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Red meat allergy in children and adults

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Abstract

Purpose of Review: To highlight recent advances in our understanding of the clinical features, prevalence and pathophysiology of red meat allergy.

Recent findings: Allergic reactions to red (ie, mammalian) meat have historically been considered rare and described primarily in young atopic children. It is now clear that red meat allergy is not uncommon in some parts of the world in other age groups. Strikingly, the majority of these cases relate to specific IgE to galactose- α -1,3-galactose (α -Gal), an oligosaccharide of non-primate mammals. The mechanism of sensitization in this syndrome relates to bites of certain hard ticks and the clinical reactions often have a delay of 3–6 hours. An additional form of red meat allergy relates to inhalant sensitization to mammalian proteins. The best characterized example involves cat-sensitized subjects with specific IgE to cat serum albumin who can react to ingested pork because of cross-sensitization to pork serum albumin.

Summary: Red meat allergy is more common than previously appreciated and relates to at least three different forms that are distinguished by mechanisms of sensitization and have characteristic clinical and immunologic features.

Keywords

red meat allergy; IgE; beef; pork-cat syndrome; alpha-gal syndrome

RED MEAT ALLERGY: NOT SO RARE AFTER ALL

Introduction

Allergic reactions to red meat, defined here as meat of mammalian origin, have historically been thought to be quite rare. Indeed, this was the conclusion of a review on meat allergy in this journal ten years ago [1]. The majority of cases that were described in the 1980's and 90's involved young atopic children and often related to sensitization to bovine serum albumin [2–4]. Some but not all of these reports documented concomitant milk allergy among the beef allergic children [4]. During this same period published cases of red meat allergy in adults were limited to sporadic case reports. However, over the last 20 years recognition of red meat allergy, especially among adults, has been increasing. For example, a

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Pubmed search for “beef allergy” reveals 349 articles, of which nearly 50% were published in the past 10 years.

Despite the fact that a mammalian product (ie, milk) is known to be a dominant food allergen, systematic epidemiologic investigations into the prevalence of allergy to other mammalian products, such as red meat, have been lacking. For example, recent major publications reporting on food allergy prevalence in the USA and Europe have not addressed meat allergy in either children or adults [5–7]. This bias likely represents historical understanding of common food allergens, but also regional variation in the prevalence of meat allergy. A recent study of 365 children in Honduras who were seen in allergy evaluation and underwent skin prick testing and oral food challenges reported that pork (1.6%) and beef (1.1%) were more common allergens than peanut, fish or soy [8]. A similarly designed study of 689 adults in Pakistan demonstrated beef allergy in 0.9% of the subjects, a number that exceeded those with allergies to peanut, fish, soy and milk [9]. A recent report of 6000 schoolchildren in eastern Turkey found that 2.6% had symptoms consistent with IgE-mediated beef allergy based on parental report [10]. The number of subjects with confirmed beef allergy upon oral meat challenges was lower at 0.3%, but only a small fraction of those with suspected allergy, and none who reported delayed beef allergy symptoms, consented to the challenges. In Virginia and parts of the southeastern United States many cases of red meat allergy have been reported since 2009, although population estimates are not available [11]. Taken together it is clear that in some regions red meat has become an important food allergen.

THREE FORMS of RED MEAT ALLERGY

As in many areas of medicine it is now clear that food allergy, including red meat allergy, represents a number of distinct entities with unique clinical, developmental and immunologic characteristics [12]. Recognizing these distinctions has important ramifications for diagnosis and management, and also for ongoing research into allergic disease. The focus of this article is on the three dominant forms of IgE-mediated red meat allergy that are currently recognized: primary beef allergy, pork-cat syndrome and the α -Gal syndrome. Characteristic features of these three forms of red meat allergy are shown in Table 1.

Primary beef allergy

Primary beef allergy has been most commonly described in young atopic children [13]. The best characterized allergen in primary beef allergy is bovine serum albumin (Bos d 6), although other epitopes, such as bovine immunoglobulin (Bos d 7), have also been identified as targets of IgE [14, 15]. Because mammalian proteins such as Bos d 6 are present in both muscle and milk of mammals it is not surprising that many subjects with red meat allergy also have reactions to milk. In a series of 28 children who presented with beef allergy reported by Martelli et al. 26 of the children (93%) were found to be milk allergic [16]. On the other hand, the frequency of children who present with milk allergy who react to beef is lower, with estimates at around 20% [4, 16]. Consistent with other IgE-mediated hypersensitivities, the reactions to beef usually occur rapidly and associated allergic symptoms can include nausea, vomiting, urticaria and anaphylaxis, although in some reports

a major manifestation was exacerbation of underlying eczema [4]. The site of sensitization in primary beef allergy is presumed to relate to exposure to the relevant allergen via the GI tract or possibly, as articulated in the dual-allergen exposure hypothesis, the skin [17]. For example, sensitization to milk could occur via the skin in young children with atopic dermatitis and result in allergy to both milk and beef. Most children with beef allergy have been reported to develop tolerance after a few years. In the cohort of Martelli et al 25 of the 28 children tolerated beef by age 8, and the median duration of the condition was 3 years [16]. There has been little investigation into whether children allergic to beef can tolerate other mammalian meat, such as pork or lamb, however a high degree of homology between mammalian albumins suggests that there is significant risk of IgE cross-reactivity between these species [18]. Several studies have shown that heat-treatment, or other approaches such as freeze-drying, can decrease the allergenicity of beef; these findings are also supported by molecular studies focusing on bovine albumin stability [1, 4, 19].

Pork-cat syndrome

Since at least the early 1990's it has been apparent that inhalant sensitization to albumin proteins of one species could lead to reactions to albumins present in the meat of a related species. The best described example of this is the pork-cat syndrome, in which subjects who are allergic to cat can have clinical reactions to ingested pork [20]. Mechanistic investigations indicate that the allergy is caused by primary sensitization to Fel d 2 (cat serum albumin) with cross-reactivity to Sus s 1 (pork serum albumin) [21, 22]. Some subjects can also react to beef, presumably because IgE in these subjects can also bind to and cross-link Bos d 6 (bovine serum albumin) [21]. Because sensitization to cat underlies the development of the allergy, some have advocated that the name 'cat-pork syndrome' would be more apt [23–25]. Other forms of meat allergy occurring as a consequence of albumin sensitization via the respiratory tract have also been reported. For example, Morisset et al recently published a case of horse-meat allergy that related to dog allergy, as evidenced by IgE cross-reactivity between serum albumins to dog (Can f 3) and horse (Equ c 3) [26]. Most studies of pork-cat syndrome have been limited to case series, however it has been estimated that 1-3% of subjects who are cat allergic have pork-cat syndrome [21]. Of cat-sensitized subjects with IgE specific to Fel d 2, about one in three had symptoms upon ingestion of pork [21]. Pork-cat syndrome has been reported in both adults and children, but is expected to be very rare in infants and toddlers given that cat allergy rarely develops in these age groups [22]. Cat allergy often presents during adolescence or early adulthood and in keeping with this many cases of pork-cat syndrome are diagnosed in this age range [21, 22, 24]. Onset of symptoms following pork ingestion typically occurs in less than an hour, which can help distinguish pork-cat from the α -Gal syndrome [22]. The natural history of pork-cat syndrome has been little studied but a case report by Savi et al suggests that the allergy may be durable [24]. Patients with pork-cat syndrome often report instances of consuming pork without having reactions. Well-cooked pork seems more likely to be tolerated, whereas fresh, dried or smoked preparations of meat are more likely to elicit reactions [21, 22]. Presumably this relates to the fact that pork serum albumin is heat labile [27].

The α -Gal syndrome

In 2009 our group reported a connection between specific IgE to an oligosaccharide present in non-primate mammals and a syndrome of delayed allergic reactions to red meat [11]. The oligosaccharide is the ‘blood-group-like’ antigen galactose- α -1,3-galactose (α -Gal). Because α -Gal is present in muscles, blood cells, parenchymal tissue and secretions of non-primate mammals, allergic reactions can occur upon exposure to a number of mammalian products, (eg- meat, kidneys, milk, gelatin, blood products) [11, 28–30]. Accordingly, the allergy is often referred to as the α -Gal syndrome [31]. Symptoms that are commonly reported in subjects with the syndrome include urticaria, abdominal cramping, and anaphylaxis. Although the initial paper was limited to an analysis of a few dozen patients, at the University of Virginia we have now consulted on over a thousand cases. Moreover, the syndrome is well documented in the southeastern United States, parts of Europe and Australia, and has been recognized on six continents [32]. A group in Memphis, TN recently reported that of 83 cases of anaphylaxis in adults where a “definite cause” was identified in their center from 2006-2016 that α -Gal was the dominant trigger, which at 33% exceeded the contribution of food or venom [33*]. In contrast to primary beef allergy, where the mode of sensitization remains enigmatic, a striking feature of α -Gal relates to the role of bites of certain species of hard ticks in IgE sensitization [34]. In North America *Amblyomma americanum* (lone star tick) is the dominant ‘vector’ of sensitization. Outside of North America ticks that have been strongly associated with α -Gal sIgE sensitization include *Ixodes ricinus* (Europe)[35], *Ixodes holocyclus* (Australia)[36] and *Amblyomma testudinarium* (Japan)[37*], but it remains likely that more species of ticks, or even other ectoparasites such as chiggers, are causally-related to α -Gal sensitization in other parts of the world [38–42]. The details of the interaction in the skin between the tick and host immune response that results in sIgE to α -Gal remain to be elucidated, but it is increasingly clear that α -Gal epitopes are present within tick saliva [38, 39*, 43*, 44].

An unusual feature of the α -Gal syndrome is that even in patients with high titers of α -Gal sIgE orally ingested mammalian products do not result in immediate symptom development. For example, Commins et al investigated 12 adult subjects with self-reported reactions to red meat and positive α -Gal sIgE titers and observed in monitored challenges that the earliest symptom onset was 150 minutes [45]. Fischer et al conducted challenges in α -Gal sensitized subjects who reported reactions to pork kidney and demonstrated that symptom onset ranged from 120-750 minutes among the 7 subjects who had reactions [30]. Because most IgE-mediated reactions are understood to occur ‘immediately’, the delay in symptom onset raises the possibility that immune mechanisms distinct from IgE underlie reactions to α -Gal [46]. On the other hand there are multiple lines of evidence that support the assertion that α -Gal syndrome is indeed an IgE-mediated disease, as outlined in a recent review [47]. See Fig 1 for a proposed explanation for the differences in the kinetics of reactions to red meat that occur in primary beef allergy and α -Gal syndrome.

Although α -Gal syndrome is commonly understood to be a dominant cause of red meat allergy in adults, it can also affect children. Kennedy et al reported that α -Gal syndrome was common among children in Virginia, and that these children shared many features with adults that had the syndrome, including the characteristic delay in onset of clinical reactions

[48]. We have recently extended those observations in a head-to-head comparison of the syndrome in 35 children and 225 adults who self-reported red meat allergy. Specific IgE to α -Gal was detected in >90% of both children and adults, urticaria and anaphylaxis were common in both populations, and symptom onset was reported to start after at least 2 hours in >80% of both children and adults (unpublished observations). A recent investigation of red meat allergy in the eastern Cape of South Africa involving oral challenges recruited 131 subjects ranging in age from 4 to 65 who reported reactions to red meat [49**]. In this cohort 84 were diagnosed with α -Gal syndrome, the median age was 12, and 70% of subjects with α -Gal syndrome were age 18 or less. Interestingly, the timing of symptom onset in the subjects in this cohort was more rapid (median 108 minutes, range 45-375 minutes) than the time reported by Commins et al and Fischer et al [30, 45]. The explanation for the difference in timing is unclear but could point to differences between children and adults, differences in the foods used for the challenges, or other factors unique to the particular population studied by Mabelane et al [49].

DIAGNOSIS and MANAGEMENT

Diagnosis of red meat allergy often relies on a combination of clinical history, skin prick testing and specific IgE blood tests. There are several important considerations in regards to testing for meat allergens. It is important to be aware that asymptomatic sensitization to meat allergens can be common in some populations [50*]. The sensitivity of skin prick testing is often inadequate for diagnosis of red meat allergy [51, 52]. Intradermal testing has greater sensitivity, however it also has greater concomitant risks and therefore should only be used judiciously. Measurement of specific IgE in serum has the advantage of being both highly sensitive and safe, and is frequently used in our practice [53, 54]. Specific IgE tests can also be carried out to purified allergen components, which now play an important role in confirming the form of red meat allergy [55]. Basophil (or mast cell) activation testing may play a role in the future but is still largely in the domain of research [52]. There is no single correct algorithm for diagnosis of red meat allergy. The skin and lab tests often used by the authors for evaluation of red meat allergy are shown in Table 2.

The mainstay of current management includes counseling patients on dietary avoidance and emergency plans, which can include prescription of an epinephrine autoinjector. To date there have been very limited reports of desensitization to red meat. A report from Turkey of successful desensitization of two cases of delayed anaphylaxis to red meat suggests that interventions to achieve sustained unresponsiveness may be possible in some cases [56]. On a related note, titers of specific IgE to α -Gal usually diminish over time in and, thus, many subjects can tolerate re-introduction of mammalian meat after a period of avoidance of one to several years. There is currently insufficient information for any of the different forms of meat allergy to predict with high sensitivity and high specificity the presence and/or severity of reactions to red meat [57]. Similar to other allergic diseases, co-factors such as alcohol, exercise and NSAIDs may play a role in contributing to the severity of clinical reactions to mammalian meat [31, 47, 58].

A recent study has raised the possibility of a connection between α -Gal sensitization and coronary artery disease [59*]. Although current data is limited to an association, a working

model posits an interaction between ingested α -Gal and IgE (or high-affinity IgG) specific to the epitope that can activate host immune cells, including mast cells, present in the walls of coronary arteries. The findings are preliminary but nonetheless in our practice we now often discuss the potential risks and benefits of consuming mammalian products with our α -Gal patients, particularly those who have established cardiovascular risk factors.

CONCLUSION

Over the last twenty years red meat has been increasingly recognized as an important food allergen and we now appreciate at least three distinct forms of red meat allergy – primary beef allergy, pork-cat syndrome and the α -Gal syndrome. Regional variation in prevalence of red meat allergy reflects, in large part, the fact that tick bites are a major cause of sensitization to an oligosaccharide that is present in non-primate mammals. A striking feature of the α -Gal syndrome is the realization that it often develops in adults who have no prior history of atopic disease. Awareness of the clinical features of different forms of red meat allergy and use of component testing play an important role in confirming the correct diagnosis, tailoring disease management, and paving the way for future research into the pathophysiology of unique forms of red meat allergy.

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List of Abbreviations:

α-Gal	galactose- α -1,3-galactose
Bos d 6	bovine serum albumin
Bos d 7	bovine immunoglobulin
Fel d 2	cat serum albumin
Sus s 1	pork serum albumin
sIgE	Specific IgE antibodies

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Key points

1. Red meat, at least in some populations, is a major food allergen.
2. Primary beef allergy, pork-cat syndrome and α -Gal syndrome represent three distinct forms of red meat allergy with unique clinical and immunologic features.
3. Primary beef allergy is predominantly a disease of young atopic children, pork-cat syndrome is most common in adolescence and early adulthood, and the α -Gal syndrome can present across the lifespan from childhood to old age.
4. There is now good evidence that tick bites are causal in α -Gal sensitization and that the α -Gal syndrome often develops in subjects without traditional atopy.
5. Specific IgE component testing plays an important role in confirming the presence and form of red meat allergy.

Fig 1. Proposed model to explain differential kinetics of allergic reactions to red meat in primary beef allergy and the α-Gal syndrome.

A) Bovine serum albumin (BSA) is present in beef and is a major allergen in primary beef allergy. Digestive processes partially degrade proteins, such as BSA, nonetheless some peptide epitopes within the BSA protein that can be recognized by IgE antibodies pass through the epithelial barrier intact. Within minutes these peptides can be bound to and cross-link specific IgE that are on the surface of tissue mast cells. Because albumin proteins also mediate the pork-cat syndrome, reactions in pork-cat also occur rapidly, consistent with traditional ‘immediate hypersensitivity’ reactions. **B)** Glycans with terminal galactose-α-1,3-galactose (α-Gal) can be linked to proteins and lipids and both forms are present in red meat. The characteristic delay of 3-6 hours that occurs in the α-Gal syndrome suggests that it is the glycolipid form of α-Gal that passes through the epithelial barrier intact and is recognized by specific IgE antibodies on the surface of mast cells. The delay is explained by the time it takes for: 1) lipids to be packaged into chylomicrons by the epithelial cells, 2) for these chylomicrons to transit to the systemic circulation via the thoracic duct, and 3) for the dietary lipids, including those bearing α-Gal, to transition to other lipoprotein particles, such as LDL, which are small enough to exit from the vasculature into the interstitium where mast cells reside. Because mast cells are present in the walls of coronary arteries and are abundant in atherosclerotic plaques this ‘glycolipid hypothesis’ could also be highly relevant

to explaining the recent observation that subjects who were sensitized to α -Gal had greater burden of coronary artery atherosclerosis.

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Table 1:

Features of the three dominant forms of red meat allergy

	Primary beef allergy	Pork-cat syndrome	α -Gal syndrome
Clinical features	Predominantly seen in young children with atopic dermatitis; concomitant milk allergy is common	Cat-allergic subjects develop allergy to pork, in some cases also extending to beef; most commonly teenagers and young adults	Can develop across the lifespan, including subjects with no history of traditional atopy; symptom onset is often, but not universally, delayed by 3-6 hours; products derived from mammals in addition to meat can elicit reactions in some patients (e.g.-dairy, gelatin, vaccines)
Route of sensitization	Presumed to be via GI tract or skin	Respiratory tract	Primarily caused by bites of ticks such as <i>Amblyomma americanum</i> that have prolonged pruritic reactions
Relevant allergen(s)	<u>Common:</u> bovine serum albumin <u>Less common:</u> Immunoglobulin, myosin light chain kinase, parvalbumin, enolase, aldolase	Albumin of cat cross-reacts with pork albumin	Galactose- α -1,3-galactose (α -Gal)
Immunologic features	Often poly-sensitized to many inhalants and food allergens	Positive IgE to cat, including cat serum albumin (Fel d 2), with cross-reactivity to serum albumins of swine (Sus s 1) and in some cases cow (Bos d 6) or other mammalian albumins	IgE to α -Gal, but also positive results to other mammalian extracts which contain α -Gal (e.g.-beef, pork, milk, cat, dog); ~50% of subjects do not have IgE to major inhalant allergens

Table 2.

A) Skin and specific IgE lab tests commonly used in the diagnosis of red meat allergy. **B)** Characteristic results from skin and specific IgE tests for the three dominant forms of red meat allergy

A		
Skin tests*	Specific IgE tests	
	Extract	Component
Beef Pork Milk Cat	Beef Pork Milk Cat	α -Gal Bos d 6 (bovine serum albumin) Sus s 1 (pork serum albumin) Fel d 2 (cat serum albumin) gelatin

B			
	Primary beef allergy	Pork-cat syndrome	α -Gal syndrome
Skin test results	Beef: + Pork: +/- Milk: +/- Cat: negative	Beef: +/- Pork: + Milk: - Cat: + to ++	Beef: +* Pork: +* Milk: +* Cat: negative
Specific IgE extract results	Beef: + Pork: +/- Milk: +/- Cat: negative	Beef: +/- Pork: + to ++ Milk: +/- Cat: + to ++	Beef: + Pork: + Milk: +/- Cat: +/-
Specific IgE component results	α -Gal: negative Bos d 6: + Sus s 1: +/- Fel d 2: negative Gelatin: negative	α -Gal: negative Bos d 6: +/- Sus s 1: + Fel d 2: + to ++ Gelatin: negative	α -Gal: + Bos d 6: negative Sus s 1: negative Fel d 2: negative Gelatin: +/-

* Intradermal testing using 1:100 dilution of extract used for prick testing (only after obtaining negative results with prick test) is often required in order to see positive skin tests in subjects with α -Gal syndrome.

* Typically only positive with intradermal testing