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Review Paper

Alpha-gal syndrome: allergy to red meat

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ABSTRACT

Meat allergies are increasingly present, both in children and in adults, and are a group of heterogeneous allergic reactions with different syndromes. Alpha-gal syndrome (AGS), also known as α-gal allergy or mammalian meat allergy (MMA) is a type of acquired allergy characterized by a delayed onset of symptoms (3–8 hours) after consumption of mammalian meat. It is a reaction to the carbohydrate, galactose-α-1,3-galactose (α-gal), where the body is overwhelmed with immunoglobulin E (IgE) antibodies when exposed to the carbohydrate. In most cases, it is the result of previous exposure to certain tick bites and was first reported in 2002. Allergy symptoms vary greatly from person to person and include rash, hives, nausea or vomiting, difficulty breathing, drop in blood pressure, dizziness or fainting, diarrhoea, severe stomach pain and possible anaphylaxis.

1. Introduction

Food allergens of animal origin are substances that the bodies of some consumers recognize as foreign and respond to by activating the immune system. The most common allergens from animal-based foods are proteins found in meat, milk, eggs, fish, shellfish, and other seafood. Meat very rarely causes allergic reactions and was first mentioned as a potential allergen about 25 years ago, at a time when increasing attention was being paid to food allergies in general (*Platts-Mills,* 2015).

It was once believed that only children with atopic dermatitis or those already allergic to cow's milk could develop an allergy to mammalian meat (*Werfel et al.,* 1997). There are no definitive estimates of the prevalence of such allergies, but what is notable are regional variations, primarily due to local dietary habits. Today, various IgE-mediated reactions and their cross-sensitizations are recognized to many types of meat species, including beef, pork, lamb, poultry, kangaroo, whale, and crocodile.

In recent years, there has been increasing mention of a new form of delayed anaphylaxis to red meat, triggered by the oligosaccharide Gal-α1,3Gal-β1,4GlcNAcR (α-gal), after which the allergy was named—α-gal syndrome (*Wilson et al.,* 2017). This type of allergy is also referred to as mammalian meat allergy (MMA) or tick bite-induced meat allergy (*Woodfolk et al.,* 2015).

1.1. Cross allergic reactions to red meat

Serum albumins are α-helical proteins with a molecular weight of approximately 70 kDa. They have the ability to pass through the capillary

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endothelium, which means they can also be found in epithelial tissues, animal fur, and bird feathers. Based on this fact, it can be concluded that individuals who are allergic to beef are often also allergic to milk, due to the presence of the serum albumin Bos d 6 (*Martelli et al.,* 2002). A similar example is the "bird-egg syndrome," where primary sensitization occurs through inhalation of bird serum albumin, but symptoms later also appear after consumption of chicken meat (*Szepfalusi et al.,* 1994). On the other hand, cross-reactivity between serum albumins of mammals and birds is rare, as it occurs only between phylogenetically similar species. The "pork-cat syndrome" involves primary sensitization to cat serum albumin (Fel d 2), followed by sensitization to pork serum albumin (Sus s 1). In some cases, due to epitope spreading of IgE, affected individuals can also become sensitized to bovine serum albumin (Bos d 6) (*Posthumus et al.,* 2013). One of the key characteristics of these proteins is that they are sensitive to heat and lyophilization (freeze-drying), so such processing methods can reduce the severity of allergic reactions (*Fiocchi et al.,* 1998).

1.2. Alpha gal (α-gal)

Alpha-gal is a sugar molecule (galactose-α-1,3-galactose) found in the cells of most mammals (except humans and primates). It is present in meat, internal organs, milk, gelatine, and other animal-derived products. It was first mentioned as early as 1925 (*Landsteiner et al.,* 1925) as a molecule structurally similar to the B blood group antigen. It is also notable for being a major target of IgM, IgG, and IgA antibodies in immunocompromised patients. The allergy to α-gal was first formally identified by Thomas Platts-Mills in 2002 in the United States, and later in 2007 by Sheryl van Nunen in Australia (*Velasquez-Manoff,* 2018). When Platts-Mills himself was bitten by a tick and developed an allergic reaction to α-gal, his team concluded that there was a link between tick bites and the development of the allergy (Figure 1).

This is the first food allergy associated with carbohydrates, rather than proteins. A defining characteristic of this type of allergic reaction is that the reaction occurs 3–6 hours after exposure to the allergen (*Commins et al.,* 2014). This delay is due to the time needed for the digestion, processing, and transport of these epitopes to the target tissue. Although most studies have focused on α-gal present in glycoproteins, it is also found in glycolipids. This supports the hypothesis that lean wild game meat is less likely to trigger a reaction in allergic individuals (*Galili et al*., 1987). Bites from some tick species—such as the Lone Star tick (*Amblyomma americanum*) and *Ixodes holocyclus*—are linked to the development of this allergic response. When a tick bites, it injects this carbohydrate into the human body via its saliva. The immune system then releases a surge of IgE antibodies to fight off this foreign sugar. After this sensitization, future consumption of red meat (beef, pork, lamb, etc.) containing the same α-gal can trigger an allergic reaction. Some individuals also develop allergic reactions to gelatine and certain dairy products derived from mammals (*CDC,* 2021). Traces of this carbohydrate can also be found in certain medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), other analgesics, and pain relievers (*Vaz-Rodrigues et al.,* 2022). It is also present in the drug cetuximab, which is used in immunotherapy for metastatic colorectal cancer, specifically in the Fab fragment of this recombinant monoclonal antibody. Allergic reactions have also been reported in α-gal syndrome patients with blood type O who received plasma or platelets from

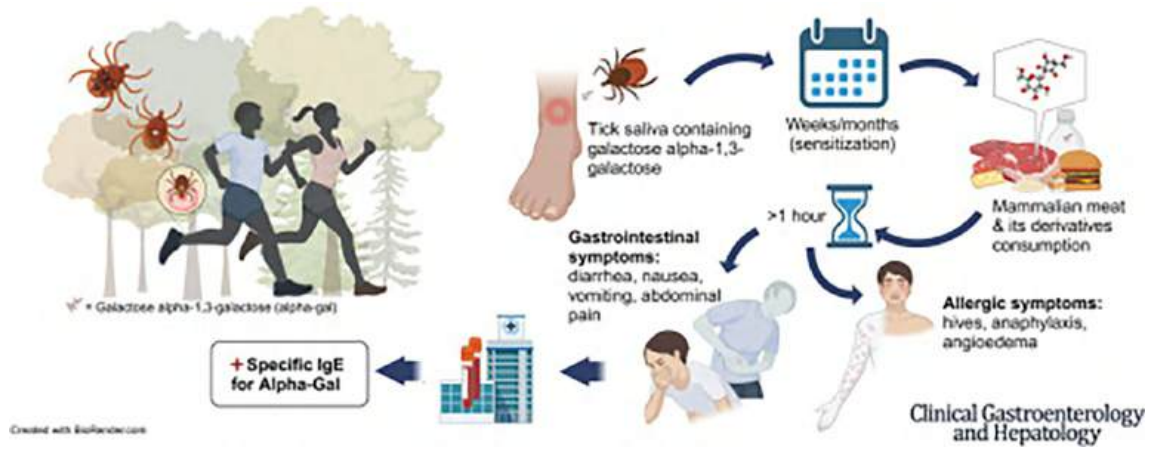

Figure 1. Formation of α-gal allergic reaction (*Lesmana et. al*, 2025)

donors with blood type B (*Miller et al.,* 2024), with the relevant moieties depicted in Figure 2.

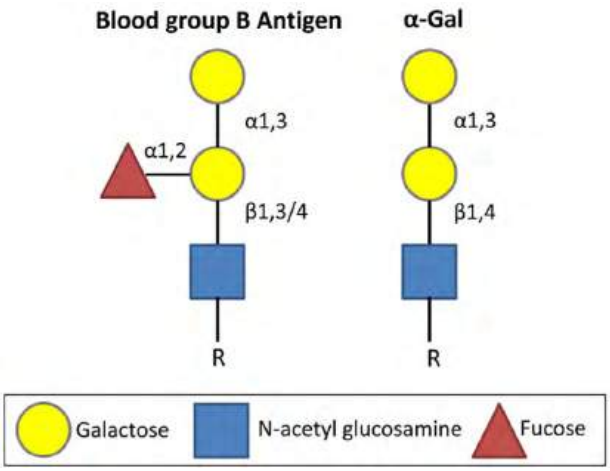

Figure 2. Comparison of the structures of α-Gal and blood group B antigen (*Lesmana et. al*, 2025)

After the delayed onset (3–6 hours), the allergic response is similar to most food allergies, particularly IgE-mediated allergies, and includes intense itching across the body, hives, angioedema, gastrointestinal symptoms, and the possibility of anaphylaxis (*Mabelane et al.,* 2019). Anaphylactic reactions occur in approximately 60% of affected individuals. There have been cases where gastrointestinal symptoms occurred without itching, hives, or other skin-related issues. In 70% of cases, the reaction is accompanied by respiratory problems, and it is particularly harmful to individuals with asthma. An increased risk has been found in people who do not have blood type B or AB, as the B blood group antigen is structurally similar to α-gal and may provide a certain level of natural protection (*Vaz-Rodrigues et al.,* 2022).

The severity of symptoms and the overall reaction to α-gal correlate with the amount of α-gal carbohydrate present in the consumed food or medication. It has been found that avoiding mammalian meat and preventing further tick bites leads to a decrease in serum IgE antibody levels (*Platts-Mills et al.,* 2020). In addition, treatment with antihistamines can be effective, while severe cases may require hospitalization and the administration of epinephrine (*Commins,* 2020). In 2020, the U.S. Food and Drug Administration (FDA) approved the genetic modification of pigs so they do not produce α-gal sugars. These pigs, developed under the trademarked name GalSafe, could be safely consumed by individuals with α-gal allergy, used in drug production, and their organs could be used for xenotransplantation (*Dolgin,* 2021).

Investigating a suspected case of meat allergy requires a multidisciplinary approach. Diagnosis of this allergic reaction begins with a clinical suspicion of α-gal syndrome, based on a detailed medical history and the individual's clinical symptoms. Diagnosis is typically challenging, and no single specific test is recommended over others. Because the onset of symptoms is often significantly delayed, it can be difficult to connect the reaction to the consumption of red meat several hours earlier. Skin prick testing with relevant animal proteins may be of limited use in this context, due to significant variability in food preparation and the lack of well-validated results. A commercially available test for α-gal includes bovine thyroglobulin and is accessible through certain manufacturers (*Apostolovic et al*., 2017).

The most commonly used test is a serological test, specifically the measurement of IgE antibodies against α-gal (>0.1 IU/mL), used in combination with the patient's clinical symptoms.

2. Conclusion

Although traditionally considered rare, meat allergy is increasingly being recognized in individuals of all ages. Raising awareness of α-gal allergy—both among healthcare professionals and the general public, especially in tick-endemic regions—is a crucial first step toward improving diagnosis and treatment. As with the management of any food allergy, treatment of this allergy is based on allergen avoidance. However, for α-gal patients, this principle of self-protection is complicated by the lack of proper labelling of mammalian-derived ingredients in food, medications, and vaccines. The approval of α-gal-free pork products would be an effective pathway for developing "α-gal-safe" foods, drugs, and implantable medical devices (*Commins, 2020*). The prevalence of α-gal allergy remains unknown and continues to pose a challenge with regard to its widespread integration into medical education and awareness efforts in the healthcare system.

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