Red meat allergy

Supporting diagnosis of anaphylaxis and severe urticaria
Red meat allergy

The role of alpha-gal in red meat-allergy
Recent research has revealed a previously not recognized clinical syndrome where skin symptoms, but most importantly anaphylaxis, occur several hours after the ingestion of red meat. Most cases have been reported in adults, but recent reports also include children.

This in many ways is contrary to our traditional learning. Allergy to red meat is rare in adults and the general understanding is that reactions to food are not delayed beyond one hour. Skin testing with commercial extracts in these patients generally yields poor or negative results. It might therefore be difficult to assess the seriousness of the case correctly when an adult patient reports reactions starting several hours after eating red meat and has a negative prick test. However, research reports show that these cases should indeed be taken seriously. As the oligosaccharide alpha-gal appears to be the culprit, measuring specific IgE to this carbohydrate is a good tool that can be used to support the diagnosis.

Galactose-alpha-1, 3 galactose (alpha-gal) is present in many animal proteins. It is unique in mammals and abundantly expressed on glycoconjugates of non-primates, including proteins in beef, pork, lamb and cat dander. The alpha-gal epitope is not expressed on glycoconjugates of old world monkeys, apes or humans, however.

IgE-mediated reactions
The first indication of alpha-gal-specific IgE-mediated allergy came from cases in the USA of systemic anaphylaxis after the infusion of cetuximab, a chimeric mouse-human antibody used for cancer therapy. These patients proved to have IgE antibodies to alpha-gal.

Further studies led to a very strong correlation between this sensitization and a history of anaphylaxis or severe urticaria that started 3-5 hours after the patients consumed red meat. These findings were first reported in a pioneering publication by Tom Platts-Mills’ research group the University of Virginia, in JACI in 2009.

Once the concept of delayed anaphylaxis after ingestion of meat became known, physicians in a large area of the southeastern USA began to recognize similar cases, with delayed reactions after eating beef, pork or lamb. There were no immediate symptoms at the time of consuming the meat, however, and eating chicken, turkey or fish did not illicit symptoms.

Scott Commins et al at the University of Virginia have documented the time course of clinical symptoms after the ingestion of mammalian meat in subjects with IgE to alpha-gal in a recently published paper. They found that ten of twelve subjects with IgE to alpha-gal had clinical evidence of a reaction during food challenge. The reactions occurred 3 to 7 hours after the initial ingestion of mammalian meat and ranged from urticaria to anaphylaxis. These results provide clear evidence of the existence of a delayed, IgE-mediated food allergy. Since the first observations in the US, several reports from Europe, Asia and Australia have also reported similar cases.
The possible role of tick bites
The primary hypothesis in the attempt to explain the causes of IgE-antibody responses to alpha-gal are that tick bites is a causative factor. The first cases of delayed anaphylaxis to red meat were concentrated to certain parts of the South and Midwest United States. This geographic distribution turned out to correlate with the distribution of a certain species of tick, and with the prevalence of a tick-born disease, Rocky Mountain spotted fever. This raised the suspicion that the tick might somehow be involved also in the chain of events leading to sensitization to alpha-Gal.

The correlation was established by the researchers at the University of Virginia, who found that patients suffering from tick bites had specific IgE antibodies to alpha-gal, and showed significant rises in these levels after recent bites. Studies in other countries, including Sweden, have later confirmed these findings. The fact that different species of ticks prevalent in different parts of the world are involved does not seem to influence the general outcome.

Prevalence alpha-gal sensitization
In a recent study Danish and Spanish researchers investigated and compared the prevalence of IgE-sensitization to alpha-gal in their respective countries. [3] The prevalence of specific IgE to alpha-Gal was 5.5% in the Danish study group and 8.1% in the Spanish one. Sensitization was found to be strongly associated with a history of tick bites. This study did not investigate the prevalence of red meat allergy, but the report concludes that as this is in all likelihood low, high levels of alpha-gal specific IgE in patients with clinical suspicion of red meat allergy should have a high positive predictive value.

Short facts
- An underdiagnosed form of severe food allergy
- Generally presents in adult age
- Tick bites weeks or months before the first reaction
- The first reaction generally appears in the summer or autumn
- Delayed allergic reaction with urticaria or anaphylaxis 2-7 hours after ingestion of red meat
- Reactions appear mostly in the evening/at night
- Allergen-specific ImmunoCAP test for alpha-gal is available for confirmation

Patient cases
Several patient cases have been described in publications. One example discussed in Journal of Allergy and Clinical Immunology [4] involved a 51-year old woman in South Carolina, USA. She had two episodes of anaphylaxis that developed in the middle of the night and required treatment in the emergency ward, and several episodes of urticaria. On one of the occasions she awoke at 3 o’clock at night with generalized urticaria and anaphylaxis. She had eaten beef for dinner at 9 pm that night. Skin tests were negative to beef, pork and environmental allergens, but laboratory tests showed a high level of IgE to alpha-Gal (88 IU/mL). The lady likes to hunt and she reported suffering at least two tick bites, although none of them had occurred immediately before the anaphylactic episodes. One of the tick bites suffered a few years previously caused a severe reaction necessitating hospital treatment. The other, several months ago, caused a large local reaction that persisted for weeks.
Commenting on the case in the journal, Scott Commins notes that the described reactions appear quite typical in terms of timing and severity and suggests that the most recent tick bite has made the patient more sensitive to mammalian meat, hence the recent reactions. A large reaction after tick bites that results in intense pruritus and persists for several weeks is frequently reported by patients with IgE to alpha-Gal, he says.

A case described in the Danish publication [9] concerns a man who suffered a tick bite in 2010, which caused local symptoms. He then started to experience recurring symptoms of nettle rash and itching. In January 2013, after tasting chili con carne, he suffered anaphylaxis and ended up in hospital. Later that year he suffered a new episode after eating mutton. This time the allergist tested for IgE to alpha-Gal, and the test was positive. Eliminating red meat from his diet has proven to reduce his skin symptoms and further episodes of anaphylaxis have been avoided.

**Summary**

There are a number of unexpected characteristics of this newly discovered form of food allergy. Whereas food allergy symptoms generally occur shortly after ingestion, this type of red meat allergy is associated with symptoms delayed 2-7 hours. In contrast to other types of food allergy, the symptoms do not include asthma, but are primarily skin symptoms, gastrointestinal and anaphylaxis. The subjects do not necessarily develop symptoms every time they have consumed meat, the reaction may be dependent on the amount ingested. And the culprit substance alpha-gal is not a protein as most other allergens, but a carbohydrate. The patients will often have a negative skin prick test to meat, but a positive IgE test to alpha-gal, and also to cat or dog, as these extracts also contain alpha-gal.

---

**References**

5. Astma-Allergi Danmark medlemsblad nr. 2 marts/april 2014, side 26