Component-Resolved Diagnostics in Alpha-Gal Mediated (Red) Meat Allergy

Scientific news, opinions and reports

A novel form of IgE-mediated food allergy

In contrast to most food allergies where symptoms develop immediately or within a couple of hours after ingestion of the culprit food, an allergy to a component of red meat gives rise to symptoms that can be 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 is augmented by co-factors 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 to available meat extracts often give weak or negative results, so quantification of IgE antibodies to α-Gal in blood is the preferred diagnostic method.

Contents

The conundrum of alpha-Gal associated meat allergy

As early as 2000, the first reports of a novel and perplexing form of delayed allergic reaction to red meat emerged.[11] 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.[2,3,4] During questioning, however, patients consistently reported having eaten beef, pork, or lamb in the 3-6 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 the 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 alpha-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 alpha-Gal mediated allergies in the US was similar to that of some tick-borne diseases,[7] suggested that tick bites could be responsible for the alpha-Gal sensitization. This was confirmed by observations of increased serum IgE to alpha-Gal following a bite from certain tick species,[7] and the presence of alpha-Gal in tick intestine[8]. Important discoveries that led to our current understanding of alpha-Gal associated meat allergy are outlined in Table 1.

Characteristics of alpha-Gal-associated meat allergy

Triggers

Delayed reactions in alpha-Gal associated meat allergy are triggered by mammalian meats, including beef, pork, lamb and game, but not by chicken, turkey or fish.[1,6,13] 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.[14] Ingestion of larger quantities of meat, such as a double hamburger or a plate of barbecued meat, induced more severe reactions.[14]

It has been recorded that different types of meats can induce symptoms of varying severity. 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).[15] 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,[15] and reactions after ingestion have been severe and rapid (in 2 hours rather than 4).[11] Kidney, in particular pork kidney, contains high amounts of alpha-Gal determinants;[15] pre-incubating serum from a patient with IgE to alpha-Gal with pork kidney extract completely blocked binding of IgE antibodies to alpha-Gal in an ImmunoCAP™ assay.[16]

Gelatin

There have been reports of allergic reactions to meat-derived gelatin in patients sensitized to alpha-Gal. Many patients with alpha-Gal associated meat allergy have positive intradermal tests to gelatin,[16] and an Australian study reported a significant relationship between positive intradermal tests to gelatin and alpha-Gal associated meat allergy.[3] Individuals with alpha-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[17]. The presence of alpha-Gal on gelatin colloids has been confirmed by in vitro studies, suggesting that an IgE response to alpha-Gal underlies the observed sensitivity in these patients[3].

Some sources of symptom-inducing gelatins, such as vaccines or colloid plasma substitute, may not be obvious. Anaphylaxis has occurred following administration of zoster vaccine[18], with parenteral administration resulting in rapid rather than delayed onset; MMR and yellow fever vaccines also contain gelatin and may induce symptoms in alpha-Gal sensitized individuals[19]. Caution is advised when using products known to contain alpha-Gal, including: marshmallows, beef collagen casings, lard, bovine and porcine heart valves, pancreatic enzyme replacement, and Crotalidae polyvalent immune Fab.[19]

Table 1. Important steps in the elucidation of alpha-Gal associated meat allergy

Cetuximab allergy	Delayed anaphylaxis to mammalian meat
• Shortly after approval of cetuximab (a monoclonal antibody used in the treatment of some cancers) in 2004, a significant number of patients experienced severe hypersensitivity reactions during their first infusion.[9,10] • These reactions were more common in the southern and eastern US.[9,10] In 2007, the prevalence of severe (Grade 3–4) cetuximab-related infusion reactions at sites in the southeast US was as high as 22%, compared with national and international rates of ≤3%.[9] • Allergic patients had IgE antibodies to the alpha-Gal oligosaccharide on the Fab portion of cetuximab that were present in patients' serum before therapy.[11,12] • At the time, it was not known what caused sensitization to alpha-Gal or why the number of individuals with IgE to alpha-Gal was higher in the southeast US compared with other regions and countries.	• 2000: At least 2 groups reported cases of allergy that started after the tick bites.[11] • 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 alpha-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 alpha-Gal in both allergies.[7] • Australian investigators noted that 24 of 25 patients in their case series had a history of large local reactions to tick bites, and postulated that patients became sensitized to alpha-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 alpha-Gal was prevalent in areas where the Lone Star tick (Amblyomma americanum) was common.[7] • Investigation showed a correlation between the presence of IgE to alpha-Gal and to tick salivary proteins. An increase in serum IgE to alpha-Gal was demonstrated following tick bites.[7]

Cetuximab

As outlined in Table 1, the monoclonal antibody cetuximab contains the alpha-Gal epitope on its Fab fragment. Severe reactions to cetuximab infusions have been reported in patients with IgE to alpha-Gal.[12] Physicians should therefore be aware of the risk of allergic reactions to cetuximab in individuals with demonstrated IgE to alpha-Gal, or with delayed meat allergy or a history of tick bites.[20]

Symptoms

Unlike most protein-based food allergies, where symptoms appear rapidly, often within minutes of ingestion,[21,22] onset of symptoms in alpha-Gal associated meat allergy is typically delayed by 3–6 hours or more.[1,11] This delay in onset after ingestion has been confirmed in provocation tests.[13] A few patients, however, experience a shorter delay, with symptoms appearing within 2 hours.[23] Onset does not appear to be related to the patient's titer of soluble IgE to alpha-Gal,[24] which has led to speculation that the time to the reaction could depend on the condition of the patient's gastrointestinal tract.[23] Route of administration also affects time to symptom onset. Parenteral administration of gelatin-containing medicines can cause rapid anaphylaxis.[19]

Patient-reported symptoms range from generalized skin reactions (pruritus and urticaria), to angioedema, respiratory distress and anaphylaxis,[1,6,13,25] with gastrointestinal symptoms a distinctive feature of the syndrome.[26] Some patients will report nausea, diarrhea, or indigestion, however, the most common symptom preceding a reaction is itching.[1] The development of alpha-Gal sensitization has been linked to a history of tick bites that have itched for 2 weeks or longer.[11] 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.[13] Presence of serum IgE to alpha-Gal was not associated with chronic respiratory symptoms, such as lung inflammation or asthma.[27]

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.[16,19,28] This is thought to occur by increased allergen absorption via dysregulation of tight junctions in the gastrointestinal epithelium, and possibly by increased cellular activation.[28]

Co-factors lower the threshold for the appearance of clinical symptoms in alpha-Gal associated meat allergy. For example, a patient sensitized to alpha-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 1 hour after eating.[17] Co-factors were present in 10 of 14 patients in a series who experienced anaphylaxis after consuming pork kidney.[15] Co-factors may also reduce the delay in appearance of symptoms; one patient sensitized to alpha-Gal experienced two episodes of anaphylaxis that occurred while exercising within 2 hours of eating beef.[1] Indolent systemic mastocytosis may also provoke more severe clinical reactions to red meat even with lower sIgE levels of alpha-Gal.[29]

Understanding the role of co-factors in the development of anaphylaxis can lower the risk of a severe allergic reaction in meat-allergic patients[20]. To mitigate this effect, Morisett 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[15]. Alpha-Gal sensitization has also been linked to atheroma burden and plaques[30]. In 118 subjects who underwent cardiac catherization, 26% had IgE levels >0.1 kU/L to alpha-Gal, and atheroma burden was significantly higher ($P<0.02$) in those who were sensitized to alpha-Gal, regardless of other risk factors for coronary artery disease. The strongest association ($P<0.001$) was for those <65 years old. This finding raises the possibility that alpha-Gal sensitization is a modifiable risk for development of atherosclerosis.[30]

Epidemiology

To date, cases of alpha-Gal associated meat allergy have been reported in the southeastern[27] northeastern and upper midwestern US,[31] Australia,[3,6] Asia,[32,33,34] and in several European countries, including France,[4,15,35] Spain,[36] Germany,[37] Switzerland,[38] and Sweden.[39]

On all continents, the ticks responsible for sensitization to alpha-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 (Figure 1) are the predominant, if not exclusive, cause of alpha-Gal sensitization.[7] There is a significant correlation between IgE to Lone Star tick bites and antibodies to alpha-Gal.[11] Warming temperatures and the availability of desirable hosts favor the continued range expansion of Lone Star ticks,[31] with reported sightings from Maine to Florida, in Wisconsin,[40] and as far west as Texas, Oklahoma and Colorado.[41] Borrelia burgdorferi, the tick that carries Lyme disease, does not appear to induce IgE to α-Gal and its bites are not associated with itching.[11] In Australia, the suspected tick is Ixodes holocyclus,[6] whereas in Europe it is Ixodes ricinus,[8] and Hematophagous ixodidae in Asia.[32]

As expected, the prevalence of detectable IgE antibodies to alpha-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 alpha-Gal, compared with only 0.7% in the north of the country where tick bites are rare.[39] 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 alpha-Gal antibodies may display red meat allergy.[14] The prevalence of IgE to alpha-Gal among Danish and Spanish adults was estimated at 5.5% and 8.1%, respectively, for levels ≥0.1 kUA/L, and at 1.8% and 2.2%, respectively, for levels ≥0.35 kUA/L.[42] Based on a survey of 1,000 Americans, 7.7% reported a history of an anaphylactic reaction, with an estimated 5.1% of that population having “probable anaphylaxis” and 1.6% “very likely” anaphylaxis.[43] 218 of the reported cases met criteria for anaphylaxis, and 85 were associated with a definitive cause; alpha-Gal was cited in 28/85 (33%) of cases with a known cause, more frequently than other food allergies (24/85 cases, 28%).[43]

Adult onset originally appeared to be a characteristic of alpha-Gal associated meat allergy.[1] In a series of 29 patients with alpha-Gal associated meat allergy in Japan, 21 were over 60 years of age.[23] Nevertheless, cases of alpha-Gal associated meat allergy have also been observed in children.[11,25] In a case series of 51 children ages 4-17 years, who had possible delayed allergic reactions to mammalian foods, 45 had high serum IgE levels to alpha-Gal, which correlated with beef IgE levels.[11] Questioning revealed a history of symptoms 3-6 hours after eating meat and of tick bites. Among adults and children, and atopic and non-atopic individuals, the levels of α-Gal IgE and the severity of reactions were similar.[44]

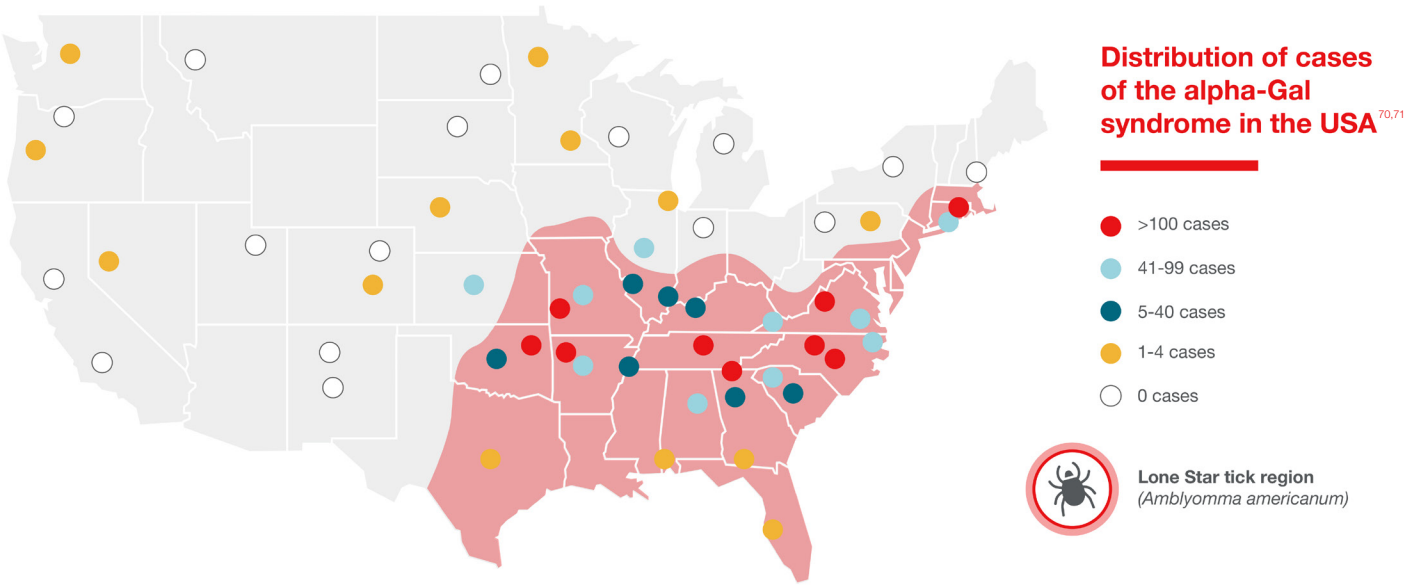

Figure 1. The Lone Star tick. Warming temperatures and the availability of desirable hosts favor the continued range expansion of Lone Star ticks,[31] with reported sightings from Maine to Florida, in Wisconsin,[40] and as far west as Texas, Oklahoma and Colorado.[41] (Centers for Disease Control and Prevention photo and map)

Adapted from Platts-Mills T. the Alpha-gal Syndrome: IgE responses to galactose alpha-1, 3-galactose induced by bites from lone star ticks. Presentation presented at AAAAI 2019.

Blood group phenotype

The B blood group phenotype appears to confer a protective effect against production of high levels of IgE to alpha-Gal, with a strong relationship between alpha-Gal associated meat allergy and absence of the B blood group phenotype.[39,44,45]

A study of the relationship between the B blood group phenotype and IgG and IgE responses to alpha-Gal found that none of the subjects with the B+ phenotype expressed IgE to alpha-Gal.[46] 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 prevalence of 18% in the Swedish population.[39] The same study reported that in a group of healthy blood donors and patients with Lyme disease with detectable IgE to alpha-Gal, the levels of IgE against alpha-Gal were very low among those with the blood group B phenotype.[39] The mechanism of this protective effect has not been fully elucidated. However, the structure of the alpha-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 alpha-Gal antigens.[46]

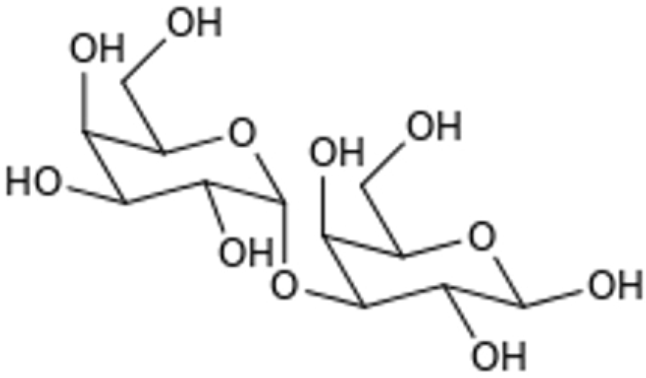

Figure 2. Structure of galactose-a1,3-galactose.

Molecular mechanisms

The alpha-Gal antigen

The α-Gal epitope (Galα1-3Galβ1-4GlcNAc-R) is a unique carbohydrate structure present in all mammals except humans and Old World monkeys (Figure 2), where it exists on the cell surface as both glycolipids and glycoproteins.[5] The onset of clinical symptoms in alpha-Gal associated meat allergy corresponds with basophil activation, implying that it coincides with the appearance of the antigen in the bloodstream[13]. 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 alpha-Gal antigens. The observation that fatty meats provoke more consistent and severe reactions is also consistent with the notion that glycolipids may play an important role.[13,14] This hypothesis is further supported by evidence that glycolipids can elicit a robust immune response in humans.[47] However, a recent screen of IgE-binding proteins from beef and pork, using sera from Japanese patients with alpha-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 these patients with beef allergy.[23]

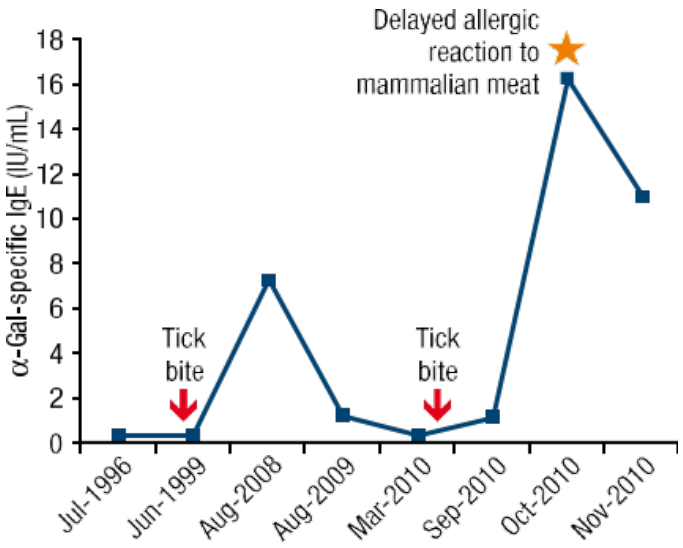

Figure 3. Levels of alpha-Gal specific IgE increase after tick bites and decline with time after the bite. Adapted from.[7]

Sensitization

Bites from ticks of the Ixodidae family are thought to be the principal cause of alpha-Gal sensitization,[14,20] and alpha-Gal has been identified in the gastrointestinal tract of Ixodes ricinus.[8] Following a tick bite, levels of IgE to alpha-Gal increase and can induce clinical symptoms when they react with alpha-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 3).[7,24]

Immune response

The immune response to tick-derived alpha-Gal epitopes appears to be mediated by an 'atypical' Th2 type immune response, characterized by elevated IgE and IgG (in particular IgG1) to alpha-Gal against a background production of IgG2.[46] Basophils are known to be involved in initiation of Th2 responses[48], 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 site.[13] Although basophil activation may mark the arrival of the antigen in the bloodstream, it is unclear if this is the cause of allergic symptoms.[13] Delayed basophil activation, as evidenced by CD63 expression, was observed after meat ingestion in subjects with no detectable IgE to alpha-Gal, but was not associated with symptoms, indicating that IgE is required for the allergic reaction.[13] As IgG and IgM antibodies against alpha-Gal are present in all immunocompetent humans, it is possible that in subjects with no IgE to alpha-Gal, basophils are activated via a distinct pathway, such as through binding of alpha-Gal complexes to Fcγ receptors.[13]

Comparison with other meat allergies

Meat allergy

Despite a high level of meat consumption in developed countries, allergy to meat is uncommon;[49,50] it is normally outgrown during the first years of life and is rare in adults.[51] Meat allergy has been estimated to occur in around 3% to >7% of children and adults with food allergies.[52,53,54] 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,[51,54,55] which corresponds to a prevalence of around 0.3% in the general population.[56]

Table 2. Important steps in the elucidation of alpha-Gal associated meat allergy

	α-Gal-mediated meat allergy[13,19]	Protein-mediated meat allergy[16,19,49,51,57,58,59,62]	Pork-cat syndrome[19,60,61]
Sensitizing allergen	Alpha-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	Alpha-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 (GI) symptoms, angioedema, and anaphylaxis	Typically less severe, but range from conjuctivitis, urticaria, angioedema, and dyspnea to anaphylaxis	Pork serum albumin 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
Diagnostic Considerations[63,69,1]	Skin prick tests (SPT) to commercially available and fresh meat extracts may be unreliable and falsely negative Specific IgE (sIgE) testing to whole allergen beef, pork, lamb may be positive Cat and/or dog dander tests (SPT and sIgE) may be positive due to alpha-Gal present in epithelium	Immediate reactions to meat Often positive to cow's milk, especially for beef sensitization May be sensitized to one or more mammalian meats (e.g. beef, lamb, pork, rabbit) May be sensitized to serum albumins and therefore positive to whole extract	Reactions to pork typically within 1 hr Can be positive to pork and beef whole extracts Some cases with additional reactions to beef Consider testing mammalian serum albumins (e.g.cat Fel d 2) as these may be the pre-existing sensitization

Patients with meat allergy are often sensitized to cross-reactive proteins, such as serum albumin, gamma globulins, tropomyosins, and actin.[57] Consequently, many patients show cross-reactivity to animal danders in SPT and immunoassays,[57,63] and a high proportion of beef-allergic patients also show clinical cross-reactions to cow's milk.[51] In contrast with alpha-Gal associated meat allergy, symptoms in individuals sensitized to protein epitopes usually appear immediately after meat is eaten[58] (Table 2).

Pork-cat syndrome

Pork-cat syndrome is a condition in which patients develop IgE to cat serum albumin that cross-reacts with porcine albumin and can cause allergic reactions within 20–45 minutes of eating pork[60,61] (Table 2). Most patients have a positive SPT to both cat dander and pork.[60] There is also some cross- reactivity with bovine serum albumin that results in some patients being unable to tolerate beef.[60] There is no evidence of IgE to alpha-Gal in patients with pork-cat syndrome,[35] and bovine serum albumin does not contain alpha-Gal.[25]

Diagnostic considerations

Delayed onset of symptoms is the most clinically distinguishing characteristic of alpha-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 alpha-Gal associated meat allergy, as results are often negative or ambiguous.[25,38] 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 alpha-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.[16] Alpha-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 alpha-Gal associated meat allergy also have positive results to cat and dog extracts and cow's milk.[1,13,25,64] Removal of alpha-Gal specific IgE from sera reverses the positive result to both cat[65] and cow's milk,[25] confirming that binding of IgE to alpha-Gal is responsible for these positive results in patients with alpha-Gal associated meat allergy, rather than co-sensitization to protein antigens.

Posthumus and colleagues utilized ImmunoCAP testing and suggest performing immunoassay testing for sIgE to pork, beef, cat serum albumin and alpha-Gal to help distinguish patients whose symptoms were caused by pork-cat syndrome from those with alpha-Gal associated meat allergy.[61] Measurement of IgE antibodies against alpha-Gal is performed using ImmunoCAP® Allergen o215, carrying the alpha-Gal containing protein bovine thyroglobulin. Alpha-Gal measurements of ≥2 IU/mL or >2% of total IgE make the diagnosis very likely.[19] In a study of 261 children and adults with red meat allergy, the relationship between alpha-Gal IgE and total IgE was strong in those with and without atopy (both $P<0.001$), suggesting that alpha-Gal sIgE contributes to total IgE regardless of atopic sensitization.[44] Serum tryptase testing can also be helpful in identifying people who may have more severe reactions to allergic triggers such as tick bites.[66] Elevated baseline tryptase levels can be indicative of mastocytosis.[20,69] Final confirmation of a correct alpha-Gal syndrome diagnosis relies on the clinical response to avoiding red meat (or other alpha-Gal containing source).

As the serum level of alpha-Gal specific IgE and the patient's clinical sensitivity decreases with time after a tick bite (Figure 3), some patients who avoid subsequent tick bites for 1 to 2 years may be able to tolerate mammalian meat again.[24] Berg and colleagues reported that they used in vitro assays to reassess the level of IgE to alpha-Gal every 8 to 12 months in sensitized patients.[24]

Management of alpha-Gal associated meat allergy focuses mainly on avoidance of mammalian meat and further tick bites (Table 3). Many patients tolerate chicken, turkey and fish without problems.[67] Others may need to eliminate dairy and gelatin-containing products from their diets.[68]

Table 3. Management of alpha-Gal associated meat allergy[26]

• The primary management strategy is avoiding mammalian meat, especially fatty cuts. – Avoid meats, including beef, pork, lamb, horse, goat, rabbit, squirrel, and venison. – Avoid mammalian organs such as liver, intestine, heart, and kidney (especially pork kidney) and other mammalian products including lard, suet, and pork rinds. – Gelatin has reportedly caused 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 may also be advised to avoid dairy foods and gelatin.
• Avoid additional tick bites by staying away from tick-infested areas, wearing protective clothing, or using products containing N,N-diemethyl-meta-toluamide may make some patients less prone to symptomatic reactions.

Conclusions

Alpha-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 (alpha-Gal). The resulting IgE antibodies react with alpha-Gal epitopes on mammalian meat, resulting in an allergic reaction and in some cases anaphylaxis after eating mammalian meat or gelatin. A distinctive feature of this allergy is the delayed onset of symptoms, which typically occur 2-6 hours after eating meat. The delayed symptom onset is thought to reflect the appearance of glycolipid alpha-Gal moieties, which are believed to be involved in the allergic reaction, in the bloodstream.

Diagnosis of alpha-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 correlating clinical history with measurement of specific IgE antibodies to alpha-Gal. If alpha-Gal sIgE results represent >2% of total IgE, a diagnosis of alpha-Gal associated meat allergy is very likely.[19] Serum tryptase testing can help identify people who may have more severe reactions to tick bites.[66] Finally, testing for the presence of IgE to alpha-Gal could identify a risk factor for medical treatment with cetuximab, eating gelatin-containing substances, or using artificial bovine tissue 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.[19]

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