REVIEW

Alpha-Gal Syndrome a Challenge for the Future - Immunological Marker of the Interaction of the Environment (Ticks), Immune System and Diet

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Abstract: Alpha-gal syndrome is an IgE-mediated allergic reaction to a carbohydrate called galactose-alpha-1,3-galactose. Unlike most food allergies, which are reactions to proteins, this syndrome is due to the introduction into the body of a sugar molecule called alpha-gal. The condition is caused by tick bites, in Europe of the species Ixodes ricinus and in North America more commonly of the species Amblyomma americanum or "Lone Star tick". This introduces into the body a sugar molecule called alpha-gal (galactose-alpha-1,3-galactose), which causes the immune system to produce specific antibodies. Alpha-gal syndrome is a new and special model in allergology for at least 2 reasons: unlike other food allergies: it is not triggered by a protein, but by a carbohydrate and occurs hours after ingestion. Mechanism of "cross-reactivity": Alpha-gal is found in most mammals, but is absent in humans and primates. Alpha-gal syndrome is an emerging food allergy characterized by delayed IgE-mediated reactions to the ingestion of mammalian-derived products. Sensitization is induced by tick bites and involves antibodies directed against galactose-α-1,3-galactose. The authors conducted a systematic review of the PubMed literature (2008–2025) to synthesize current data on the pathophysiology, clinical manifestations and management of AGS. Twenty eight relevant studies were included. Alpha-gal syndrome presents an atypical clinical profile, with onset of symptoms at 3-6 hours after ingestion, and is frequently underdiagnosed. Recent data suggest possible links to cardiovascular inflammation and the role of the gut microbiome. Alpha-gal syndrome can be conceptualized as an allergy dependent on lipid antigen kinetics, which redefines the classical paradigms in allergology.

Keywords: *alpha-gal syndrome, red meat allergy, tick bites, IgE, delayed anaphylaxis, galactose.*

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INTRODUCTION

Alpha-gal syndrome (AGS) is a distinct clinical entity within food allergies, being the first described form of IgE-mediated hypersensitivity to a carbohydrate.

Its discovery was initially correlated with reactions to cetuximab and later with sensitization induced by tick bites. The increase in incidence is associated with the expansion of vectors (ticks) and climate change. The delayed nature of the reactions makes AGS frequently underdiagnosed in clinical practice [1].

Brief history of the discovery of the syndrome: in the early 2000s, the use of the drug cetuximab in oncology was introduced, and oncologists noticed an unusually high number of patients with severe anaphylactic reactions upon administration of the first dose. Curiously,

the anaphylactic reaction occurred upon administration of the first dose as if the patients' immune systems already knew something about the drug. Dr. Thomas Platts-Mills' team discovered that the patients had IgE antibodies to a sugar called galactose-alpha-1,3-galactose (alpha-gal), present in the drug's structure. During the investigation of cetuximab, the anaphylactic reactions overlapped almost perfectly with the incidence map of Rocky Mountain spotted fever, a disease transmitted by the Lone Star tick (Amblyomma americanum). In Australia, immunologist Sheryl van Nunen had already observed a similar link between bites from local ticks (Ixodes holocyclus) and meat allergies, publishing the first observations in 2007 [2,3].

PATHOPHYSIOLOGY

Alpha-gal syndrome is mediated by IgE antibodies specific for alpha-gal, generated following exposure to antigens in tick saliva. Unlike classic food allergies, in which proteins are the main antigens, AGS involves a carbohydrate determinant. A defining aspect is the delay of the allergic reaction, explained by the slow absorption of the antigen by means of lipid chylomicrons. This particular kinetics determines the late activation of mast cells. Conceptually, AGS can be defined as an allergy dependent on lipid antigen kinetics, suggesting that the dynamics of antigen uptake is a major determinant of the clinical phenotype of IgE-mediated reactions.

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Symptoms may vary from person to person: Digestive problems (most common): Severe abdominal pain, cramps, nausea, vomiting or chronic diarrhea. Sometimes this is the only symptom: Hives, intense itching, redness of the skin or swelling of the lips, face or tongue. Breathing difficulties: wheezing or feeling suffocated. Anaphylaxis: sudden drop in blood pressure and collapse. This is a zero-grade emergency. Some patients can eat beef for months without problems, only to then have a violent reaction. Sensitivity can fluctuate depending on the amount of fat consumed (fat contains more alpha-gal) or the physical effort made after eating. The clinical manifestations of allergy to mammalian meat include two types of allergic reactions, the immediate type and the delayed type, although both are mediated by IgE antibodies. The immediate type manifests allergic symptoms shortly after ingestion of meat and is mainly triggered by serum albumin and immunoglobulin, which are the main allergenic components. However, the delayed type is characterized by the onset of allergic symptoms 2-6 hours after ingestion of red meat and is mediated by IgE specific to alpha-gal oligosaccharides [2-4].

Tick bites are now thought to play a key role in red meat allergy: when ticks bite certain victims, they transfer alpha-gal into the human immune system, which can change them from alpha-gal IgE negative with red meat tolerance to α-gal IgE positive with red meat allergy [5].

However, the mechanism remains unknown. It has been hypothesized that α-gal from the digestive tract and salivary glands of ticks originates from non-primate mammals that have been previously bitten. Clinical manifestations can be typical and atypical Typical manifestations: delayed reactions after mammalian meat, urticaria,

generalized pruritus, abdominal pain, nausea, vomiting, diarrhea, angioedema, anaphylaxis and most often onset after an episode with multiple tick bites. Among the atypical or subtle manifestations, we note predominantly digestive symptoms. The onset of symptoms typically occurs 3-6 hours after ingestion of mammalian meat, frequently during the night. Diagnosis is based on the determination of alpha-gal-specific IgE, suggestive anamnesis and temporal correlation of food-symptoms and tick bite. The mechanism of delay is due to the fact that the epitope is not a protein but a carbohydrate, and the response is slower and dependent on metabolic processing. Alpha-gal is present mainly in lipids and glycoproteins in meat. After digestion, the lipids are incorporated into chylomicrons that enter the lymphatic circulation and not directly into the blood, a process that takes hours. That is, the antigen "reaches" the immune system much later than in classic allergies. Chylomicrons release alpha-gal into the circulation progressively. Exposure of mast cells and basophils to the antigen is gradual. The IgE activation threshold is reached only after a few hours→onset of anaphylaxis [6].

The correct diagnosis of alpha-gal syndrome requires a combination of history+specific laboratory tests, because it is an atypical allergy (with delayed reactions). The doctor will look for a specific pattern: with allergic reactions (urticaria, angioedema, anaphylaxis), occurring at 3-6 hours after consuming red meat and a significant history of tick bites (sometimes in recent months).

Biological investigations: blood test that measures: IgE anti-alpha-gal antibodies. It is considered that elevated values support the diagnosis but must be correlated with symptoms (not every positive result=clinical disease).

In certain cases, additional tests are performed: IgE for: beef / pork / lamb, skin prick test - sometimes less sensitive for alpha-gal and food challenge test-rarely used (risk of severe reactions). There may be situations that can be interpreted as frequent diagnostic traps such as symptoms appearing late→the patient does not link them to food, reactions are variable (do not occur with every meal), some "hidden" products contain alpha-gal (gelatin, medications).

CONCLUSIONS

It is not the "initial" food that causes sensitization but a vector (the tick) that "rewrites" the immune response. Correct diagnosis=typical history+anti-alpha-gal IgE test+epidemiological context. Without these three elements, the syndrome is frequently missed. Importantly, unlike other food allergies: it is not triggered by a protein, but by a carbohydrate and appears hours after ingestion, not immediately. Recent research draws attention to immunomodulation through the microbiome where there is a hypothesis that the microbiota influences sensitization to alpha-gal→possible targeted probiotic treatment. Perhaps vaccines can be developed that prevent tick attachment and could reduce the incidence of AGS. There is a need for personalized desensitization, which must, however, be adapted for carbohydrates. Alpha-gal syndrome represents a new model in Allergology.

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Both authors contributed to the critical revision of the manuscript for valuable intellectual content. Both authors have read and agreed with the version of the manuscript.

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"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

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