest reaction rate (53%), followed by pork (47%). Lamb and venison demonstrated a significantly lower prevalence of reactions (9.1% and 7.3%, respectively). Notably, some patients exhibited no response to the tested meats but experienced anaphylaxis after consuming offal containing indeterminate amounts of α-Gal (71). Exogenous and endogenous factors influence the digestive process quantitatively and qualitatively. Physical exercise, alcohol consumption, non-steroidal anti-inflammatory drugs, infections, and menstruation can affect the intestinal absorption of food allergens. When allergen concentrations exceed a critical threshold, an immune response is triggered, manifesting as an allergic reaction (70,72).

Eating meat and organs from a much more comprehensive range of mammals in Europe and Türkiye is normal. This includes cloven hoof and soliped animals' liver, lung, heart, tripe (intestine) or kidney. Clinical symptoms within two hours of ingesting mammalian viscera are typically more severe and progress rapidly (15,69,73). Studies have revealed that pig kidney harbours significantly higher amounts of α-Gal epitopes than muscle meat. This observation suggests a potential link between the severity and temporal heterogeneity of anaphylaxis in AGS patients and the amount of bioavailable α-Gal in ingested meat sources (69,74).

Epidemiology of Alpha-Gal

All continents except Antarctica have reported cases of AGS following tick bites. Studies have found that the highest incidence rates are in the United States of America, Canada, and Australia (75,76). The prevalence of α-Gal sensitisation exhibits variability contingent upon geographic regions, the demographic composition under examination, and the designated threshold for defining a positive α-Gal IgE level (22).

Since 2007, researchers, including Commins and Platts-Mills, have identified the epitope in red meat that triggers the specific IgE antibody (20). They have also gathered evidence supporting van Nunen's observation that tick bites can lead to mammalian meat allergy (17). The global identification of AGS has resulted in establishing a connection between AGS and tick bites, offering valuable insight into the mechanisms through which various tick species can trigger IgE sensitisation in humans (Table 1). In 2007, a significant milestone in medical research was achieved with the emergence of the inaugural report, which shed light upon the remarkable ability of ticks to instigate the development of a perplexing condition known as red meat allergy. During this time, van Nunen et al. (77), a distinguished expert in his field, conducted an extensive investigation, meticulously examining the reactions of a considerable cohort of 25 patients after they consumed red meat. Astonishingly, the results of this groundbreaking study revealed that a staggering 92% of the participants, a total of 23 individuals, exhibited unmistakable signs of allergic responses. These cases occurred in the southern parts of Australia and the Sydney coast, endemic areas inhabited by the *I. holocyclus* tick. Thus, the first hypothesis was confirmed and paved the way for further research in this fascinating field (28,78).

In 2008, instances of hypersensitivity reactions to a pharmaceutical formulation containing the monoclonal antibody cetuximab, which is employed in cancer treatment, were identified in specific regions within the borders of the USA (79,80). It was determined that individuals who experienced hypersensitivity reactions to this drug possessed IgE antibodies specifically targeting cetuximab within their serum, implying that these antibodies play a potential role in the progression of anaphylaxis (81). Subsequent investigations unveiled a direct correlation between tick bites and the emergence of IgE antibodies directed against red meat. It has also been reported that the incidence rate of AGS has increased in regions of the United States where the *A. americanum* tick has a significant presence. In addition, climatic factors contribute to the possibility of ticks being seen in different regions. Consequently, it is thought that the incidence of AGS will continue to increase (11,17,18,42). The preliminary records of the AGS in the United States in 2009 accounted for a mere 24 officially reported cases. However, a subsequent study has since revealed a significant escalation in the prevalence, updating the documented instances to 34,000 (82). Again, in the United States, 295,400 people were tested as part of a comprehensive study covering the years 2017-2022. As a result of this rigorous research, 90,018 people, approximately 30.5 percent of the study sample, tested positive. The study also documented a significant

Table 1. Tick species associated with Alpha-Gal sensitisation (71)

Scientific name	Commonly used name	Geographical range
Amblyomma americanum	Lone Star Tick	North America (Southeastern USA, Canada, Mexico)
Amblyomma cajennense	Cayenne Ticks	North and Central America
Amblyomma hebraeum?	South African Bont Tick	South Africa
Amblyomma sculptum	N/A	South America
Amblyomma testudinarium	N/A	South Asia (India, Sri Lanka) and East Asia
Amblyomma variegatum?	Tropical Bont Kenes,	Southeast Asia, Africa
Haemaphysalis longicornis	Asian Longhorned Tick, Bush Tick	Japan
Ixodes australiensis	N/A	Australia
Ixodes holocyclus	Paralysis Tick	Australia, South Asia
Ixodes nipponensis?	Cattle Tick	Asia (including Korea and Japan)
Ixodes ricinus	Sheep Tick	North America, Europe and North Asia, Africa
Ixodes scapularis	Deer Tick	Central America, North America
Rhipicephalus spp.	Asian Blue Tick, Australian Cattle Tick	South Asia, South America, North America

A question mark after the name of the tick concerned means that the tick species listed are suggested but not definitively linked to the development of α syndrome.
N/A: There is no commonly used name

increase in the prevalence of positive test results, from just 13,371 cases in 2017 to 18,885 cases in 2021 (83).

Relying on the identification of α-Gal within salivary glands, the *H. longicornis* tick has been hypothesised as a potential causative agent for AGS. Reports of AGS cases in Japan further corroborate the association with bites from the *H. longicornis* tick. At the termination of the investigation, it was documented that sure tick bites in Japan resulted in the production of IgE antibodies against α-Gal, which is present in the salivary glands of the *H. longicornis* tick (21). Furthermore, it was found that the salivary gland proteins of the *H. longicornis* tick were detected in the sera of most patients who exhibited symptoms of red meat allergy (21,82). Similarly, Hamsten et al. (84) conducted a study which uncovered traces of α-Gal in the midgut of the *I. ricinus* tick, thereby formulating a hypothesis that this particular carbohydrate may contribute to the development of red meat allergy in Sweden. Subsequently, researchers undertook a comparative analysis of α-Gal epitopes derived from *A. americanum* and *I. ricinus* ticks. These ultimately disclosed specific distinctive characteristics shared by both species, albeit with some variations (84,85). This significant finding implies the possible existence of a correlation between *I. ricinus* ticks and red meat allergy. In addition to the countries above, Spain, Türkiye, Germany, and Switzerland have also reported cases of the AGS (86).

In seroprevalence studies in various South African countries, individuals exhibited IgE antibodies targetting explicitly towards the α-Gal antigen. It is essential to highlight that, despite the existence of these antibodies, no evident allergic responses was documented after ingesting red meat (10). It is pertinent to note that comprehensive information regarding AGS cases in Central America remains unavailable, emphasising the need for further research and surveillance in this region. Several other tick species that fall under the taxonomic classification of the genera *Amblyomma* and *Ixodes*, which have been identified in various South and Central American geographical areas, can feed on human blood (28). Nevertheless, research has demonstrated that the saliva of *A. sculptum* obtained from its natural habitat in Brazil harbours α-Gal containing epitopes, which can stimulate an immune reaction and may play a role in the emergence of red meat allergy in Brazil. In Türkiye, instances of α-gal allergy have been documented in regions where *I. ricinus* species are prevalent and hazelnuts are cultivated (87). In a study conducted in 2021, IgE ratios were examined in the blood of 18 patients and anti-α-Gal specific antibody ratios were found to be high in 14 of them. In addition, it was reported that 16.7% of the patients with positive results had similar allergy symptoms in their family members after red meat consumption (88).

How Do Tick Bites Induce An IgE Response?

It is of utmost significance to make a discerning observation that the mechanisms behind the manifestation of an IgE response as a result of tick bites are subject to no less than three distinct theories: Firstly, the induction of said response may be attributed to the ordinary components of saliva that are inherent to ticks. Secondly, mammalian-derived glycoproteins or glycolipids in a tick acquired during a previous blood meal may be essential in triggering the α-Gal response. Lastly, it is plausible that the initiation of the reaction may be attributed to the presence of another organism within the tick (42,89).

Recent studies have provided robust evidence suggesting the possibility of an anti-α-Gal IgE response being primarily linked to ticks. In their enlightening research, Hamsten et al. (84) successfully conducted immunolocalisation experiments, enabling them to observe the α-Gal epitope within the gastrointestinal tract of the *I. ricinus* ticks. Building upon this groundbreaking discovery, Araujo et al. (90) further strengthened the argument by employing ELISA and immunoblotting techniques to identify this epitope's presence in *Amblyomma sculptum* ticks' saliva. The researchers additionally made a significant observation, noting that the α-Gal epitope derived from tick saliva had the uncanny ability to elicit an immune response, thereby stimulating the production of anti-α-Gal IgE antibodies in α-galactosyltransferase knockout mice following the administration of tick saliva via both injections and bites. To delve deeper into the molecular intricacies underpinning the endogenous synthesis of α-Gal in ticks, the researchers successfully identified three α-galactosyltransferase

genes within the tick species *I. scapularis* genome. Each noteworthy finding collectively provides substantial evidence to support the notion that tick-borne α-Gal is a potent trigger for allergy development, thus further solidifying claims (91).

Here add a topic sentence. The tick-borne pathogen *A. phagocytophilum* has been found to induce an increase in α-Gal levels within the cells of infected ticks, as reported in various studies. Furthermore, certain bacteria belonging to the *Enterobacteriaceae*, *Rizobiaceae*, and *Caulobacteriaceae* families possess the α-1.3-GT enzyme (92,93). Interestingly, similar bacteria from these families and groups have also been identified within the tick salivary microbiome. Thus, exploring the potential impact of bacterial presence within ticks and its association with α-Gal would be highly intriguing (94).

Host and Tick Factors in the Development of AGS

Information regarding the host factors contributing to AGS development is limited in scope. Although there have been studies documenting the presence of high levels of anti-α-Gal IgE antibodies, it has been observed that some individuals fail to manifest AGS symptoms (95,96). Based on the available body of evidence, two primary categories of factors have been implicated in accounting for this variability within the host population: a) genetic factors associated with the host, such as blood type and atopy, and b) associated factors encompassing the host's microbiome, dietary patterns, and medication usage. These multifactorial elements could contribute to the observed variation in AGS manifestation. Additionally, individuals who exhibit hypersensitivity to specific chemotherapeutic agents like cetuximab and drugs containing gelatin, as well as those with a history of idiopathic anaphylaxis and systemic mastocytosis, have been identified as being more prone to developing mammalian meat allergy after a tick bite (58,76). In addition, individuals who have previously undergone procedures involving organ and tissue transplantation, such as bovine or porcine bioprosthetic heart valves, may also be at increased risk of developing AGS (97). Apart from the factors mentioned, individuals in certain occupational groups, such as forestry workers, rural workers and individuals whose working life is in open areas, were associated with a high rate of α-Gal IgE sensitisation (98).

A comprehensive investigation in Spain unveiled that the titres of α-Gal IgE among individuals engaged in forestry-related activities and those employed in the forestry sector were notably greater when compared to the general population serving as the control group. It has been established that individuals with occupational exposure to outdoor environments or those residing in rural regions face an elevated vulnerability towards acquiring sensitisation to α-Gal, primarily due to the heightened probability of being subjected to tick bites originating from ticks closely associated with their habitats (98,99).

Several investigations have documented variations in the immune response against α-Gal among individuals with different blood types. For instance, a study conducted in Sweden revealed that individuals with B-negative blood type exhibited a higher prevalence of α-Gal allergy than those with other blood types (84). Interestingly, B-positive individuals demonstrated the presence of a-Gal-specific antibodies, whereas B-negative individuals show cased antibodies that exhibited cross-reactivity with the B antigen. Some scientific studies have indicated that genetic predisposition or atopy may play an essential role in the development of food allergies (17). Individuals with atopy typically demonstrate a pronounced Type I hypersensitivity in their immune responses, characterised by excessive production of IgE in response to common allergens such as mites and food (100). Several studies have indicated a potential connection between atopy and the presence of anti-α-Gal IgE antibodies (68,79). The levels of anti-α-Gal IgE are elevated in individuals with increased total IgE, suggesting that atopy may be a significant predisposing factor in AGS development (22). However, another study found no correlation between AGS and previous atopic tendencies (101). In addition, the presence of a prior occurrence of atopic disease is inadequate to establish AGS (102). Patients diagnosed with AGS may be evaluated to determine their likelihood of developing additional allergic conditions, such as conventional food protein allergies (89).

By utilising a wide range of research studies conducted within the discipline, one can identify numerous intricate factors that are inherently connected with ticks and have the potential to impact the development of AGS. These factors can be neatly classified into two distinct groups, namely, intrinsic factors and extrinsic factors. Intrinsic factors, which are fundamental components existing inside ticks, involve the intricate interaction between the tick microbiome, denoting the varied population of microorganisms residing in the tick, and the tick glycosylation mechanism, relating to the mechanism through which glycosylation, or the attachment of sugar molecules, that takes place within the tick's organism. The tick microbiome plays a crucial role in various physiological processes within the tick, influencing its overall physiology and ability to transmit pathogens. In contrast, the tick glycosylation mechanism modifies proteins and other molecules essential for tick survival and reproduction. The significance of tick intrinsic factors holds paramount importance in understanding AGS development. Current research suggests that extrinsic and intrinsic factors contribute to the distinct N-glycan patterns observed in *Ixodes scapularis* and *Amblyomma americanum* ticks (91,103). Intrinsic factors within the tick are thought to be responsible for synthesising or recycling α-Gal, potentially sensitising the host to this antigen during blood feeding (104).

The feeding process begins with the tick penetrating the host's skin using its barbed mouthparts, followed by attachment and continuous secretion of saliva rich in antigens (105). Blood acquisition by the tick's mouthparts disrupts the integrity of the skin barrier, causing trauma and potentially facilitating the introduction of tick-borne microbes. The composition of the tick microbiota is believed to play a critical role in the context of AGS (106). The microbiota within ticks plays a crucial role in the context of AGS. Microbiota-derived galactose is an essential energy molecule and a pivotal component for synthesising glycosylated exopolysaccharides or lipopolysaccharides (LPS), which may act as α-gal antigens. These findings underscore the significance of investigating the involvement of tick microbiota in AGS, as they may play a role in modulating ticks' metabolic activities and glycosylation mechanisms (104).

Human Immune System and AGS

Ticks pose a growing threat to human and animal health globally with the many organisms they carry. Notably, some animal species exhibit acquired tick resistance (ATR) following exposure to tick infestations. This resistance has been associated with a tick-specific IgE response. For instance, ATR is related

to allergic density, which impedes tick feeding and potentially confers resistance to tick-borne tularemia. Moreover, it is worth noting that human tick infestations have been closely associated with AGS, characterised by an IgE-mediated allergic reaction to the α-Gal carbohydrate. This particular glycan can be found in tick salivary proteins and on the surface of tick-borne pathogens responsible for causing Lyme disease and granulocytic anaplasmosis. It is essential to highlight that although most individuals sensitised to α-Gal develop specific IgE antibodies, only a subset of these individuals progress to AGS, indicating the complexity and variability of the immune response to this particular allergen (107).

The tick-host interface is a complex battlefield. A host-directed hemostatic response is initiated when the tick damages the host's skin with its spiny hypostome, disrupting the epithelial barrier (108) Haemostasis is the host's natural protective mechanism triggered in response to physical harm. It encompasses blood coagulation, platelet aggregation, and vasoconstriction (105,109). During the initial stage of tick attachment to the skin, the humoral and cellular components of the host's natural immune system react by activating the complement system, inducing inflammation, and facilitating the infiltration of leukocytes into the area of the tick bite (110). Following a tick bite, keratinocytes, endothelial cells and leucocytes are triggered by tick saliva and hypostome exposure (111). These cells unleash the secretion of antimicrobial peptides, pro-inflammatory chemokines, and cytokines, such as interleukin-8 (IL-8), interleukin-1b (IL-1b), and tumour necrosis factor (TNF), to facilitate the recruitment of an assortment of inflammatory cells, including neutrophils. Consequently, the adaptive immune system undergoes a division, with activated T and B-cells (in the event of secondary invasion) intensifying the inflammatory response via cytokine release and generating targeted antibodies against the tick. This, in turn, induces the further activation of the complement system and sensitises mast and basophil cells (109,111).

Choudhary and colleagues conducted research utilising the α-Gal knockout mouse model to investigate how tick bites elicit an immune response targeting anti-α-Gal IgE antibodies (112). Their analysis of these genetically modified mice showed that exposure to tick saliva led to the generation of IgE antibodies directed explicitly against α-Gal, consequently leading to hypersensitivity reactions upon consumption of mammalian meat (56,110,112). These studies reveal the critical role of tick saliva in developing α-Gal allergy. Tick saliva encompasses a multifaceted array of compounds, a considerable proportion possessing immunomodulatory characteristics capable of dampening host immune responses. This initiates wound-healing mechanisms in the host (109). The components present in insect saliva have been shown to stimulate the activation of T-cells towards the Th2 phenotype, which causes reactions (94). While some studies propose that tick saliva possesses immunomodulatory properties that promote Th2 polarisation, most individuals exposed to bites from blood-feeding insects experience only transient, localised IgE-mediated hypersensitivity reactions (95).

In order to ensure a constant blood flow without causing an immune reaction in the host, the tick secretes a complex combination of substances that relieve pain and itching in the host during the feeding process. This mixture includes agents that inhibit vasodilation, platelet aggregation and molecules that inhibit the cascade process of blood clotting (113,114). Additionally, ticks secrete diverse salivary compounds that reduce pro-inflammatory cytokine production, including TNF-α, interleukin-12, and IL-1β. Concomitant with activating immune cells, the tick bite also induces the synthesis of anti-inflammatory molecules, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). This shift towards a Th2-dominant immune response is believed to be critical for developing AGS. Disruption of the skin epithelium by the tick bite triggers wound healing processes, where M2 macrophages play a crucial role. These macrophages suppress inflammation and potentially attenuate the excessive Th1 cell response by upregulating cytokines that reduce inflammation and oedema, such as IL-10 and TGF-β (111). Furthermore, various constituents within tick saliva, including prostaglandins, sphingomyelinase, and cysteine protease inhibitors, have been documented as crucial elements in modulating the innate immune response by promoting the induction of a TH2 profile (115-118).

Tick saliva is enriched with prostaglandin E2 (PGE2), and this molecule contributes to various mechanisms of AGS development. Prostaglandin E2 promotes vasodilatation, facilitates blood flow during feeding, and reduces inflammation at the bite site (119). However, this anti-inflammatory effect could help healing by hindering fibroblast migration. Additionally, PGE2 stimulates the recruitment and activation of macrophages, which can further amplify PGE2 production, creating a positive feedback loop. Studies show that this PGE2-mediated modulation of the immune response shifts it towards a Th2 phenotype characterised by B-cell proliferation and increased antibody production (120).

Cabezas-Cruz et al. (56) documented that tick saliva elicits reactions resembling those of a venom antigen, engaging with the immune system and instigating immune sensitisation. The first encounter between the salivary antigen secreted by the tick and host immune cells occurs in the skin epithelium during a tick bite. Following tick bite exposure, antigen-presenting cells (APCs) within the skin, such as Langerhans cells (LCs) and dendritic cells (DCs), play a critical role in initiating the immune response to α-Gal. These APCs recognise, capture, and process α-Gal antigens from tick saliva. Subsequently, they migrate to the lymph nodes, where they participate in the sensitisation of B-cells. These sensitised B-cells then present processed α-Gal antigens to T-cells, releasing pro-inflammatory cytokines and eventually activating mast cells and basophils, critical effector cells in allergic reactions (Figure 2) (112,121).

Various human cells are involved during the development of AGS and the allergic response. In the early sensitisation phase, skin-resident antigen-presenting cells are of vital importance. DCs connect the innate and adaptive immune systems. The cells possess unique receptors for the innate immune response and act as cells that present antigens, facilitating the initiation of the adaptive immune response. In the skin and mucosal tissues, immature DCs detect antigens (122). Dendritic cells undergo maturation and subsequently migrate to the draining regional lymph nodes by simultaneously activating receptors that recognise patterns. In the given context, dendritic cells play a critical role in presenting processed antigens to T-cells, which occurs within the groove of major histocompatibility complex (MHC) I or MHC II molecules. This process initiates a subsequent adaptive immune response (122). The primary function of these cells revolves around the processing of antigens bound to α-Gal and introduced into the body through tick injections (123).

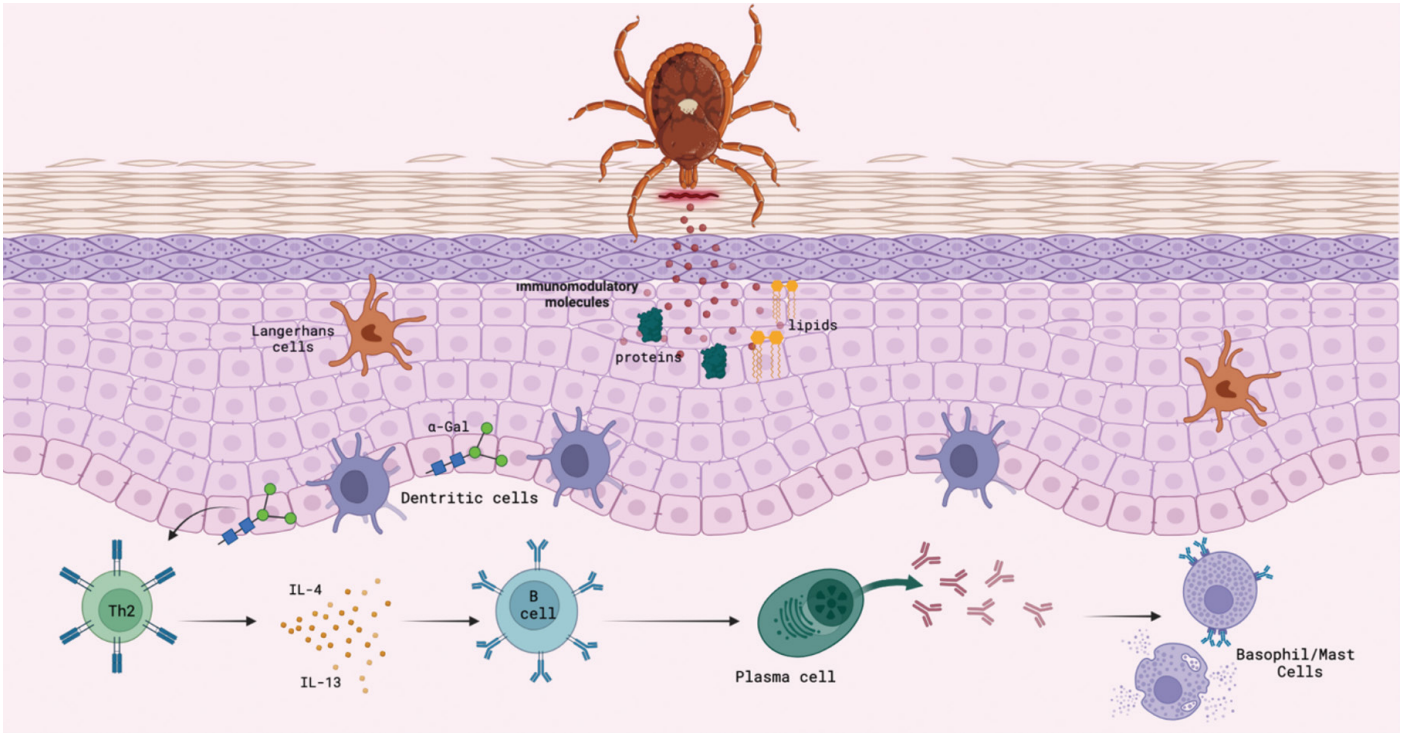

Figure 2. Sensitisation phase of AGS. During feeding, tick mouthparts cause physical trauma to the skin epithelial barrier and introduce α-Gal, potentially pathogenic bacteria and adjuvants in tick saliva. Antigen-presenting cells (APCs), specifically Langerhans cells located in the epidermis and dermal dendritic cells residing in the dermis, exhibit reactivity towards antigens secreted by ticks. These antigens encompass glycoproteins, glycolipids, and tick cement containing α-Gal moieties. In a pro-inflammatory Th2 microenvironment, skin-resident APCs internalise α-Gal and present it to naïve CD4+ T-cells, prompting their differentiation into Th2. The Th2 subset, specific to α-Gal, induces B-cell activation, facilitating their class switch to produce anti-α-Gal-specific immunoglobulin E (IgE). This immunoglobulin variant contributes to the generation of plasma cells. After synthesis, anti-α-Gal IgE binds to high-affinity IgE receptors (FcεRI), expressed on mast cells and basophils

AGS: Alpha-Gal syndrome

The saliva of the *I. ricinus* tick, which has been linked to the development of α-Gal syndrome, can impede the maturation and movement of specialised APCs, as indicated by recent research (124). These dendritic cells play a crucial role in initiating allergic reactions to other protein allergens, as they are responsible for presenting the allergens to T-cells and creating an environment that promotes the activation of pro-allergic Th2 cells. Therefore, *I. ricinus* tick saliva may disrupt this process and hinder the progression of allergic reactions (124). Dendritic cells exposed to the saliva of the *I. ricinus* tick species effectively inhibit their ability to elicit pro-inflammatory Th1 or Th17 responses, instead favouring the promotion of Th2 pro-allergic responses. Additionally, it is noteworthy that the presence of α-Gal on the glycoprotein may enhance the efficiency of antigen internalisation by dendritic cells (125).

Basophils, categorised as granulocytes circulating in the bloodstream, are similar to mast cells expressing the IgE receptor FceRI. When activated, these cells degranulate, leading to the release of histamine and various other mediators. It should be noted that basophils are important in chronic allergic inflammation and contribute to the development of protective immunity against parasites, as proven in the scientific literature (126). Within the specific immune response to tick infestation, it has been conclusively established that basophils mobilise to the tick-feeding site during subsequent infestations. Basophils accumulate in the skin and play an essential role as tick rejection factors in tick infestation. Given these findings, it is hypothesised that basophils may trigger the allergic response following exposure to α-Gal, an allergen of particular interest (127). Basophils secreting interleukin-4 (IL-4) are essential in allergic sensitisation and initiating Th2 immune responses. Moreover, they enable the differentiation of CD4+ T-cells into Th2 cells. This ability of basophils suggests that they could potentially serve as key players in the complex network of events that result in the development of an allergic reaction and subsequent activation of Th2 cells (128).

Given that the α-Gal epitope might also be present in glycolipids, it is conceivable that lipids containing α-Gal could also exist in tick saliva. In such a scenario, natural killer T-cells (iNKT), a subset of T-cells, contribute to the sensitisation process to α-Gal. iNKT cells can recognise lipids and generate IL-4 (129). In one study, patients with α-Gal allergy exhibited a 2.5-fold increase in circulating CD69+ iNKT cells. Consequently, it was observed that circulating iNKT cells displayed heightened cellular proliferation in individuals with α-Gal allergy (130).

AGS Diagnosis and Prevention

The diagnosis of AGS is often distinguished from typical food allergies by the delay in the onset of symptoms after mammalian meat is consumed. Nonetheless, the time at which symptoms

commence heavily relies on the source of the allergen (offals have a greater potency than muscle meat) and numerous modifying factors (e.g., alcohol and exercise) that abbreviate the time preceding reactions. The allergic reactions triggered by tick bites and the distinct manifestation of AGS render the diagnosis intricate and demanding. Consequently, a comprehensive patient history encompassing all clinical facets should be considered before conducting laboratory tests (71,131).

Determining the preliminary diagnosis entails conducting skin prick tests (SPT) and ascertaining the presence of serum-specific IgE antibodies (132). Employing α-Gal containing extracts to expose the patient's skin is a frequently utilised diagnostic method; however, significant variations in the sensitivity of skin tests have been documented. SPTs, particularly those employing commercially available meat extracts, are unreliable, often yielding feeble or false-negative outcomes, thus potentially misleading patients (17). Furthermore, SPT with local meat and meat products frequently gives false negative or only weak skin reactions. The subcutaneous injection of freshly prepared pig or bovine kidney extracts, specifically through intradermal testing, has demonstrated heightened sensitivity compared to consuming cooked or raw muscle meat derived from the same animal species (17,71).

The gold standard for the diagnosis of food allergies is still recognised as food testing. However, the delayed allergic reaction seen in AGS has rendered this test inadvisable. The use of food testing to diagnose AGS carries the risk of causing severe and potentially fatal anaphylactic reactions. Instead, the only recommended strategy to prevent recurrent episodes of allergic reactions in patients with AGS is to avoid foods, supplements and medications containing α-Gal. By strictly adhering to this avoidance strategy, patients can significantly reduce their risk of experiencing allergic reactions associated with AGS (133,134)

CONCLUSION

The hypersensitivity responses mediated by IgE antibodies against the glycan α-Gal, as opposed to specific food proteins, present numerous challenges and are currently reshaping our understanding of the underlying mechanisms that govern the pathogenesis of food allergies. The intricate and particular mechanisms through which tick bites sensitise individuals to α-Gal, ultimately leading to the onset of AGS, remains insufficiently elucidated, thus necessitating further investigation and research. The triggering response that leads to AGS is the IgE antibody response to α-Gal; however, the specific molecules and immune mechanisms that orchestrate this phenomenon have yet to be fully identified. Comprehensive and detailed characterisation of these molecules and mechanisms is crucial. It may improve the accuracy and efficiency of AGS diagnosis and enable the development of preventive and therapeutic strategies to manage and control this disease effectively.

The confirmation of the α-Gal epitope's presence in various species of ticks has provided valuable insights into the molecular nature of these organisms. However, much is still to be discovered about the intricate processes involved in these molecules' synthesis, origin, and transduction at the tick-host interface, which warrants further investigation. Moreover, a significant knowledge gap persists in understanding how the tick microbiome influences AGS development. In order to bridge this gap, it is imperative to conduct a comparative analysis of the microbiomes found in different tick species and explore their underlying genetic mechanisms using genomic and transcriptomic approaches. Extensive research using omics technologies could potentially uncover novel genes that play an essential role in synthesising the α-Gal epitope, thus improving our understanding of AGS and its consequences.

The occurrence of AGS has become increasingly common in various regions across the globe, such as America, Asia, Europe, and Australia, where ticks are abundant. It is worth noting that the spread of ticks in these areas is greatly influenced by climate change. Furthermore, the accelerated expansion of tick populations due to climate change is expected to contribute to a rapid escalation in the prevalence of AGS. Additional research is essential to a comprehensive understanding of the epidemiology, incidence, geographical distribution, and risk factors associated with AGS. These investigations should focus on examining the population and cohorts frequently exposed to tick environments to shed light on various aspects of this syndrome.

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*** Ethics**

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