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Delayed Anaphylaxis to Red Meat in Patients with IgE Specific for Galactose alpha-1,3-Galactose (alpha-gal)

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Abstract

Anaphylaxis is a severe allergic reaction that can be rapidly progressing and fatal. In instances where the triggering allergen is not known, establishing the etiology of anaphylaxis is pivotal to long-term risk management. Our recent work has identified a novel IgE antibody (Ab) response to a mammalian oligosaccharide epitope, galactose-alpha-1,3-galactose (alpha-gal), that has been associated with two distinct forms of anaphylaxis: (1) immediate onset anaphylaxis during first exposure to intravenous cetuximab, and (2) delayed onset anaphylaxis 3–6 h after ingestion of mammalian food products (e.g., beef and pork). The results of our studies strongly suggest that tick bites are a cause, if not the only significant cause, of IgE Ab responses to alpha-gal in the southern, eastern and central United States. Patients with IgE Ab to alpha-gal continue to emerge and, increasingly, these cases involve children. This IgE Ab response cross-reacts with cat and dog but does not appear to pose a risk for asthma; however, it may impair diagnostic testing in some situations.

Keywords

Anaphylaxis; Delayedanaphylaxis; Alpha-gal; Galactose; Food allergy; IgE; Mammalian meat; Tick bites; Asthma; Red meat

Introduction

When the syndrome of delayed anaphylaxis to red meat was first described in 2009, the report included details on 24 cases [1]. Within a year, it was obvious that the cases should be counted in hundreds rather than dozens. By 2012, it was clear that there are thousands of cases across a large area of the southern and eastern US [2•]. Furthermore, it is clear that the same syndrome is present in several countries in Europe and also in Australia [3–6]. The syndrome came to light because of an enigmatic regional prevalence of anaphylactic

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reactions to the monoclonal antibody cetuximab [7]. It was investigation of those cases which established that they were causally related to pre-existing IgE antibodies to an oligosaccharide on the FAB portion of the monoclonal Ab [8]. That oligosaccharide, galactose alpha-1,3-galactose (alpha-gal), is a major blood group substance of the non-primate mammals, and is well recognized as a target of IgG antibodies which are present in the serum of all immunocompetent individuals [9]. Since that time, it has become clear that these IgE antibodies are strongly associated with the syndrome of delayed anaphylaxis to red meat [1], and also that the predominant, if not exclusive, cause of these IgE antibodies in the USA is bites from the lone star tick *Amblyomma americanum* [10••].

Section I

Geographic Distribution of IgE Antibodies to Alpha-gal and Delayed Anaphylaxis

a) Within the United States—The distribution of these antibodies first became clear from the states in which reactions to cetuximab were occurring, i.e. Virginia, North Carolina, Tennessee, Arkansas, Oklahoma, and Missouri [8]. Subsequently, it has become clear that the syndrome of delayed anaphylaxis to red meat is most common in these same states [1]. In fact, it was the similarity between the region for reactions to cetuximab and the maximum incidence of rocky mountain spotted fever that suggested that tick bites might be relevant to these reactions [10••]. Subsequently, evidence came from many different sources supporting the idea that tick bites were the primary cause of those antibodies in the United States [2•, 10••, 11]. Evidence that the lone star tick is the primary cause has come from individual cases, from the correlation between IgE antibodies to alpha-gal, and IgE antibodies to this tick, and from the known distribution of the tick [10••]. This tick is being followed closely by the Centers for Disease Control and Prevention (CDC) because it is the primary vector of Ehrlichiosis [12–14]. Interestingly, there is good evidence both from the CDC and also from the army that the lone star tick is steadily expanding its range [15•].

While it is easy to argue that, with the increasing number of deer, ticks and tick bites have caused a progressive increase in the disease, that would be more difficult to prove. We have case histories and serological evidence that the IgE antibodies and the syndrome existed in the 1980s. On the other hand, it would be difficult to estimate the prevalence of a syndrome 30 years before it had been described. It is important to remember that there are two distinct elements: the production of IgE antibodies and the urticarial or anaphylactic reactions to red meat.

b) Prevalence and distribution of delayed anaphylaxis outside the USA—The first report that tick bites could give rise to allergic reactions to meat was made by Dr. Sheryl Nunen to the Sydney Allergy Society in 2006. She published those results in 2009, and subsequently Mullins et al. confirmed in 2012 that patients in Australia with reactions to mammalian meat have IgE Ab to alpha-gal [3, 4]. By contrast, there were already reports from Europe of similar cases [5, 6]. In particular, the food allergy group in Nancy in France reported cases in 2009, and have recently reported evidence that kidneys are particularly rich is alpha-gal [16••]. Reports of delayed anaphylaxis have also come from Dr. Van Hage and her colleagues in Stockholm and from Dr. Uta Jappe in Germany [6, 17]. In each case, they have confirmed that the patients had serum IgE antibodies specific for galactose-alpha-1,3-galactose. Although cetuximab is not as widely used in Europe as in the United States, there have been reports of immediate reactions including a recent death from France [18]. The tick species that appears to be responsible for these responses in France is *Ixodes ricinus*, while in Australia it is *Ixodes holocyclus* [3, 4, 16••].

c) IgE antibodies to alpha-gal in countries where helminth and ecto-parasites are common—Oligosaccharides are well recognized as a target for antibody response to

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helminths [19, 20]. In addition, it is well recognized that helminth and ecto-parasites such as scabies can give rise to IgE ab responses. Two reports from Africa have shown the presence of IgE antibodies to alpha-gal in sera from children and adults [21, 22]. Dr. Sibanda in Zimbabwe working with Drs. Van Hage and Valenta have reported that IgE antibodies to alpha-gal are common in Harare, but they did not discuss reactions to meat [23 ••]. Similarly, we have reported a high prevalence of IgE antibodies to alpha-gal among children in a rural village 100 miles north of Nairobi [10 ••]. Interestingly, in both cases, the antibodies were initially thought to be specific for cat [21, 23••]. In the Kenyan village, we were not aware of reactions to meat, but the children were not directly questioned [21]. At present, it would be difficult to identify the stimulus that gives rise to IgE antibodies to alpha-gal in sub-Saharan Africa—possible candidates include cestodes, nematodes, scabies, ticks, and a variety of other ecto-parasites. What is potentially very interesting is that there are no reports of delayed anaphylactic or urticarial reactions to red meat in sub-Saharan Africa. If this is true, it could provide an important insight into the mechanism of the delayed reactions.

Section II

IgE Antibodies to Alpha-gal are not Associated with Rhinitis or Asthma

In the early studies on patients, who presented with delayed anaphylaxis to red meat, two things were obvious: (1) these patients gave positive skin tests and blood tests for cat, and (2) they did not report allergic symptoms related to cat exposure [1]. From several types of study, it became clear that the sensitivity to cat extracts could be explained by IgE antibodies binding to alpha-gal on cat-derived proteins. The best defined of these proteins is cat IgA. In 2007, Gronlund and his colleagues in Sweden recognized the presence of an oligosaccharide epitope on cat IgA [24]. After the recognition of IgE Ab to alpha-gal, it was established that the epitope on cat IgA was alpha-gal [17]. In addition, it is well established that all mammalian thyroglobulins are heavily “decorated” with alpha-gal [25]. By contrast, many proteins which are important targets for IgE antibody responses, such as Fel d 1 and cat albumin, are not glycosylated with alpha-gal [17]. Recently, we have investigated a large group of patients, who presented with delayed symptoms after eating red meat, for history of symptoms, lung function, and evidence of lung inflammation. The results provide compelling evidence that IgE Ab to alpha-gal do not create a risk for asthma [2•]. Initially, we found that in vitro assays for IgE Ab to cat extract were consistently positive in patients with IgE to alpha-gal [1]. However, this is much clearer using epithelial extracts which include multiple proteins present in the pelt than with extracts made from “dander” only (Fig. 1). Recently, the immunoCAP assay for IgE to cat was changed to become purely dander, and as a result it is in effect an assay for Fel d 1, and may underestimate IgE to cat albumin or alpha-gal [2•].

The results on asthma included a study on acute asthma in the University of Virginia emergency department, where we had previously found confusing data, with a higher than expected prevalence of IgE to cat among controls [26, 27]. Further analysis of those sera showed that the IgE antibodies to cat included IgE to both alpha-gal and Fel d 1. The IgE to alpha-gal showed no association with asthma while IgE Ab to Fel d 1 was highly significantly associated with asthma [2•]. The results together provide strong evidence that the risk of asthma is related to protein allergens which are inhaled (Fig. 1). Equally, the evidence argues that IgE antibodies to alpha-gal provide an excellent model of the kind of IgE responses that can be induced by parasites but are not related to rhinitis or asthma.

Interesting, the studies on the relevance of ticks and those on the risk of asthma provided some insight into the prevalence of these IgE antibodies in the community. The apparent prevalence in Virginia, Tennessee, and North Carolina may be as high as 10 % [10••]. This

raises a question to which we only have tentative answers, that is what proportion of subjects with IgE Ab to alpha-gal experience urticaria or anaphylactic reactions to red meat. Our best estimate from the number of cases in central Virginia is that the true value is unlikely to be greater than 10 %.

Section III

Description of Pork–Cat Syndrome

Despite meat being an important source of protein in western diets, development of meat allergy is uncommon [28]. This paradox may not be unexpected for mammalian meat, however, as the extensive homology of plasma and tissue proteins across mammalian species decreases the likelihood of a specific IgE response [29, 30]. In fact, when clinically relevant reactivity to meats has been demonstrated, the results point to cross-reactivity among the identified proteins (e.g., bovine serum albumin, serum gamma globulins, actin, and tropomyosins) and not to a sensitization with meat-specific epitopes [31]. The syndrome of delayed anaphylaxis due to IgE Ab to alpha-gal is different in that the IgE antibodies bind to a specific oligosaccharide which is present on proteins and lipids from a large number of non-primate mammals. Among the cross-reactive syndromes, however, is the notable “pork–cat syndrome” [32, 33]. In this uncommon syndrome, patients develop an IgE Ab response specific for cat serum albumin that cross-reacts with porcine albumin and can lead to severe or even fatal allergic reactions when pork is consumed [32–34]. Interestingly, the reported cases of pork–cat syndrome are largely European. In our ongoing evaluation of delayed anaphylaxis or urticaria after the consumption of mammalian meat due to IgE Ab to alpha-gal [1], we have evaluated sera from numerous patients with suspected “meat allergy”. Mainly because of this focus, we have identified several cases of pork–cat syndrome in the US.

Published data regarding pork–cat syndrome have suggested that sensitization to cat albumin represents the primary event in the development of the cross-reactive IgE [33]. In most instances, patients with pork–cat syndrome have cat exposure (often ownership in our experience); positive responses on skin test to cat dander or pork; and report inconsistent (but not delayed) reactions after eating pork. The fact that reactions are not delayed has been an important clue in our evaluation of patients as this aspect is *not* in keeping with symptoms following red meat exposure in patients with IgE Ab to alpha-gal [1]. Moreover, in general patients with pork–cat syndrome, neither react to beef nor have serum evidence of sensitization [32, 33]. Again, this creates a distinction from patients with IgE Ab to alpha-gal, where serum IgE to beef is uniformly present [1].

Pork–cat syndrome is similar to other food allergies in that a range of presentations are seen (from oral itching to anaphylaxis), and the clinical symptoms are not consistently predicted by the titer of IgE to the allergen, cat serum albumin. Similar to delayed anaphylaxis from IgE Ab to alpha-gal, pork–cat syndrome can affect children and adults. Although pork–cat syndrome does not appear to be related to tick bites, both syndromes do not arise early in life: most reported patients are older than age 5 with the majority being adults or teens [32–34]. It appears that the primary sensitization to cat serum albumin develops over time and, therefore, the onset of a “new” food allergy in an older child or adult may merit consideration of pork–cat syndrome as a diagnosis, especially if a history of tick bites is absent.

Interestingly, and not unusual for meat allergy, patients do not report reactions with each instance of eating pork. Hilger et al. also address this point and, further, state that only one-third of appropriately sensitized patients report allergic symptoms in relation to pork consumption [33]. This has been in keeping with our experience and may be due to high

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cooking temperatures which can cause the albumin to denature [33]. In patients with pork–cat syndrome, reactions to pork begin soon after eating the meat. Both pork–cat and alpha-gal food allergies are IgE-mediated, involve mammalian meat, and can show similar responses with certain skin tests and immunoassays; however, symptoms from pork–cat syndrome usually occur within 30–45 min and can occur as rapidly as oral itching during the meal. Due to the inconsistency of these reactions (likely owing to the preparation of the meat), there may not be a simple or obvious pattern to suggest that pork is the culprit food. Hence, if a careful history reveals the possibility that mammalian meat could be associated with episodes, we suggest performing immunoassay testing for sIgE to pork, beef, cat serum albumin, and alpha-gal. Further investigations may be required, but this simple panel would identify patients whose symptoms were most likely to be explained by pork–cat syndrome.

Section IV

IgE Ab to Alpha-gal in Children

One of the interesting aspects recently of delayed meat allergy has been the emergence of numerous cases in children. While we had diagnosed children with IgE Ab to alpha-gal in central Virginia, we have now been made aware of children presenting with IgE Ab to alpha-gal in numerous centers throughout the eastern and central United States. Colleagues at Duke University (Dr. Michael Land and Dr. Moira Breslin), Kansas City Children's (Dr. Paul Dowling and Dr. Tara Federly) and in East Hampton, New York (Dr. Erin McGintee) have diagnosed pediatric patients with IgE Ab to alpha-gal and the characteristic delayed reactions to mammalian meat. In most instances, these children were seen by allergists; however, a few of the cases were diagnosed in emergency departments. Unlike their adult counterparts who frequently present with anaphylaxis, it has been our experience that the majority of children with this syndrome present with urticaria rather than acute episodes of delayed anaphylaxis. In keeping with published data regarding tick bites giving rise to the IgE Ab to alpha-gal in adults [15•], children with alpha-gal allergy also report a history of tick bites (unpublished data).

Children who develop IgE Ab to alpha-gal may have positive skin, intradermal or immunoassay, testing to milk, beef, pork, cat, or dog [11]. It is important to understand that many children suffer from milk allergy, but IgE to alpha-gal is distinct from the more traditional, protein-based cow's milk allergy. Alpha-gal-related reactions are present in older children, many of whom have no history of either food allergy or any allergic disease [1]. Clinicians should recognize that the carbohydrate moiety galactose-alpha-1,3-galactose is found in mammalian milk as evidenced by the positive immunoassay results to cow's milk and goat's milk. Therefore, in a patient who has an apparent new onset milk allergy over the age of 5, IgE Ab to alpha-gal should be considered as an alternative diagnosis to protein-based milk allergy. In our experience, we have not a priori removed milk or dairy products from the diet of adults with this syndrome if they have previously tolerated these products. We have continued a similar approach in the pediatric population, unless the allergic episodes persist, at which time we would suggest removing dairy products from the diet.

While there are multiple potential causes for both acute and chronic urticaria, as well as angioedema and idiopathic anaphylaxis, physicians should keep the syndrome of delayed reactions to mammalian meat in mind in pediatric patients. IgE Ab to alpha-gal should be diagnostically considered in children with chronic urticaria, angioedema, or idiopathic anaphylaxis, particularly in those patients living in areas where the lone star tick is common or where the history is consistent with the disease syndrome, including delayed symptoms after ingestion of beef, pork, lamb, or even milk.

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Section V

Delayed Reactions: Clinical Experience and Impressions

Since establishing the assay for IgE Ab to alpha-gal, large numbers of sera have been screened. The results showed that these IgE Ab were regionally distributed and that they were also associated with a novel form of anaphylaxis. As mentioned, these patients reported delayed symptoms after eating mammalian meat but they had had no trouble with chicken, turkey, or fish [1, 11, 35]. Thus, their symptoms matched the specificity of IgE antibodies present in their serum, which accurately reflected the known distribution of alpha-gal in mammals [1, 36]. The nuances of the delayed reactions seem to reflect that dose, temporal proximity to tick bites and composition of meat are important in influencing the allergic reactions. Food challenge studies with research subjects have shown that a relatively small amount of mammalian meat (i.e. a single strip of bacon) is frequently tolerated without clinical evidence of a reaction. Large doses are not required, however, as two pork sausage patties (~86 g) reliably induces clinical symptoms in our challenge studies. When patients and subjects do consume larger doses of mammalian meat, such as a double hamburger, rack of ribs, or a plate of barbecue, the reactions are often more severe in nature with several organ systems affected (i.e. anaphylaxis).

Similarly, food challenge studies and several hundred case descriptions have taught us that fattier meats (or mammalian products such as pork rinds) provoke episodes more consistently and the reactions are more severe. In fact, many patients describe having eaten lean meats such as deli ham or venison tenderloin without any evidence of a reaction, whereas having spare ribs the same week has led to emergency treatment. Another facet of the mammalian meat syndrome is that reactions to red meat, and even dairy, can be easier to elicit in the setting of recent tick bite(s) (1–4 weeks). The IgE Ab to alpha-gal appears to decrease over time, but this trend can be reversed by additional tick bites [10••]. Thus, patients can be led to believe that they are no longer allergic to mammalian meat because they have eaten small amounts of meat without reactions (likely, their IgE Ab to alpha-gal has fallen quite low). Overall, the factors which feed into the equation to produce a reaction are clearly complex and variable, especially in the setting of an IgE Ab to alpha-gal that may ‘naturally’ decrease over time. It is not surprising that many of these cases have only been diagnosed over the course of years.

The reason(s) for the 3–6-h delay in this IgE-mediated food allergy has not yet been elucidated. Given the apparent role for lipids in producing the clinical reaction, it may well be that absorption of lipid is the rate-limiting step in the delay. Biochemically, fats are absorbed and processed much differently than are carbohydrates and proteins. Fats ultimately enter the bloodstream via the thoracic duct 3–4 h after a meal. The conversion and processing of fats to chylomicrons and then further in LDL particles of various sizes may also explain a portion of the delay. Alternatively, chylomicrons themselves may transport alpha-gal antigens from the gut and intestinal epithelium via mesenteric lymph nodes to the circulation [37]. Intestinal epithelial cells have been postulated to secrete antigen on newly formed chylomicrons [37], a process that could also help to explain the delayed response to mammalian meat in patients with IgE Ab to alpha-gal.

Conclusions

The discovery of IgE Ab to the oligosaccharide galactose alpha-1,3-galactose has made it possible to investigate several novel aspects of allergic disease. These IgE Ab bind to a wide range of mammalian proteins, and we recognized the syndrome of “delayed anaphylaxis to mammalian meat” [1, 11]. However, the most interesting feature of the reactions may be that first symptoms occur 3–6 h after eating meat and would normally be regarded as

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‘spontaneous’ or ‘idiopathic’ anaphylaxis. Understanding the factors that control the delay may provide real insight into the factors that control anaphylaxis. Moreover, understanding how ticks induce this form of response will be important as we explore the control of IgE Ab responses in general.

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Abbreviations

alpha-gal	galactose-α-1,3-galactose
Ab	antibody

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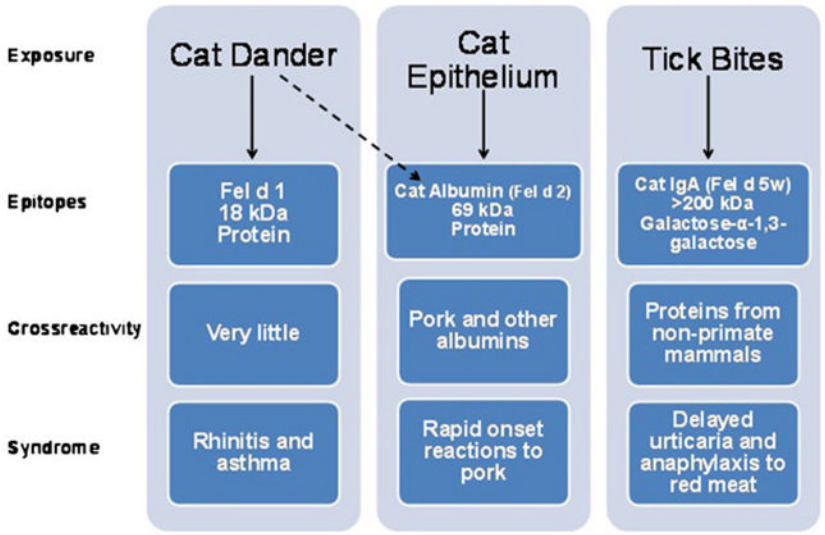

Fig. 1.
Comparison of cat exposure (direct or indirect) and the IgE response to cat-related proteins in terms of epitope, cross–reactivity, and the allergic syndrome

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