

Journal

ImmunoDiagnostics

A novel form of IgE mediated food allergy

In contrast to most food allergies where symptoms develop within a couple of hours after ingestion of the culprit food, a newly described allergy to red meat gives rise to symptoms that are delayed many hours after the meal. The reactions are commonly severe and many patients react with anaphylactic shock. The disease suddenly appears in people who have tolerated meat for years and are augmented by cofactors such as exercise and alcohol. Affected patients have IgE antibodies to the carbohydrate alpha-Gal, a sensitization they seem to have acquired via tick-bites.

The diagnosis of delayed red meat allergy is thus supported by a history of tick bites. Skin prick tests often give weak or negative results, why quantification of IgE antibodies to alpha-Gal in blood is the preferred diagnostic method.



3 α -Gal-associated meat allergy

An allergy that hit the news



In this issue of ImmunoDiagnostics Journal we present a summary on alpha-Gal mediated meat allergy – a truly unconventional type of food allergy.

This unusual form of meat allergy was initially described in Australia where it was the topic of an abstract for the Australasian Society of Clinical Immunology and Allergy (ASCI) 18th meeting in 2007, but not long after the reports of from the southwest of USA followed where people reacting to infusions of a biologic drug also reported delayed allergic reactions to beef and pork. This was the start of an interesting and fascinating unravelling of the cause of the disease and the route of sensitization, all of which was elegantly elucidated by mapping its co-existence with tick-borne diseases that geographically coincided with anaphylactic reactions to a cancer treatment.

Alpha-Gal associated red meat allergy is now understood as a disease induced by tick-bites. Ticks live all over the globe, and delayed reactions to meat and offal are now described from many continents – patient reports have come from Korea and Japan, Spain, Germany, Sweden and France and many other countries. This atypical food allergy has also hit the news rooms – from creating headlines in Washington Post, to being the topic of TV shows. The reason being that this disease suddenly affects previously healthy adults who never before were allergic and that all of a sudden become seriously ill after enjoying their barbecue and a beer. And the same disease can be the reason why some people have suffered gastrointestinal distress or unexplained hives for many years without understanding why. What they all have in common is having spent time out-doors in tick-rich areas.

Next time you go for a hike perhaps you will choose to put on high boots and take a shower afterwards!



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The conundrum of α -Gal-associated meat allergy

In 2009, the first reports of a novel and perplexing form of delayed allergic reaction to red meat emerged. Individuals experienced symptoms ranging from urticaria and angioedema to anaphylaxis, without any apparent trigger⁽¹⁾. Strangely, these symptoms frequently appeared during the night and seemed to be unconnected with any provoking event⁽¹⁻⁴⁾. During questioning, however, patients consistently reported having eaten beef, pork, or lamb in the 3 to 6 hours prior to the appearance of symptoms, but owing to the delay in onset, many did not suspect meat as the trigger⁽¹⁾. To add to the puzzle, all patients were adults who had eaten meat for many years with no problems, and many had negative results in skin prick tests (SPT) with meat extracts or fresh meat⁽¹⁾.

The first clue to understanding this syndrome came when serological analyses revealed that affected individuals had

IgE antibodies to galactose- α -1,3-galactose (α -Gal), an oligosaccharide present in all mammals, except humans and Old World monkeys⁽⁵⁾. This suggested that the reactions were caused by an IgE-mediated response to α -Gal epitopes on mammalian meat; however, the origin of the sensitization remained unclear. Anecdotal reports of recent tick bites in individuals with delayed meat allergy^(1,6), and the observation that the distribution of α -Gal-mediated allergies in the US was similar to that of the some tick-borne diseases⁽⁷⁾, suggested that tick bites could be responsible for the α -Gal sensitization. This was confirmed by observations of an increase in serum IgE to α -Gal increases following a bite from certain tick species⁽⁷⁾, and the presence of α -Gal in tick intestine⁽⁸⁾. Important discoveries that led to our current understanding of α -Gal-associated meat allergy are outlined in **Box 1**.

Characteristics of α -Gal-associated meat allergy

Triggers

Delayed reactions in α -Gal-associated meat allergy are triggered by mammalian meats, including beef, pork, lamb and game, but not by chicken, turkey or fish^(1,6,9). The severity of symptoms usually increases with the amount of meat consumed. Patients are often able to tolerate small amounts of meat without a clinical reaction; however, two pork sausage patties (around 86 g) reliably induced clinical symptoms⁽¹⁰⁾. Ingestion of larger quantities of meat, such as a double hamburger or a plate of barbecued meat, induced more severe reactions⁽¹⁰⁾.

Different meats induce symptoms of varying severity, with fatty meats generally inducing more consistent and severe reactions than leaner cuts⁽¹⁾. Pork and beef kidney are particularly allergenic, and reliably induce severe anaphylactic reactions that have a quicker onset than those observed with other offal or skeletal muscle meat (within 80 minutes of a challenge)⁽¹¹⁾. In a patient allergic to pork kidney, ingestion of as little as 2.1 g was sufficient to trigger anaphylaxis, even though she tolerated other mammalian meats⁽¹¹⁾. Kidney, in particular pork kidney, contains high amounts of α -Gal determinants⁽¹¹⁾; pre-incubating serum from a patient with IgE to α -Gal with pork kidney extract completely blocked binding of IgE antibodies to α -Gal in an ImmunoCAP[®] assay⁽¹²⁾.

Gelatin

There have been reports of allergic reactions to meat-derived gelatin in patients sensitized to α -Gal. Many patients with α -Gal-associated meat allergy have positive intradermal tests to gelatin⁽¹²⁾, and an Australian study reported a significant relationship between positive intradermal tests to gelatin and α -Gal-associated meat allergy⁽³⁾. Individuals with α -Gal-associated meat allergy have reported urticaria and bronchospasm following administration of only 1.2 g of intravenous gelatin colloid⁽³⁾, and delayed flatulence, abdominal cramps, flushing, tachycardia and diarrhea after consuming 250 g of gelatin-containing sweets and performing physical exercise⁽¹³⁾. The presence of α -Gal on gelatin colloids has been confirmed by *in vitro* studies, suggesting that an IgE response to α -Gal underlies the observed sensitivity in these patients⁽³⁾.

Cetuximab

As outlined in **Box 1**, the monoclonal antibody cetuximab contains the α -Gal epitope on its Fab fragment. Severe reactions to cetuximab infusions have been reported in patients with IgE to α -Gal⁽¹⁴⁾. Physicians should therefore be aware of the risk of allergic reactions to cetuximab in individuals with demonstrated IgE to α -Gal, or with delayed meat allergy or a history of tick bites⁽¹⁵⁾.

Box 1

Important steps in the elucidation of α -Gal-associated meat allergy*Cetuximab allergy*

- Shortly after approval of cetuximab in 2004 (a monoclonal antibody used in the treatment of some cancers), a significant number of patients experienced severe hypersensitivity reactions during their first infusion^(53, 54).
- These reactions were more common in the southern and eastern states of the US^(53, 54). In 2007, the prevalence of severe (Grade 3–4) cetuximab-related infusion reactions at sites in the southeast of the US was as high as 22%, compared with national and international rates of $\leq 3\%$ ⁽¹⁾.
- Allergic patients had IgE antibodies to the α -Gal oligosaccharide on the Fab portion of cetuximab that were present in patients' serum before therapy⁽¹⁴⁾.
- At the time, it was not known what caused sensitization to α -Gal or why the number of individuals with IgE to α -Gal was higher in the southeast US compared with other regions and countries.

Delayed anaphylaxis to mammalian meat

- In 2009, Commins and colleagues described a syndrome of delayed anaphylaxis to mammalian meat in the southeastern US⁽¹⁾. In the same year, similar cases were reported in Australia⁽⁶⁾.

- Allergic individuals were found to have detectable IgE antibodies to α -Gal⁽¹⁾.
- Most allergic patients were adults who had tolerated red meat for many years before developing the allergy, indicating that some new exposure in adulthood had caused sensitization⁽¹⁾.
- Investigators observed that the geographical distribution of cases was strikingly similar to that of hypersensitivity to cetuximab, suggesting that the same sensitizing antigen might be responsible for the IgE antibodies to α -Gal in both allergies.
- Australian investigators noted that 24 of the 25 patients in their case series had a history of large local reactions to tick bites, and postulated that patients became sensitized to α -Gal epitopes on tick salivary proteins that cross-react with proteins in mammalian meat⁽⁶⁾.
- Around the same time, American investigators received anecdotal evidence of tick bites from individuals with delayed meat allergy, and observed that serum IgE to α -Gal was prevalent in areas where the Lone Star tick *A. americanum* was common⁽⁷⁾.
- Investigation showed a correlation between the presence of IgE to α -Gal and to tick salivary proteins. An increase in serum IgE to α -Gal was demonstrated following tick bites⁽⁷⁾.

Symptoms

Unlike most protein-based food allergies, where symptoms appear rapidly, often within minutes of ingestion^(16, 17), onset of symptoms in α -Gal-associated meat allergy is typically delayed by 3–6 hours or more⁽¹⁾. This delay in onset has been confirmed in provocation tests⁽⁹⁾. A few patients, however, experience a shorter delay, with symptoms appearing within 2 hours⁽¹⁸⁾. Onset does not appear to be related to the patient's titer of soluble IgE to α -Gal⁽¹⁹⁾, which has led to speculation that the time to the reaction could depend on the condition of the patient's gastrointestinal tract⁽¹⁸⁾.

Patient-reported symptoms range from generalized skin reactions (pruritus and urticaria), to angioedema, respiratory distress and anaphylaxis^(1, 6, 9, 20), with gastrointestinal symptoms a distinctive feature of the syndrome⁽²¹⁾. Some

patients report nausea, diarrhea, or indigestion before the appearance of symptoms; however, the most common sign preceding a reaction is itching⁽¹⁾.

These patient-reported symptoms have been confirmed in provocation tests. Likewise, initial symptoms were frequently itching, such as palmar and plantar pruritus with erythema and often urticaria. Several reactions progressed from localized to systemic urticaria, with some progressing further to include gastrointestinal distress or hypotension⁽⁹⁾. Presence of serum IgE to α -Gal was not associated with chronic respiratory symptoms, such as rhinitis, lung inflammation or asthma⁽²²⁾.

Co-factors can lower the threshold for symptoms

Co-factors, such as infections, physical exercise, and consumption of alcohol or non-steroidal anti-inflammatory drugs (NSAIDs) are known to significantly lower the allergen dose needed to trigger anaphylaxis in some allergies^(12, 23). This is thought to occur by increased allergen absorption via dysregulation of tight junctions in the gastrointestinal epithelium, and possibly by increased cellular activation. Co-factors lower the threshold for the appearance of clinical symptoms in α -Gal-associated meat allergy. For example, a patient sensitized to α -Gal who did not experience allergic symptoms after eating 350 g of grilled pork, experienced delayed urticaria after eating the same amount of pork and performing 20 minutes of physical exercise one hour after eating⁽¹³⁾. Among a series of 14 patients who experienced anaphylaxis after consuming pork kidney, co-factors were present in 10 patients⁽¹¹⁾. Co-factors may also reduce the delay in appearance of symptoms; one patient sensitized to α -Gal experienced two episodes of anaphylaxis that occurred while exercising within 2 hours of eating beef⁽¹⁾.

Understanding the role of co-factors in the development of anaphylaxis can lower the risk of a severe allergic reaction in meat-allergic patients⁽¹⁵⁾. To this effect, Morisset and colleagues advised that patients allergic to pork and beef kidney should avoid risk factors, especially physical exercise, within 4 hours after a meal and intake of alcohol, aspirin, or NSAIDs⁽¹¹⁾.

Epidemiology

To date, cases of α -Gal-associated meat allergy have been reported in the southeastern US⁽²²⁾, Australia^(3, 6), Asia^(18, 24-26), and in several European countries, including France^(4, 11, 27), Spain⁽²⁸⁾, Germany⁽²⁹⁾, Switzerland⁽³⁰⁾, and Sweden⁽³¹⁾.



Red meat allergy – described worldwide

On all continents, the ticks responsible for sensitization to α -Gal belong to the Ixodidae family of hard ticks, with each continent harboring its native species. In the US, bites from the Lone Star tick *Amblyomma americanum* are the predominant, if not exclusive, cause of α -Gal sensitization⁽⁷⁾. In Australia, the suspected tick is *Ixodes holocyclus*^(3, 6, 11), whereas in Europe it is *Ixodes ricinus*⁽⁸⁾, and *Hematophagous ixodidae* in Asia⁽²⁴⁾.



As expected, the prevalence of detectable IgE antibodies to α -Gal is highest in areas where Ixodidae ticks are common. In Sweden, around 10% of 143 healthy blood donors in the greater Stockholm area had IgE antibodies to α -Gal, compared with only 0.7% in the north of the country where tick bites are rare⁽³¹⁾. It is, however, unclear exactly what proportion of sensitized individuals experience allergic symptoms after eating mammalian meat. Commins and Platts-Mills estimated that around 10% of individuals with detectable α -Gal antibodies may display red meat allergy⁽¹⁰⁾. The prevalence of IgE to α -Gal among Danish and Spanish adults was estimated at 5.5% and 8.1%, respectively for levels ≥ 0.1 kU_A/L, and at 1.8% and 2.2%, respectively for levels ≥ 0.35 kU_A/L⁽³²⁾.

Adult onset appears to be a characteristic of α -Gal-associated meat allergy⁽¹⁾. Among a series of 29 patients with α -Gal-associated meat allergy in a Japanese study, 21 were over 60 years of age⁽¹⁸⁾. Nevertheless, cases of α -Gal-associated meat allergy have also been observed in children⁽²⁰⁾.

Blood group phenotype

The B blood group phenotype appears to confer a protective effect against production of high levels of IgE to α -Gal, with a strong relationship between α -Gal-associated meat allergy and absence of the B blood group phenotype⁽³¹⁾.

A study of the relationship between the B blood group phenotype and IgG and IgE responses to α -Gal found that none of the subjects with the B phenotype expressed IgE to α -Gal⁽³³⁾. Among 39 Swedish patients with delayed meat allergy, only two (5%) had blood group B or AB, which is significantly lower than the expected overall value of 18% in the Swedish population⁽³¹⁾. The same study reported that in a group of healthy blood donors and patients with Lyme disease with detectable IgE to α -Gal, the levels of IgE against α -Gal were very low among those with the blood group B phenotype⁽³¹⁾. The mechanism of this protective effect has not been fully elucidated. However, the structure of the α -Gal epitope is closely related to that of the blood group B antigen, and it appears that the presence of the group B antigen induces tolerance and eliminates most B cell clones that could otherwise interact with tick-derived α -Gal antigens⁽³³⁾.

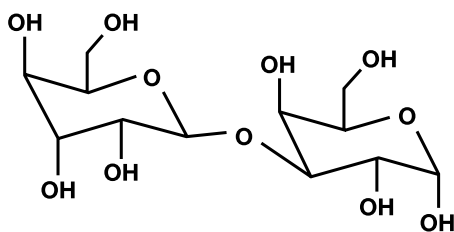


Figure 1. Structure of galactose- α ,1,3-galactose.

Molecular mechanism

The α -Gal antigen

The α -Gal epitope (Gal α 1-3Gal β 1-4GlcNAc-R, or Gal α 1-3Gal α 1-3GlcNAc-R) is a unique carbohydrate structure present in all mammals except humans and Old World monkeys (Figure 1), where it exists on the cell surface as both glycolipids and glycoproteins⁽⁵⁾. The onset of clinical symptoms in α -Gal-associated meat allergy corresponds with basophil activation, implying that it coincides with the appearance of the antigen in the bloodstream⁽⁹⁾. Lipids enter the bloodstream 3–4 hours after a meal, suggesting that the delay in symptom onset could reflect the time required for absorption and digestion of glycolipid α -Gal antigens⁽¹⁰⁾. The observation that fatty meats provoke more consistent and severe reactions is also consistent with the notion that glycolipids may play an important role^(9, 10). This hypothesis is further supported by evidence that glycolipids can elicit a robust immune response in humans⁽³⁴⁾.

However, a recent screen of IgE-binding proteins from beef and pork using sera from Japanese patients with α -Gal-associated meat allergy, identified α -Gal on the glycoproteins laminin γ -1 and the collagen α 1 (VI) chain as likely common IgE-reactive proteins in Japanese patients with beef allergy⁽¹⁸⁾.

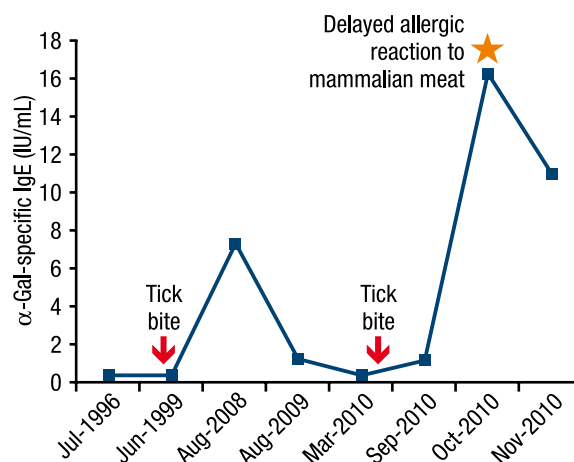


Figure 2. Levels of α -Gal-specific IgE increase after tick bites and decline with time after the bite. Adapted from (7).

Sensitization

Bites from ticks of the Ixodidae family are thought to be the principal cause of α -Gal sensitization^(10, 15), and α -Gal has been identified in the gastrointestinal tract of Ixodes ricinus⁽⁸⁾. Following a tick bite, levels of IgE to α -Gal increase and can reach a level where they induce clinical symptoms when they react with α -Gal epitopes on mammalian meat. IgE levels decrease in the absence of further tick bites, and given sufficient time, will fall to a level below which clinical reactivity is unlikely; however, levels will increase again if the individual receives further tick bites (Figure 2)^(7, 19).

Immune response

The immune response to tick-derived α -Gal epitopes appears to be mediated by an 'atypical' Th2 type immune response, characterized by elevated IgE and IgG (in particular IgG₁) to α -Gal against a background production of IgG₂⁽³³⁾. Basophils are known to be involved in initiation of Th2 responses⁽³⁵⁾, and in some patients the initial site of itching after eating meat was at the site of a prior tick bite, suggesting that basophils, mast cells, or eosinophils remain present at the bite⁽⁹⁾. Although basophil activation may mark the arrival of the antigen in the bloodstream, it is unclear if this is the cause of allergic symptoms⁽⁹⁾. Delayed basophil activation, as evidenced by CD63 expression, was observed after meat ingestion in subjects with no detectable IgE to α -Gal, but was not associated with symptoms, indicating that IgE is required for the allergic reaction⁽⁹⁾. As IgG and IgM antibodies against α -Gal are present in all immunocompetent humans, it is possible that in subjects with no IgE to α -Gal, basophils are activated via a distinct pathway, such as through binding of α -Gal complexes to Fc γ receptors⁽⁹⁾.

Comparison with other meat allergies

Meat allergy

Despite a high level of meat consumption in developed countries, allergy to meat is uncommon^(36, 37); it is normally outgrown during the first years of life and is rare

in adults⁽³⁸⁾. Meat allergy has been estimated to occur in around 3% of children and adults with food allergies⁽³⁹⁻⁴¹⁾. Allergy to beef is the most commonly reported form of meat allergy, affecting 1.5 to 6.5% of children with atopic dermatitis or food allergies^(37, 42, 43), which corresponds to a prevalence of around 0.3% in the general population⁽⁴⁴⁾.

Table 1. Features of α -Gal-mediated meat allergy, protein-mediated meat allergy, and pork-cat syndrome (1, 6, 8-9, 11-13, 20-21, 38, 45, 47-49, 52, 55)

	α-Gal-mediated meat allergy	Protein-mediated meat allergy	Pork-cat syndrome
Sensitizing allergen	α -Gal epitope from tick bite	Bovine serum albumin (Bos d 6) or immunoglobulin (Bos d 7), actin, myoglobin Chicken serum albumin (Gal d 5)	Cat serum albumin (Fel d 2)
Clinical features			
Triggers	α -Gal on mammalian meat and offal proteins, milk in some patients Gelatin from mammalian sources Co-factors can increase the sensitivity to food triggers Non-oral triggers: Cetuximab infusion, vaccines and colloids containing mammalian gelatin	Sensitizing meat proteins	Pork serum albumin
Symptoms	Often severe, ranging from generalized pruritus and urticaria, to gastrointestinal symptoms, angioedema, and anaphylaxis	Typically less severe, but range from conjunctivitis, urticaria, angioedema, and dyspnea to anaphylaxis	Typically less severe, but ranging from abdominal cramping, diarrhea, nausea, itching, hives to anaphylaxis Oral pruritus can occur during the meal
Symptom onset	Delayed reactions - generally 3-6 hours after consuming mammalian meat, but longer delays are not uncommon Co-factors can reduce the time to onset	Rapid - within 2 hours of consuming meat	Rapid – usually within 1 hour of consuming pork
Age group affected	Predominantly adults, but also children	Predominantly children	Predominantly adults and teenagers
Diagnosis			
SPT	Unreliable - many patients show negative SPT results with meat extracts and fresh meat preparations	Positive to mammalian serum albumins and beef, lamb, pork and rabbit meat (can be negative to these meats after cooking) Often positive to cow's milk	Positive to cat and other animal danders and meats
Immunoassay	Can show positive results to beef, pork, milk, cat and dog dander	Can be positive to mammalian meats (beef, lamb, pork, rabbit), serum albumins and epithelium (dog, cat, cow, sheep, pig), and to cow's milk	Can be positive to pork and beef, and mammalian serum albumins (cat, dog, cow)

Patients with meat allergy are often sensitized to cross-reactive proteins, such as serum albumin, gamma globulins, tropomyosins, and actin⁽⁴⁵⁾. Consequently, many patients show cross reactivity to animal danders in SPT and immunoassays^(38, 46), and a high proportion of beef-allergic patients also show clinical cross-reactions to cow's milk⁽³⁸⁾. In contrast with α -Gal-associated meat allergy, symptoms in individuals sensitized to protein epitopes usually appear immediately after meat is eaten^(47, 48) (Table 1).

Pork-cat syndrome

Pork-cat syndrome is a condition in which patients develop IgE to cat serum albumin that cross-react with porcine albumin and can cause allergic reactions within 30–45 minutes of eating pork⁽⁴⁹⁾ (Table 1). Most patients have a positive SPT to both cat dander and pork⁽⁴⁹⁾. There is also some cross reactivity with bovine serum albumin that results in some patients being unable to tolerate beef⁽⁴⁹⁾. There is no evidence of IgE to α -Gal in patients with pork-cat syndrome⁽²⁷⁾, and bovine serum albumin does not contain α -Gal⁽²⁰⁾.

Diagnostic considerations

Delayed onset of symptoms is the most clinically distinguishing characteristic of α -Gal-associated meat allergy, compared with protein-based meat allergies. However, accurate information on the timing of symptom onset is not always available from the patient.

Skin prick testing with commercial meat extracts and raw meats is not a reliable diagnostic test for α -Gal-associated meat allergy, as results are often negative or ambiguous^(20, 30). When positive responses are seen, skin reactions are weak, with wheals measuring less than 5 mm^(1, 2). In a series of 25 patients with IgE to α -Gal and allergic symptoms after consuming pork kidney, mammalian meat or gelatin, only two patients had positive SPT results with commercially available pork, beef, lamb, or horse meat extracts⁽¹²⁾.

α -Gal-associated meat allergy and pork-cat syndrome have several features in common that can complicate diagnosis. Both are IgE-mediated reactions triggered by mammalian meat, and can show similar responses in SPT and immunoassays with meat extracts and other animal-derived antigens due to cross-reactivity. For instance, in addition to showing positive immunoassay results for beef, pork, and lamb, most patients with α -Gal-associated meat allergy also have positive results to cat and dog extracts and cow's milk^(1, 9, 20, 50). Removal of α -Gal-specific IgE from sera reverses the positive result to both cat⁽⁵¹⁾ and cow's milk⁽²⁰⁾, confirming that binding of IgE to α -Gal



Box 2

Management of α -Gal-associated meat allergy⁽²¹⁾

- The primary management strategy is avoidance of mammalian meat, especially fatty cuts.
 - Meats to avoid include beef, pork, lamb, horse, goat, rabbit, squirrel, and venison.
 - Mammalian organs such as liver, intestine, heart, and kidney (especially pork kidney) and other mammalian products including lard, suet, and pork rinds should also be avoided.
 - Gelatin has been reported to cause severe reactions, either as jelly sweets and marshmallows or as intravenous preparations.
- Although most patients tolerate dairy products and gelatin, patients who continue to have unexplained symptoms while avoiding mammalian meat may also be advised to avoid dairy foods and gelatin.
- Avoiding additional tick bites by staying away from tick infested areas, wearing protective clothing, or using products containing N,N-diethyl-meta-toluamide may make patients less prone to symptomatic reactions.

is responsible for these positive results in patients with α -Gal-associated meat allergy, rather than co-sensitization to protein antigens.

Posthumus and colleagues recommended ImmunoCAP® testing for IgE to pork, beef, cat serum albumin and α -Gal to help distinguish patients whose symptoms were caused by pork-cat syndrome from those with α -Gal-associated meat allergy⁽⁵²⁾. Measurement of IgE antibodies against α -Gal is performed using ImmunoCAP® Allergen o215, carrying the α -Gal-containing protein bovine thyroglobulin.

As the serum level of α -Gal-specific IgE and the patient's clinical sensitivity decreases with time after a tick bite (Figure 2), some patients who avoid subsequent tick bites for 1 to 2 years may be able to tolerate mammalian meat again (19). Therefore, regular monitoring of α -Gal-specific IgE in these patients can help predict the risk of a severe allergic reaction. Berg and colleagues reported that they used in *vitro* assays to reassess the level of IgE to α -Gal every 8 to 12 months in sensitized patients⁽¹⁹⁾.

Management of α -Gal-associated meat allergy focuses mainly on avoidance of mammalian meat and further tick bites (Box 2).

Conclusions

α -Gal-associated meat allergy is a recently described syndrome in which individuals who have been bitten by ticks of the Ixodidae family become sensitized to the carbohydrate determinant galactose- α -1,3-galactose (α -Gal). The resulting IgE antibodies react with α -Gal epitopes on mammalian meat, resulting in an allergic reaction and in some cases anaphylaxis after eating meat or gelatin. A distinctive feature of this allergy is the delayed onset of symptoms, which occur 3 to 6 hours after eating meat. The delayed symptom onset is thought to reflect the appearance of glycolipid α -Gal moieties, which are believed to be involved in the allergic reaction, in the bloodstream.

Diagnosis of α -Gal-associated meat allergy may not be straightforward, especially in children, as the syndrome can be confused with protein-based meat allergies. While negative SPT results are unreliable, the syndrome can be confirmed by measurement of IgE antibodies to α -Gal.

Testing for the presence of IgE to α -Gal could identify a risk factor for medical treatment with cetuximab, gelatin-containing substances or artificial bovine blood in areas where hard body ticks are common, particularly in individuals with a history of a tick bite or demonstrated allergy to mammalian meat or gelatin.

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