

Tick Bites and Red Meat Allergy

AUTHORS DETAIL

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INTRODUCTION

Red meat allergy, also known as an alpha-gal syndrome (AGS), is symptomatically associated with the consumption of glycan galactose-alpha-1,3-galactose (alpha-gal) (Chung et al. 2008).

Alpha-gal is a carbohydrate present in mammals except for humans and Old-World monkeys. The gene (GGTA1) responsible for the synthesis of the enzyme (alpha-1,3-galactosyltransferase) that is involved in the glycosylation of alpha-gal is absent in humans and Old-World monkeys. Therefore, immunocompetent persons can show anti-alpha-gal antibodies in a natural way Galili et al. 1987; Singh et al. 2021). Symptoms of red meat or mammalian meat allergy include angioedema, anaphylaxis, and gastrointestinal (GI) symptoms such as abdominal pain, nausea, diarrhea, heartburn, joint pain and pruritus (Iweala et al. 2018; Mabelane et al. 2018; Wilson et al. 2019). These symptoms occur 3-8 hours after the consumption of mammalian meat

(beef, pork, or lamb) or other mammalian-derived products (gelatin, dairy products and pharmaceutical products containing alpha-gal). The delayed onset of the symptoms is due to the time taken for the digestion of lipids and protein containing alpha-gal and entry of alpha-gal into the blood circulation. Due to the delay in symptoms, it is difficult for doctors and clinicians to diagnose it as a food allergy (Flaherty et al. 2017).

Ticks are responsible for different allergic reactions in different countries across the world. The tick *Ambloymma (A.) americanum* is the vector for Rocky Mountain spotted fever and is also responsible for red meat allergy in the United States (Van Nunen et al. 2019). Similarly, red meat allergy is a tick-induced hypersensitivity reaction and is associated with anaphylaxis, angioedema, and urticaria. In this disease, IgE antibodies are produced against alpha-gal and cause hypersensitivity reactions in humans. Red meat allergy is different from other food allergies as IgE-mediated responses are produced against a carbohydrate (alpha-gal). While in other food allergies IgE mediated reactions are produced against proteins or other ingested allergens. Antibodies production against alpha-gal in red meat allergy is associated with tick bites rather than the ingestion of some allergen (Commins et al. 2011).

Association Between Tick Bites and Red Meat Allergy

The increased levels of specific IgE and IgG antibodies against alpha-gal epitope are characteristics of AGS or red meat allergy patients, and most of the individuals with red meat allergy who may have withstood the mammalian meat for several years can develop alpha-gal sensitization after tick bites (Platts-Mills et al. 2015; Kollmann et al. 2017). It is discovered that the different tick species, especially the most abundant *Ixodes (I.) ricinus* species in Europe, contain alpha-gal in their cement and salivary glands (Hamsten et al. 2013). The process of inducing sensitization to this epitope by tick bites and, ultimately, mammalian meat allergy is not fully understood yet. It is evident that only the alpha-gal exposure is not responsible for the IgE response; it may be due to the ticks' salivary proteins containing alpha-gal antigens or may be due to the prostaglandin E2 (PGE2) in the saliva (Carvalho-Costa et al. 2015).

There is an association between tick bites and red meat allergy, and is reported worldwide. Concentrations of alpha-gal IgE in the blood of patients decrease as they avoid the recurrent tick bites, and the level of decrease varies from person to person (Commins et al. 2011).

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In the U.S., it was observed that there were similarities in the geographical distribution of the reported patients of alpha gal syndrome and Rocky Mountain spotted fever (Commins and Platts-Mills 2013; Crispell et al. 2019). The tick *A. americanum* is responsible for the transmission of the causative agents of these diseases (*Rickettsia* and *Ehrlichia*). In this preview, it was hypothesized that the lone star tick (*A. americanum*) is the cause of sensitization to alpha-gal (Commins et al. 2009; Commins et al. 2011). Other reports also give evidence that the high titer alpha-gal IgE is associated with more than two tick bites, and the titers are low in the individuals avoiding tick bites, suggesting the relation of ticks as sensitizing agents (Hashizume et al. 2018). Initially, it was stated that alpha-gal transmitted to human hosts by mature ticks is derived from mammals during blood meal, but latter evidence showed that larval ticks transmitted alpha-gal that was never fed mammalian blood (Stoltz et al. 2019).

Worldwide Distribution of Ticks-induced Mammalian Meat Allergy

Alpha-gal in the meat is responsible for the production of IgE in the human host. Data on the red meat allergy after tick bites have been reported (Van Nunen et al. 2007).

In Europe, the prevalence of IgE production to alpha-gal has been found to be 5.5% in Denmark, 15.7% in Spain, and 24.7% in a rural region of northeast Italy (Joral et al. 2022). More than 5000 cases have been reported in the U.S. The work about this disease started when a cancer patient in the U.S. developed a hypersensitivity reaction to cetuximab (a medicine used in the treatment of cancer). During the clinical processes, there was a low risk of allergy against the drug but in the cases from the specific region of the U.S. developed, severe drug hypersensitivity reactions. Later, researchers found that the patients, who showed allergic reactions, already had IgE antibodies that bound with the alpha-gal present in the murine portion of cetuximab (Chung et al. 2008).

The number of cases increased with hypersensitivity reactions after eating red meat in the U.S. In these cases, many individuals who have been consuming red meat for years never developed symptoms before (Commins et al. 2016). The IgE response developed against the alpha-gal present in red meat. It was noted that both drug-induced and meat-induced allergy individuals belonged to the same area abundant with lone star tick (Steinke et al. 2015).

Fig. 1 shows the occurrence of red meat allergy reported for the first time in different areas of the world.

Many cases were also reported in Australia having a history of tick bites. The first research on tick bites causing red meat allergy in Australia was published in 2007. Starting from those days, this disease is turning into a global issue and is influencing almost all continents. In Australia, two species of ticks *I. holocyclus* and *I. australiensis* responsible for causing red meat allergies (Binder et al. 2021).

Clinical Features of Red Meat Allergy

The disease shows similar kind of symptoms in children and adults. Angioedema, GI symptoms and most severe anaphylaxis causing adverse meat allergies contribute almost 65.6% (Fischer et al. 2016). Nearly 10 % of the cases that are sensitive to red meat also react to the gelatin obtained from mammals. Intravenous or intramuscular administration of gelatin may increase the chances of anaphylaxis and may be the initiation of red meat allergy. Clinical reactions were reported when gelatin was administered orally and through the intravenous route and few cases were reported with positive gelatin tests and negative red meat tests (Mullins et al. 2012). The role of co-factors in red meat allergy is very important. Knowledge about the factors that increase the impact of mammalian meat allergy is important to know for the safety purposes. These factors, individually or with the synergism, increase the severity of alpha-gal sensitivity reactions to red meat (Wölbing et al. 2013). The major contributing factors of the disease include consumption of a high amount of allergen, alcohol intake with food, use of spices (chili & capsicum), physical activity, use of anti-inflammatory non-steroidal agents, to be in the premenstrual period, and cooking impacts (Versluis et al. 2016). Moreover, the level of alpha-gal is different in many products, such as egg and pork kidneys have high levels of alpha-gal and increase the chances of sensitivity. The milk obtained from cows also has alpha-gal, and the sensitivity of alpha-gal has vanished on heating this milk. Hence, pasteurization of this milk makes it tolerable (Commins et al. 2014).

Process of Development of Red Meat Allergy

The development of red meat allergy via tick bites is an example of the initiation of an allergy. It is a phenomenon in which climatic change (High tick population, increased tick bites), inheritance, host immune shifts due to parasites and the presence of a pathogen in ticks (rickettsiosis) are involved (van Nunen and Sheryl A 2018).

As it is evident from the fossils that the process of development of red meat allergy due to tick bites started 28 million years ago. The enzyme responsible for the production of alpha-gal was inactivated in our ancestors at that time, this is why the human body gets alpha-gal as a pathogenic particle, and alpha-gal IgE antibodies are produced, hence giving defense to the pathogenic bacteria, coated viruses and protozoa that contain alpha-gal (Galili 2013).

As per available literature, alpha-gal is an external particle for humans that prepares them after bites from ticks and initiates the pro-allergy Th2 cells cytokines in the humans that starts the preparation of anti-alpha-gal antibodies (Abs) by the IgG and ultimately the IgE Abs from B cells (Ferreira and Silva 1999). Proteins from the ticks are glycosylated, which promotes this process leading to an increase in immunity. So, when IgE class Abs to ticks proteins are

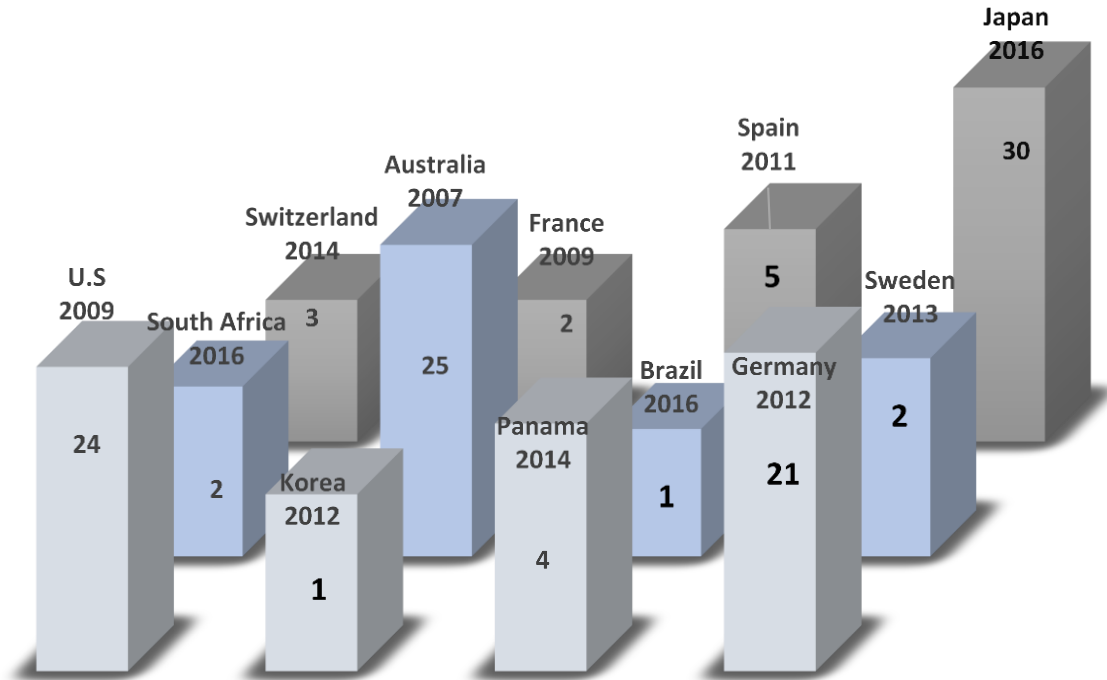


Fig. 1: Graphical representation of number of cases reported first time in different countries (Van Nunen and Sheryl A 2018).

generated at the same time, alpha-gal IgE Abs are also produced. The IgE production mechanism is activated by the tick bites against the alpha-gal, and when this person consumes mammalian meat, the IgE production starts against the alpha-gal present in meat, and hypersensitivity reactions occur, causing red meat allergy (Dorey 1998).

The last important thing in the red meat allergy reactions is the delay in the occurrence of these reactions. This procrastination in the appearance of the symptoms is because of the time required for the transport of alpha-gal from the gastrointestinal tract to the blood circulations. Glycoproteins, as well as glycolipids, also contain alpha-gal. The complete breakdown of lipids takes many hours, and after that, the absorption of chylomicron having alpha-gal starts in the small intestine into the lymphatics and then into the bloodstream stimulating basophil mediators' production in the blood (Commins et al. 2014).

Management of Red Meat Allergy

To date, there is no cure for this disease, but to get rid of this disease, prevention strategies are adopted. Avoidance of mammalian meat, mammal-derived things, and sometimes dairy is advised for the patients (Patel and Iweala 2020). Evidence showed that more tick bites increase the level of IgE in the blood, and the prevention of tick bites reduces the amount of IgE in the patients and also the sensitivity to red meat (Kim et al. 2020). In a study, 12% of patients who avoided tick bites for nearly five years reduced their IgE level

to less than 0.1 IU/mL and included red meat in their meals successfully (Commins et al. 2016).

No study is conducted yet showing the relationship between the use of red meat and dairy products influencing the levels of IgE in red meat allergy patients. Another observation also supports this concept when some patients developed mild or no symptoms and tolerated red meat on an event, severe sensitivity reactions to red meat appeared in the same patients in another event. This difference is not due to the quantity of meat used but due to the level and quality of alpha-gal present in meat or may be due to the inclusion of co-factors and current bites from the ticks (Iweala et al. 2018). Following preventive measure should be taken to reduce the chances of red meat allergy.

Avoiding Meat from Mammals

Firstly, the new cases reported of red meat allergies are strictly instructed to skip mammalian meat such as Lamb, pork, beef, and venison. Organ meat, specifically pork kidney, also causes sensitivity reactions, so it should be excluded from the diet (Fischer et al. 2014). Meat rich in fats is also associated with the severity of reactions and symptoms. Alpha-gal is not decomposed by heating meat, but the fat content is decreased, which minimizes the severity of the reaction (Apostolovic et al. 2014). Other mammalian meats and products should not be consumed. Some cases also develop signs of red meat allergy when air droplets arising from the heating of meat are inhaled, but no document has been published yet.

Avoiding Dairy Products

Products from dairy, such as cheese and milk, are not recommended in red meat allergy patients on a daily basis because nearly 81-90% of cases do not show reactions to these products (Levin et al. 2019). Some experts' opinions and research work suggest the complete avoidance of these products in the cases who are not consuming meat and still, there is no significant decrease in symptoms (Commins 2016).

Non-dairy and Mammalian Derived Products

Non-dairy and mammalian-derived products may also pose a risk of allergy when mammal-derived ingredients are mixed in these foods. A major risk factor is the availability of non-labeled products. In the market, some of these items mentioned that alpha-gal content (cetuximab) is included, while in some, it is missing (glycerine) because of the reason obtained from the mammals. Mammalian-derived bovine serum albumin does not consist of alpha-gal, so being obtained from mammals does not mean that it consists of alpha-gal (Thall and Galili 1990).

The occurrence of hypersensitivity reactions in individuals who have removed all known forms of alpha-gal from their diets is due to the presence of a hidden form of alpha-gal in those foods. Special attention is given to foods that contain high levels of mammalian-derived lipids, particularly when they are associated with exercise, alcohol, sickness, and menses etc (Scott 2020).

Foods high in fat and added fats are also linked with the severity of reactions. Lard is used in food preparations, gravy, and sauce. It is also used as a flavor enhancer. Mammal-derived fat such as suet and tallow are also used in food preparations. Different types of sausages contain casings (a chemical that contains alpha-gal) obtained from the pig gut. Turkey and chicken sausages also resulted in sensitivity reactions in some cases. Carrageenan, as well as gelatin, are commonly used food additives obtained from mammals and contain alpha-gal (Scott 2020). Gelatin is an important content of gelatin desserts and its sensitivity is common in patients, but in many cases, it is tolerated if present in low quantity in daily uses (Caponelto et al. 2013). Carrageenan is obtained from reddish esculent seaweed and is commercially used in food preparation as a thickening and stabilizing agent. The chances of developing symptoms after eating these products are very low (Chauhan and Saxena 2016). The problem is that it is a plant-origin food that is alpha-gal-free foods. So, the cases who are avoiding the diets but still have sensitivity should be analyzed for carrageenan use.

Medical Therapies of Red Meat Allergy

In the drug therapy, long active oral antihistamine (fexofenadine) is preferably used two times a day. Another feasible method that can be used is the application of short-

active oral antihistamines, as many cases have endured the Unisom and SleepMelt tablets (Scott 2020). Those cases who are avoiding specific foods but still showing gastrointestinal tract signs and symptoms are advised to use oral solutions of cromolyn. It is recommended four times a day with a dose range of 100-200 mg (Scott 2020).

Red meat allergy individuals having severe and recurrent sensitivity with asthma can be treated with oral corticosteroids. Omalizumab has been used successfully for the control of continued reactivity in some patients, and those individuals added small amounts of red meat in their meals showing no harm (Scott 2020). In a study, six cases were using Metformin during the preparations of gastric bypass surgery, started consuming dairy products, and then included mammalian meat in their meal (Samavedam et al. 2016). In another research, it is evident that Metformin's impact on the unfolded protein response can change the cytokine environment and potentially reprogram the immune system (Samavedam et al. 2016).

Therapeutic Prevention

Alpha-gal is a component of many drugs and medicines and can be dangerous in some new therapies for the persons who are allergic to alpha-gal (Galili 2013).

- ◆ Because of the alpha-gal present in cetuximab, dangerous reactions appeared by its intake.
- ◆ Vaccines such as measles and mumps as well as zoster contain alpha-gal can cause allergic reaction in the person sensitive to alpha-gal (Stone et al. 2017).
- ◆ Gelatin is also mammalian derived and is component of vaccine, tablet, capsule and implants (Mullins et al. 2012).
- ◆ Antivenom against snakes, scorpions, spiders, jellyfishes etc. also contain alpha-gal and cause sensitivity reactions in the red meat allergy patients when used (Fischer et al. 2017).

Expert's Opinion

Knowledge about red meat allergy to professionals in healthcare is important to diagnose and manage this disease. In the regions abundant in the population of ticks and where bites from the ticks are usual, mammalian meat allergy is in the process of recognition and diagnosis. Alpha-gal IgE tests are suggested in these areas. A magazine having mammalian meat allergy-related information for the patient's families and healthcare providers should be developed. Similar to other food allergies, avoid exposure to allergens and tick bites. Proper labeling of ingredients in the food obtained from mammals, medicines, drugs, and vaccines is recommended for mammalian meat allergy cases. Manufacturing of porcine products with no alpha-gal will give a source of 'sensitivity-free' food and medicines. A detailed understanding needs to be developed of the chances of reactivity for the different products that contain small concentrations of mammal-derived ingredients (Scott 2020).

Conclusion

Red meat allergy is different from other conventional food allergies. Tick bites play a role in triggering this disease, but this association is not fully proven yet. It has been diagnosed across the world but is more prevalent in areas abundant with ticks' population. The role of alpha-gal in the development of mammalian meat allergy after tick bites has strong scientific evidence. The reactions might appear immediately when the medicines (containing alpha-gal) are given via the parenteral route, and there is a delay in the appearance of the symptoms from 3-6 hours if meat from mammals, dairy, and other mammal-derived products are consumed via the oral route. The best management of this syndrome is to avoid further tick bites, mammalian meat, and other mammal-derived products.

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