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Alpha-gal syndrome: exploring the link between tick bites and red meat allergy

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Abstract

Introduction: Alpha-gal syndrome (AGS) arises from tick bites, triggering excessive IgE antibodies to galactose- α -1,3-galactose (α -Gal). Symptoms vary, often appearing post- α -Gal ingestion, ranging from mild to severe, including urticaria, angioedema and respiratory issues. Delayed symptom onset complicates diagnosis, posing challenges for patients. AGS can also result from contact with medical animal-derived products, such as bovine-derived heart valves, necessitating heightened healthcare provider awareness, especially in tick-exposed

regions. Management involves allergen avoidance and emergency medications like epinephrine. Further research is needed to refine diagnostic and therapeutic approaches.

Purpose: Through literature review and clinical presentation description, we aim to raise awareness and enhance understanding of alpha-gal syndrome.

Description of the state of knowledge: AGS, an emerging atypical food allergy, stems from immune reactions to α -Gal oligosaccharide in mammalian meat and other animal products. Avoiding medical items containing alpha-gal is crucial to prevent iatrogenesis.

Summary: Understanding AGS etiology and symptoms is vital for diagnosis and management. Healthcare providers' lack of awareness may lead to underdiagnosis, inadequate patient care, and underestimation of affected individuals.

Keywords: Alpha-gal syndrome; AGS; α -Gal; red meat allergy; anaphylaxis; tick bite.

A brief description of allergy

An allergy is an abnormal immune system response to normally harmless substances, called allergens.[1] When a person allergic to a specific allergen comes into contact with it, their immune system reacts excessively, producing antibodies known as immunoglobulin E (IgE).[2] These antibodies trigger the release of chemical substances, such as histamine and others proinflammatory mediators, leading to the onset of allergic symptoms.[3,4] Allergy symptoms may include sneezing, runny or itchy nose or eyes, pruritus, skin rash, urticaria, swelling, difficulty breathing, wheezing and bronchospasm, stomach pain, nausea, vomiting, abdominal cramping or diarrhea.[5,6] Allergies can involve various substances, such as plant pollen, animal dander, insect venoms, fungal spores, foods, medications, or chemical components.[7,8] The allergy can diminish the quality of life of the individual.[9,10] The most perilous type of allergic reaction is anaphylaxis.[11]

Anaphylaxis

Anaphylaxis is a sudden and serious allergic reaction that can be life-threatening.[12] It is the result of excessive and rapid release of chemical substances, including histamine, from mast cells and basophils, upon exposure to an allergen.[13]

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled[14]:



Figure 1. Diagnostic criteria for anaphylaxis according to the European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update).

Diagnosis is based on clinical symptom observation and medical history regarding potential allergen exposure.[15] In suspected cases of anaphylaxis, prompt administration of intramuscular adrenaline is crucial.[16] According to Kim SY et al. and Motosue MS et al. the most common causes of anaphylaxis in adults are medications, foods, and insect stings. In some cases, despite thorough diagnostics, the cause of anaphylaxis cannot be identified (idiopathic anaphylaxis).[17,18]

Specific allergy – alpha-gal syndrome

Alpha-gal syndrome, also known as AGS, is an allergy to mammalian meat, dairy and products derived from animals such as cows, lambs and pigs.[19] Unlike most food allergies, which involve reactions to proteins, alpha-gal syndrome is unique as it revolves around a

carbohydrate molecule – oligosaccharide galactose- α -1,3-galactose (α -Gal), eliciting the production of IgE antibodies against this molecule.[20,21]

While the precise mechanisms underlying alpha-gal syndrome remain incompletely understood, it is thought to entail the immune system's reaction to the α -Gal molecule introduced into the body through tick saliva during a tick bite.[22]

According to Perusko M et al. AGS manifests in a spectrum of symptoms, typically emerging several hours after consuming α -Gal-containing products.[23] The severity and swiftness of allergic responses in alpha-gal syndrome differ based on the quantity of α -Gal consumed and the type of food ingested. Individuals allergic to α -Gal may experience quick symptom onset after consuming organ meats like pork kidney, known for their high alpha-gal content. In contrast, allergic reactions are delayed when consuming fatty mammalian products.[24] According to Fischer J et. al anaphylactic reactions to α -Gal that are delayed are most commonly seen following the consumption of beef and pork.[25] While patients may react to red meat, they tolerate turkey, chicken, duck, quail fish, molluscs and shellfish.[26]

Symptoms range from mild to severe and may vary among individuals. Common manifestations include urticaria, angioedema, gastrointestinal discomfort and respiratory distress.[27] Skin symptoms, such as itching and redness, are prevalent and often the earliest signs.[28,29] In some cases, AGS can lead to anaphylaxis, characterized by rapid-onset systemic reactions involving multiple organ systems, potentially culminating in life-threatening consequences if not promptly treated.[30] Notably, the delayed onset of symptoms poses diagnostic challenges, as patients may not immediately associate their reactions with recent meat consumption. Moreover, the severity and timing of symptoms can vary, complicating diagnosis and management.[31] Furthermore, it's crucial to note that AGS can also be triggered by contact with items manufactured using animal-derived components. For instance, exposure to medical products such as bovine-derived heart valves or certain medications containing gelatin derived from mammalian sources can provoke allergic reactions in individuals with AGS.[32]

Additionally, in nearly 85% of patients with AGS, the following characteristic features are observed:

1. Describing significant local reactions to tick or other arthropod bites, often including a description of a "trigger" bite that behaved differently compared to previous bites.

2. Adult onset after consuming mammalian meat without issues for many years.
3. Testing positive for α -Gal IgE (>0.1 IU/mL).
4. Symptom improvement with the implementation of an appropriate avoidance diet.[33]

Serum α -Gal specific IgE detection is commonly employed to aid in diagnosing red meat allergy induced by alpha-gal syndrome. An oral food challenge, if conducted and yielding positive results, confirms the diagnosis.[34] Various sources of α -Gal sugar are utilized in these serum-based specific IgE assays, with beef thyroglobulin or the cancer drug cetuximab, both alpha-gal glycoproteins, being typical choices.[35]

Alpha-gal syndrome and common meat allergy: different allergen profile and molecular responses

While alpha-gal syndrome is a type of meat allergy, not all meat allergies are alpha-gal syndrome. Each condition may have distinct triggers, symptoms, and underlying mechanisms. Meat allergy, in a broader sense, encompasses various allergic reactions triggered by the consumption of different types of meat, including poultry, fish or mammalian meat. Some meat allergies may be triggered by specific proteins present in the meat rather than the galactose- α -1,3-galactose.[36]

Molecular elucidation of meat allergens has been constrained by limited studies, yet several proteins have been identified as pivotal allergenic entities. Specifically, the WHO/IUIS Allergen Nomenclature designates Bos d 6, Bos d and Gal d 5 as prominent meat allergens. Additionally, while Bos d 6 and Gal d 5 are categorized as serum albumins, Bos d 7 represents immunoglobulins, thus exemplifying the diverse molecular targets of meat-induced hypersensitivity.[37]

Clinical presentations of meat allergies often include delayed systemic symptoms, observed hours after consumption. Elevation of specific IgE antibodies directed against Bos d 6, Bos d 7 and Gal d 5 is a hallmark of such hypersensitivity reactions.[37] Cooking can reduce the allergenicity of meat, but some allergens may persist, warranting caution in food preparation. Bovine serum albumin degrades at high temperatures, allowing patients to safely consume fully cooked meat and boiled milk, while raw or undercooked meat should be avoided.[38] Alpha-gal maintains its immunogenic properties even when exposed to normal cooking temperatures, unlike proteins which undergo denaturation.[39]

Alpha-gal syndrome in Poland

The first case report of alpha-gal syndrome in Poland was published online 2021 august 28 in Central European Journal of Immunology. Brzozowska M et al. described a case of a 32-year-old male who underwent five anaphylactic episodes in the past three months. These episodes typically presented with abdominal discomfort and an itchy, raised rash on various parts of the body - on the torso, forearms and lower limbs. On one occasion, he also experienced difficulty breathing and throat constriction. Symptoms emerged 3 to 6 hours post-consumption of red meat (pork, beef, or mutton) and 2 to 3 hours after ingesting red meat alongside alcohol or moderate physical activity. The reaction severity was proportional to the meat intake. Relief was attained through an antihistamine (bilastine). There were no adverse effects observed after consuming chicken. The patient had been bitten by ticks twice, likely *Ixodes ricinus*, with the first bite preceding the anaphylactic symptoms by two weeks. Laboratory results showed notably high levels of α -Gal-specific IgE antibodies (72.6 kAU/l, reference range <0.35 kAU/l), confirming alpha-gal syndrome. Management involved immediate intervention and avoidance of mammalian meat and α -Gal-containing products, effectively preventing further incidents.[40]

Treatment strategies

The primary approach to managing alpha-gal allergy involves avoiding red meat.[41] Complete avoidance strategies are necessary for patients who exhibit clinical reactivity to all mammalian products. Iron and vitamin B12 supplements are recommended to prevent deficiencies in patients who require long-term avoidance of mammalian meat.[42]

Alpha-gal syndrome can significantly impact an individual's diet, lifestyle and overall well-being.[43] Insufficient awareness and understanding of AGS among healthcare professionals likely result in underdiagnosis of this condition, inadequate patient management and underestimation of the number of AGS patients.[44] Altshuler E and colleagues emphasize the crucial significance of recognizing AGS. It's not just about easing the burden of symptoms but also about preventing iatrogenic harm. Avoiding products containing mammalian components, like cat-gut suture, porcine-derived heart valves and bovine-derived vaccines, is essential for patients with AGS. Since individuals with AGS might show up in diverse clinical settings, it's imperative for physicians across specialties to be adept at identifying the symptoms.[45]

Increasing awareness of this condition among healthcare professionals and the general public is crucial for prompt diagnosis, appropriate treatment and prevention of allergic reactions associated with alpha-gal allergy.

Summary

Alpha-gal syndrome presents a distinctive clinical profile characterized by allergic reactions to the oligosaccharide galactose- α -1,3-galactose, commonly found in mammalian meat and derived products. Clinical manifestations encompass a spectrum of symptoms, spanning from mild cutaneous reactions to severe anaphylaxis. Given the ubiquity of tick vectors and the anticipated impact of climate change on their prevalence, there is an imperative to enhance awareness among healthcare practitioners regarding this emerging allergenic condition. Such initiatives are paramount for ensuring timely recognition, accurate diagnosis, and implementation of tailored dietary strategies aimed at minimizing exposure to α -Gal-containing substances, thereby enabling individuals with AGS to circumvent adverse and potentially life-threatening anaphylactic reactions.

Author's contribution

Conceptualization, Julia Szymonik; methodology, Julia Szymonik and Sebastian Szopa; software, Sebastian Szopa; check, Sebastian Szopa; formal analysis, Sebastian Szopa; investigation, Julia Szymonik; resources, Julia Szymonik and Sebastian Szopa; data curation, Julia Szymonik and Sebastian Szopa; writing - rough preparation, Julia Szymonik; writing - review and editing, Julia Szymonik; visualization, Sebastian Szopa; supervision, Sebastian Szopa; project administration, Julia Szymonik;

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Conflict of Interest Statement

All authors affirm that they do not have any conflicts of interest.

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