Late-onset food allergy as a manifestation of alpha-gal syndrome: a description of two patients

ALERGIA POKARMOWA O PÓŹNYM POCZĄTKU JAKO OBJAW ZESPOŁU ALFA-GAL: OPIS PRZYPADKU DWÓCH PACJENTÓW

JULIA TARKOWSKA*, MAŁGORZATA CIEŚLAK, ALEKSANDRA WARDZYŃSKA

CLINIC OF IMMUNOLOGY AND ALLERGY, CENTRAL CLINICAL HOSPITAL OF THE MEDICAL UNIVERSITY IN LODZ

* AUTOR KORESPONDENCYJNY

Streszczenie

Zespół alfa-gal (alpha-gal syndrome, AGS) jest rzadką postacią alergii pokarmowej IgE-zależnej, wywołanej reakcją immunologiczną przeciwko galaktozo-α-1,3-galaktozie (α-Gal), obecnej w tkankach ssaków. Charakterystyczną cechą tej choroby jest opóźnione występowanie objawów, zwykle 2–6 godzin po spożyciu mięsa ssaków lub produktów zawierających α-Gal, co znacząco utrudnia diagnostykę. Patogeneza AGS jest związana z wcześniejszymi ukłuciami kleszczy, które indukują produkcję swoistych przeciwciał IgE przeciwko α-Gal.

Celem pracy było przedstawienie dwóch przypadków pacjentów z rozpoznanym zespołem alfa-gal oraz zwrócenie uwagi na trudności diagnostyczne związane z tą jednostką chorobową. U 58-letniego mężczyzny oraz 72-letniej kobiety występowały nawracające reakcje alergiczne pojawiające się kilka godzin po spożyciu produktów pochodzenia ssaczego. W pierwszym przypadku doszło do epizodu anafilaksji po spożyciu wieprzowiny, natomiast w drugim obserwowano nawracającą uogólnioną pokrzywkę. W obu przypadkach stwierdzono wysokie stężenia swoistych przeciwciał IgE przeciwko α-Gal przy braku istotnej sensytyzacji na inne alergeny pokarmowe.

Rozpoznanie AGS umożliwiło wdrożenie odpowiednich zaleceń dietetycznych oraz leczenia doraźnego. Przedstawione przypadki podkreślają znaczenie uwzględnienia zespołu alfa-gal w diagnostyce opóźnionych reakcji alergicznych pojawiających się po raz pierwszy w wieku dorosłym.

Słowa kluczowe: alfa-gal, kleszcz, czerwone mięso, wołowina, podroby, anafilaksja, alergia pokarmowa

Summary

Alpha-gal syndrome (AGS) is a rare form of IgE-mediated allergy with delayed onset of symptoms caused by an immune response to galacto-α-1,3-galactose (α-Gal) present in mammalian meat and certain animal products. This disease poses a major diagnostic challenge because of the atypical time relationship between exposure and symptom onset, as well as the variety of clinical manifestations. In addition, symptoms may first appear later in life after many years of tolerance to foods containing α-Gal. This study presents two cases of patients diagnosed with AGS who experienced recurrent allergic reactions after consuming products containing α-Gal, including episodes of generalized urticaria and anaphylaxis. In both cases, high concentrations of specific IgE against α-Gal were observed in the absence of significant sensitization to other food allergens. The diagnosis of AGS enabled the introduction of appropriate dietary recommendations and emergency treatment, which contributed to improved patient safety. The presented cases emphasize the importance of considering AGS in the differential diagnosis of delayed allergic reactions that first appear in adulthood, as well as the importance of detailed medical history and molecular diagnostics in clinical practice.

Key words: alpha-gal, tick, red meat, beef, offal, anaphylaxis, food allergy

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Adres do korespondencji/Address for correspondence

Lek. Julia Tarkowska

jtarkowska@csk.umed.pl

Introduction

Alpha-gal syndrome is a unique example of an IgE-mediated food allergy in which the allergen is not a protein but a carbohydrate: galactose-α-1,3-galactose, which is found on glycoproteins and glycolipids in mammals other than humans and higher primates [1–3].

An important component of AGS pathogenesis is sensitization through tick bites, which in Europe is caused by *Ixodes ricinus*. Tick saliva contains α-Gal and immunomodulatory factors that promote the induction of a Th2-type response [2, 5, 7]. This process leads to the production of specific IgE antibodies directed against α-Gal, as confirmed by the strong correlation between the number of tick bites and sIgE levels [3, 8, 9] (Figure 1). This mechanism distinguishes AGS from classic food allergies, in which sensitization typically occurs via the gastrointestinal tract [1]. Alpha-gal syndrome can be diagnosed at any age; however, most confirmed cases involve adults, including the elderly. The clinical presentation of AGS is diverse and includes cutaneous and systemic reactions, as well as a phenotype limited exclusively to the gastrointestinal tract. One of the characteristic clinical features of AGS is the delayed onset of symptoms, usually 2–6 h after consuming mammalian meat. Understanding the immunological basis of AGS, particularly in the context of the gastrointestinal phenotype, is crucial for improving the diagnosis and clinical management of patients with unexplained recurrent gastrointestinal symptoms.

Owing to its nonspecific clinical presentation and frequent diagnostic delays, AGS poses a significant challenge in clinical practice. This study aimed to present two cases of patients with late-diagnosed alpha-gal syndrome and to emphasize the importance of considering this condition in the differential diagnosis of delayed allergic reactions occurring after the consumption of mammalian meat in older adults.

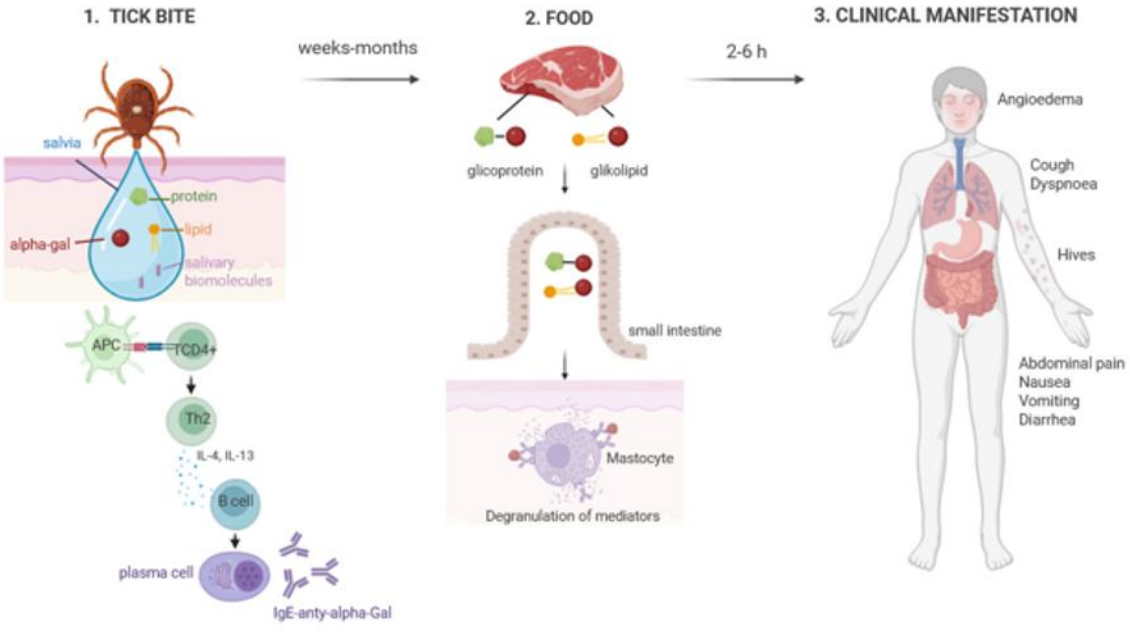

Figure 1. Clinical course of Alpha-gal syndrome. 1. After a tick bite, antigens in the tick's saliva are presented in the local lymph node. This causes Th lymphocytes to polarize toward Th2. Cytokines produced by Th2 cells induce a change in the classes of antibodies synthesized by B cells. As a result, IgE antibodies against alpha-gal appear. 2. Months or years later, exposure to foods containing alpha-gal triggers a reaction. Antibodies against alpha-gal bound to cells and cause the release of mediators, primarily histamine. 3. This leads to variety of symptoms including anaphylaxis. APC - Antigen presenting cell

Case study 1

A 58-year-old man visited an allergy clinic with an episode of anaphylaxis, presenting with shortness of breath and generalized urticaria, occurring 2–3 h after eating pork knuckle pâté. Several years earlier, he had experienced similar symptoms, but less severe, including generalized itching of the skin with a rash a few hours after eating stewed pork and an episode of itching and erythema in the wrist flexion areas, which occurred 3–5 h after consuming a small amount of pork fat. In all these cases, the meals were not associated with cofactors such as alcohol or physical exertion. An in-depth interview regarding food allergies revealed that for approximately two years, after eating cow's milk and its products (cheese, cottage cheese, and yogurt), the patient began to experience abdominal pain and loose stools, which suggested lactose intolerance. The patient tolerated butter, beef, rabbit meat and poultry. Other symptoms included upper respiratory tract hyperreactivity, such as a runny nose, sore throat, and sneezing, caused by exposure to nonspecific irritants in the fall and winter. The patient's medical history revealed significant exposure to ticks. In 2022, he was diagnosed with Lyme disease and treated with two antibiotics. The patient did not have any other comorbidities.

Laboratory tests revealed no abnormalities in peripheral blood morphology and slightly elevated total IgE (85.3 kU/L, N < 85 kU/L). sIgE levels against cow's milk proteins (Bos d 6, Bos d lactoferrin, Bos d 8, Bos d 5, Bos d 4), soy, sesame, and hymenoptera venom were negative (class 0). However, a significantly elevated concentration of sIgE against α-Gal (19.3 kU/L, class 4) was noted. Skin prick tests with a panel of inhalant allergens (Dermatophagoides farinae, Dermatophagoides pteronyssinus, alder, hazel, birch, grass mix, cereal mix, mugwort, dog hair, cat hair, A. alternata, Cladosporium) were negative, and spirometry results were normal. Based on the clinical picture and test results, alpha-gal syndrome was diagnosed. The patient was prescribed emergency treatment, including adrenaline, and was advised to avoid mammalian meat and other products containing α-Gal.

Case study 2

A 72-year-old woman visited an allergy clinic with generalized urticaria that occurred approximately 4 hours after consuming pork kidneys in pork sauce. She took previously prescribed medications, including prednisone and bilastine, after which her symptoms disappeared within a few hours. She emphasized that she had eaten pork kidneys many times before without experiencing any similar symptoms. Over the past five years, she had experienced a few episodes of urticaria and facial swelling after eating various foods, including groats with meat, cold cuts, and grilled meat, several hours after meals. In all cases, the meals were not associated with either alcohol consumption or physical exertion. An in-depth interview regarding food allergies revealed that the patient generally tolerated pork, beef, lamb, mutton, rabbit meat, lard, products containing gelatin (cold feet), poultry, cow's milk and its products (cheese, cottage cheese, yogurt, and butter), goat's milk, and sheep's milk. Past skin tests showed positive results for weed allergens and cat hair; however, exposure to these factors did not cause any symptoms. During the interview, the patient reported several tick bites (the last one was two years ago [in 2024]). The comorbidities included type 2 diabetes, cardiac arrhythmia, and nodular thyroid goiter.

Two years prior, the patient had been diagnosed with suspected food hypersensitivity; however, the cause of her symptoms could not be determined at that time. Laboratory tests performed at that time showed normal values for CRP, ESR, thyroid hormones (FT3, FT4), anti-TPO, and anti-Tg antibodies, complement components (C4), and C1 inhibitor concentration and activity. The ANA test showed a titer of 1:80 for the cytoplasmic-type. Peripheral blood counts showed slight eosinophilia (0.22 $\times 10^3/\mu L$). The total IgE concentration was elevated (849 kU/L). The inhalant allergen profile was also negative. The food profile showed elevated specific IgE to chicken egg protein (4.2 kU/L, class 4 – clinically insignificant; the patient tolerated the consumption of egg white), while the other food allergens tested (egg yolk, cow's milk, baker's yeast, wheat flour, rye flour, rice, soy, peanuts, hazelnuts, almonds, apples, kiwis, apricots, tomatoes, carrots, potatoes, celery, cod, and crab) were in class 0. After the onset of urticaria following the consumption of pork kidneys, the diagnosis was expanded, and an extended food profile was performed (shrimp, cod, gluten, chicken, beef, pork, rice, oat flour, rye flour, and wheat flour), which was negative (class 0). However, a very high concentration of sIgE against α-Gal (sIgE>100 kU/l, class 6) was found.

The patient was diagnosed with alpha-gal syndrome. Oral glucocorticosteroids and antihistamines were recommended in cases of allergic symptoms, and avoidance of mammalian meat and other products containing α-Gal was advised.

Discussion

Available scientific data indicate that the rate of diagnosis of alpha-gal syndrome (AGS) in Poland and Central and Eastern Europe remains very low. The literature emphasizes that until recently, there was a lack of documented diagnoses in this region; the first clinical diagnosis in Poland was published in 2021 as a single case [4].

More data are available for Western Europe. Studies indicate that the prevalence of α-Gal sensitization (sIgE-positive) is approximately 5.5-8.1% of the population [18]. However, the study data show that the percentage of symptomatic cases is significantly lower. For example, in a German study involving occupationally exposed individuals (foresters and hunters), 35% of the participants showed sensitization, while only 8.6% of those with positive sIgE levels exhibited clinical symptoms of AGS [19]. This means that the actual prevalence of clinical disease may be lower than the prevalence of sensitization. A comparison of these values clearly indicates a large disparity between the prevalence of immunological sensitization and the clinically diagnosed syndrome and suggests that in Central and Eastern Europe, the actual prevalence of AGS is most likely significantly underestimated.

AGS diagnosis remains a clinical challenge. The determination of specific IgE against α-Gal is a key diagnostic tool, although its interpretation should always consider the patient's clinical picture [4, 10].

In the described cases, the measurement of specific IgE antibodies against α-Gal was performed using the fluoro-immunoenzymatic assay (FEIA) method with a Phadia 200 analyzer (Thermo Fisher Scientific). Antibody concentrations were measured in units of KU/L. A value in the range of 0.00–0.35 KU/L was considered

negative, a concentration of 0.35–0.70 KU/L was considered weakly positive, and a concentration above 0.70 KU/L was considered positive. The literature also describes attempts to use the basophil activation test to distinguish clinically significant α-Gal allergies [13].

The clinical presentation of AGS is highly variable and ranges from isolated skin symptoms to severe anaphylactic and gastrointestinal symptoms [5, 6, 10]. In some patients, gastrointestinal symptoms predominate, including nausea, vomiting, abdominal pain, and diarrhea, which can lead to a misdiagnosis of functional gastrointestinal disorders and a significant delay in establishing the correct diagnosis [6].

A characteristic clinical feature of AGS is the delayed onset of symptoms, usually 2–6 h after consuming mammalian meat [4–6]. This phenomenon is explained by the pharmacokinetics of α-Gal-containing glycolipid absorption, which, after fatty food consumption, are transported in chylomicrons and enter the systemic circulation with a delay [8, 11]. Degranulation of mast cells and basophils occurs only after exceeding the activation threshold, followed by the release of allergic reaction mediators [5, 9].

The first manifestation of food allergies in older adults can pose diagnostic challenges, initially suggesting other, more likely diagnoses. Furthermore, the course of the reaction may be modified by factors such as aging of the gastrointestinal tract, dysfunction of the gastrointestinal epithelium, fat content in the meal, or exposure to cofactors such as medications (including nonsteroidal anti-inflammatory drugs, NSAIDs), physical exertion, and alcohol [12].

Notably, the patients described in this study generally tolerated mammalian products, including beef and pork, and their consumption occasionally caused symptoms. These observations highlight the complex and heterogeneous nature of the syndrome. In both cases, the manifestations of AGS varied; however, gastrointestinal symptoms were not observed in either case. Furthermore, in the first patient, there was a clear progression of the clinical picture, with initial symptoms being mild and limited to skin lesions, whereas the last episode was associated with a generalized systemic reaction. In contrast, in the second patient, the severity of symptoms remained at a similar level over the subsequent years.

Alpha-gal syndrome requires differential diagnosis owing to its nonspecific clinical presentation. First, AGS should be distinguished from IgE-mediated food allergies, particularly those to mammalian meat proteins, cow milk, eggs, and other common food allergens. In contrast to AGS, reactions in classic IgE-mediated allergies typically occur shortly after exposure (within 30–60 min) and are associated with sensitization to proteins rather than carbohydrate epitopes [20]. Another group of conditions in the differential diagnosis includes non-IgE-mediated food intolerances, such as lactose intolerance, hypersensitivity to fermentable components (FODMAP), and histamine hypersensitivity [21]. In these cases, gastrointestinal symptoms predominate, while cutaneous and systemic reactions, including anaphylaxis, do not occur, and the mechanism is not associated with the production of a specific IgE. The differential diagnosis should also include diseases associated with mast cell activation, such as mastocytosis [22, 23] and mast cell activation syndrome (MCAS) [24, 25]. These conditions may present with episodes of urticaria, hypotension, and multisystemic symptoms; however, they do not show a causal relationship with exposure to α-Gal or a characteristic temporal association with mammalian meat consumption. The key distinguishing features of AGS from other conditions are the delayed onset of symptoms, the presence of specific IgE antibodies against α-Gal, and a significant history of exposure to tick bites. The correlation between these features and clinical presentation remains the basis for a correct diagnosis.

Patients with ASG are advised to avoid exposure to all potential sources of α-Gal. This may require the elimination of mammalian meat, gelatin-containing products, and dairy products from the diet. Caution should also be exercised when using medications that may contain substances of animal origin.

Sources of α-gal include products of mammalian origin, such as cetuximab, gelatin (intravenous and in vaccines), thyroid hormones, sera and biological materials, heparin, and pancreatic enzymes. Reactions ranging from mild to severe have been reported. The most severe clinical reactions, including perioperative anaphylaxis, occur following intravenous exposure, particularly to gelatin and cetuximab. Cases of drug reactions associated with hypersensitivity to α-gal, as described in the literature, are summarized in Table I.

In the event of a sudden onset of severe symptoms, emergency treatment, including the administration of an epinephrine auto-injector, is recommended [4].

Table 1. Medications containing alpha-gal: sources and potential clinical reactions (including risk of severe hypersensitivity).

Drugs / Therapeutics	Risk of severe reaction	Possible clinical reactions (incl. perioperative)	Potential sources of α-gal exposure	Reference
Cetuximab	High	Anaphylaxis, anaphylactic shock, hypotension, shortness of breath, hives (often during the first infusion)	Recombinant monoclonal antibody	[14–16]
Gelatin intravenous (for intravascular volume expansion)	High	Severe anaphylactic reaction, perioperative hypotension, bronchospasm, angioedema	Animal-derived gelatin (bovine/porcine) in colloidal liquids	[14]
Thyroid hormone (porcine/bovine) (Armour Thyroid)	High	Allergic reactions, hives, and, less commonly, anaphylaxis; delayed reactions are possible	Thyroid preparations derived from pigs or cattle	[14]
Antisnake venom therapy	High	Anaphylaxis, serum sickness, infusion-related reactions (fever, hypotension)	Heterologous immunoglobulins (equine/sheep)	[14]
Heart valves (porcine/bovine)	Medium	Inflammatory reactions, possible hypersensitivity reactions, rarely peri-implant anaphylaxis	Biological valves of porcine/bovine origin	[14–15]
Vaccines with gelatin (MMR, TBE)	Medium	Hives, anaphylactic reactions (usually immediate), rarely delayed reactions	Gelatin stabilizers in vaccines	[14–16]
Heparin	Low (higher risk with UFH i.v. than LMWH s.c.)	Hypersensitivity reactions, rarely anaphylaxis, skin reactions, perioperative hypotension	Heparin from pig mucous membranes	[14–15]
Pancreatic enzyme (porcine)	Low	Allergic symptoms (hives, itching), rarely systemic reactions	Pancreatic enzymes derived from pigs	[14]
Gel capsules	Low	Usually mild skin reactions; occasionally allergic symptoms	Gelatin capsules (bovine/porcine)	[14,16]

UFH - Unfractionated Heparin; LMWH - Low Molecular Weight Heparin

Conclusions

Alpha-gal syndrome is an atypical IgE-mediated allergy with a delayed onset, induced by tick bites, and associated with the consumption of mammalian meat or products containing α-Gal. It can occur in adulthood and should be considered when the first symptoms of food allergies appear in older adults. The heterogeneous clinical presentation of this disease highlights the crucial role of a thorough clinical history and α-Gal-sIgE testing.

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