Tick-induced allergies: mammalian meat allergy and tick anaphylaxis

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This Narrative Review includes individual journals not accessible via PubMed — due to their earlier date of publication — and a PubMed search for original and review articles published between 1940 and October 2017. In addition, specialist societies' publications and guidelines were examined to formulate an evidence-based review of the spectrum of tick-induced allergies, their discovery, distribution, clinical features, management and prevention, and mechanisms of development.

Spectrum of tick-induced allergies

Tick-induced allergies comprise large local reactions to tick bites, mammalian meat allergy after tick bites, and tick anaphylaxis.[1,2] *Ixodes holocyclus* (the Australian paralysis tick) (Box 1) is responsible for the majority of bites in humans in Australia and is therefore the tick that causes most tick-induced allergies.[3] The colloquial term "paralysis tick" is commonly used, but it mostly refers to effects on non-human mammals, such as dogs.

Large local allergic reactions to tick bites, while incapacitating at the time, are the least severe form of tick-induced allergies. The commonest presentation of a serious tick-induced allergy is mammalian meat allergy after a tick bite, which may manifest as anaphylaxis, recurrent angioedema or gut symptoms after ingestion of mammalian meat — all typically delayed by 3–6 hours.[1,2,4-6] Mammalian meat allergy is an emergent allergy that has become increasingly prevalent in tick-endemic areas of Australia and the United States, and has been reported worldwide where *Ixodes* spp, *Amblyomma* spp and *Haemaphysalis longicornis* are endemic and known to bite humans (Box 2). The most severe manifestation of a tick-induced allergy is anaphylaxis to ticks, and it has resulted in four deaths in Australia.[22,23] Tick anaphylaxis, which occurs most commonly in Australia,[24-32] is becoming increasingly prevalent.[1-3] Each of these reaction types relies on IgE mediation, but presents differently.

Large local reactions are restricted to the tick bite site, commence within 4–12 hours of the tick bite, reach their height by 72 hours, take 7–10 days to resolve, and are due to a late-phase allergic reaction primed by insect-specific IgE,[32] as seen with many other insect bites and stings.[33]

Mammalian meat allergy is due to an IgE-mediated reaction to a carbohydrate moiety, α-gal (galactose-α-1,3-galactose),[6] which is present in all mammals (except humans, great apes and Old World monkeys)[34-36] and is therefore in all mammalian meat (and mammalian products) eaten by humans. The delay of 3–6 hours in these allergic reactions is due not to arcane immunological influences, but rather to factors modulating the uptake of the allergen (α-gal) from the gut and its subsequent presentation to the host circulation.[1,37]

Tick anaphylaxis is a classic immediate IgE-mediated reaction directed against a protein (in this instance a tick salivary protein) that is injected into the host by the tick when it is disturbed during feeding.[32,38-42]

Summary

- Mammalian meat allergy after tick bites and tick anaphylaxis are the most serious tick-induced allergies. They are often severe, should be largely avoidable and offer fascinating insights into the development and prevention of allergies.
- Australian clinicians reported the first cases of tick anaphylaxis and discovered the association between tick bites and the development of mammalian meat allergy. The subsequent finding of the allergen epitope within the meat responsible for the allergic reaction, α-gal (galactose-α-1,3-galactose), stimulated further interest in this emergent allergy.
- Reports of mammalian meat allergy associated with bites from several tick species have now come from every continent where humans are bitten by ticks. The number of diagnosed patients has continued to rise.
- Clinically, mammalian meat allergy and tick anaphylaxis present quite differently. The prominent role of cofactors in triggering episodes of mammalian meat allergy can make its diagnosis difficult.
- Management of mammalian meat allergy is complicated by the manifold potential therapeutic implications due to the widespread distribution of the mammalian meat allergen, α-gal. Exposures to α-gal-containing medications have proved lethal in a minority of people, and fatal tick anaphylaxis has been reported in Australia. Prevention of tick bites is prudent and practicable; killing the tick in situ is crucial to both primary and secondary prevention of allergic reactions.
- Mechanisms in the development of mammalian meat allergy constitute a paradigm for how allergies might arise.

Discovery of the association between tick bite and mammalian meat allergy

In 2007, van Nunen and colleagues[4] described the cases of 25 adults who developed red meat allergy after tick bites. This was a serendipitous finding, insofar as van Nunen was practising in a region of Australia where the condition occurs (along the Eastern seaboard) at a time when it was becoming more prevalent.

Making a direct link between having tick bites and the subsequent development of an allergy to a previously tolerated food (mammalian meat), however, also required a long familiarity with investigating anaphylaxis (leading to van Nunen skin-testing patients with all foods eaten at the meal before their anaphylaxis, even though their anaphylaxis had occurred an unprecedented 3–6 hours beforehand) and van Nunen's experience in using fresh food skin prick testing in anaphylaxis diagnosis ("prick-prick"; ie, prick the food and then prick the patient using fresh, raw, organic meats) before it became routine (the commercially available skin testing agents for beef, pork and lamb gave reactions small enough to be dismissed as

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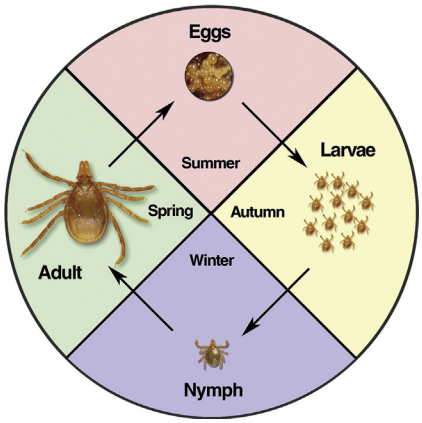
Podcast with Sheryl van Nunen available at https://www.mja.com.au/podcasts

1 *Ixodes holocyclus* (Australian paralysis tick): stages and life cycle*



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2 Mammalian meat allergy: a worldwide phenomenon (initial reports)

Year	Country	Tick	*n*	Reference
2007	Australia	*Ixodes holocyclus*	25	4
2009	United States	*Amblyomma americanum*	24	6
2009	France	*Ixodes ricinus*	2	7
2011	Spain	*Ixodes ricinus*	5	8
2012	Germany	*Ixodes ricinus*	21	9
2012	Korea	*Ixodes nipponensis*?	1	10
2012	Japan	*Ixodes nipponensis*?	1	11
2013	Sweden	*Ixodes ricinus*	2	12
2014	Switzerland	*Ixodes ricinus*	3	13
2014	Panama	*Amblyomma cajennense*	4	14
2015	United Kingdom	*Ixodes ricinus*	1	15
2016	Italy	*Ixodes ricinus*?	1	16
2016	South Africa	?	2	17
2016	Japan	*Haemaphysalis longicornis*?	30	18
2016	Brazil	*Amblyomma sculptum*?	1	19
2016	Ivory Coast	*Amblyomma variegatum*?	1	20
2017	Norway	*Ixodes ricinus*	1	21

being clinically insignificant).[5,6,37] Moreover, it necessitated an understanding of the nexus between IgE, parasites and allergy, and the consequent recognition of the potential for an immunological response to a parasite to skew the host's immune system to a T helper type 2 cells "pro-allergy" predominance.[43,44]

Distribution of mammalian meat allergy after tick bite: a worldwide phenomenon

Since 2007, Commins and colleagues[6] and Platts-Mills and colleagues[37] have determined the epitope (α-gal) within the meat against which the specific IgE antibody is directed. These researchers and many others around the world[7-21,45-57] have also produced considerable data providing convincing evidence confirming the observation by van Nunen and colleagues[4,5] of the development of mammalian meat allergy after tick bites.

Cases have now been reported from Australia,[4,5,48,55] the United States,[6,47] Europe (France,[7,49-51] Spain,[8] Germany,[9,52,54] Switzerland,[13] Sweden,[12,53] the United Kingdom,[15] Italy[16] and Norway[21]), Asia (Korea[10] and Japan[11,18]), Central America (Panama[14]), South America (Brazil[19]) and Africa (South Africa[17] and Ivory Coast[20]) (Box 2); that is, on all continents where humans are bitten by ticks.

Estimates of mammalian meat allergy prevalence are currently 113/100 000 in the Sydney Basin, Australia, 13/100 000 in Virginia, US, and 4/100 000 in Baden-Württemberg, Germany.[28] The locations of reports of mammalian meat allergy after tick bite in Australia correlate with the distribution of *Ixodes holocyclus* (Box 3) — around 50% of Australians are potentially exposed to bites from this species.[58] In late 2016, a case of mammalian meat allergy was diagnosed in a man bitten by *Ixodes australiensis* in Western Australia, suggesting another tick species may be capable of inducing the condition in Australia. In other countries reporting cases of mammalian meat allergy, the association with exposure to ticks endemic to their regions has also been confirmed.[7,9,10,12,14,28,45-48,50,56,57]

Clinical features of mammalian meat allergy and tick anaphylaxis

Both adults and children with mammalian meat allergy after tick bites have similar findings, ranging from angioedema or gut symptoms alone through to life-threatening anaphylaxis, with severe allergic reactions being more common (65.5%).[28,47] The clinical features of mammalian meat allergy after tick bite are summarised below (Box 4).

Reactions to mammalian gelatine

Fewer than 10% of patients who are allergic to mammalian meat react to mammalian gelatine as well. Mullins and colleagues[48] established that parenteral administration of gelatine increased the likelihood of anaphylaxis, and observed that gelatine allergy may be the initial presentation of mammalian meat allergy. The authors documented clinical reactivity to both intravenous and oral gelatine, and reported a small number of patients with positive gelatine tests and negative mammalian meat tests who reacted to gelatine challenge.[48] Mullins and colleagues[48] confirmed that bites from *Ixodes holocyclus* (Australian Capital Territory and New South Wales' south coast), α-gal sensitisation and allergy to red meat are associated.[48]

The role of amplifying factors (cofactors) in mammalian meat allergy

An understanding of the crucial role of cofactors in triggering a reaction in patients with mammalian meat allergy is important in ensuring their safety. As with all food allergens, to a greater or lesser degree, modulating factors all separately and collectively confer an increased risk of an α-gal-sensitised individual having an allergic reaction to mammalian meat at any particular time.[28,50,59,60] These comprise ingesting a greater amount of allergen, co-ingestion of alcohol, exercise (particularly within 2 hours), the inclusion of spices (usually chilli and capsicum), the prior administration of non-steroidal anti-inflammatory agents, being otherwise unwell, being in the perimenstrual phase, and the effect of cooking (slow cooking or reheating of the meat dish).[28,50,59,60] In addition, the

3 Distribution of *Ixodes holocyclus* (Australian paralysis tick)*

* Map adapted from Roberts FHS. Australian ticks. Yeerongpilly, QLD: CSIRO; 1970, by TAGS, Conroy B and Fischer N. ◆

4 Clinical features of mammalian meat allergy after tick bites

Clinical features	References
• Patients with a history of tick bites present with allergic reactions after ingesting mammalian meat (or meat products) — reactions which are typically delayed (ie, "middle of the night" anaphylaxis) and often severe	5,8,10-14,28,47,49,53,57
• The interval between mammalian meat ingestion and the allergic reaction is 2–10 hours, usually 3–6 hours, depending on exposure to cofactors (eg, alcohol or exercise)	6,7,28,49-51,57
• Anaphylaxis occurs in up to 60% of patients, delayed urticaria or angioedema features and gut symptoms may occur alone	4-6,8,12,14-16,28,47,49,53
• There is a history of previous tick bite. Occasionally, evidence for the tick bite can be obscure	58
• A history of a large local reaction to a tick bite is not uncommon	4,5,57
• Bites from either nymphs or adult ticks may provoke the condition	
• Individuals with mammalian meat allergy will almost invariably have α-gal-specific IgE detectable in their serum, and/or positive skin tests to raw, organic mammalian meats and/or cetuximab	4-7,13

concentration of α-gal varies between different mammalian meat products.[50] Offal (eg, pork kidney) has the highest α-gal concentration,[50] increasing the likelihood of a reaction. On the other hand, while cow's milk contains α-gal, boiling cow's milk abolishes α-gal reactivity,[61] so pasteurised cow's milk is often tolerated. The effect of cofactors is so striking in mammalian meat allergy that European authors have drawn parallels with food-dependent exercise-induced anaphylaxis.[28,50] Accounting for the role of cofactors is pivotal in mammalian meat challenge design[28] if reliable advice is to be forthcoming.

Pitfalls in the diagnosis of tick bite-induced mammalian meat allergy

The diagnosis of tick bite-induced mammalian meat allergy is beset by a number of pitfalls summarised below (Box 5). Notably, the prevalence of α-gal-specific IgE sensitisation does not necessarily equate to clinical reactivity, as is the case with almost all allergens. The prevalence of α-gal sensitisation throughout Europe (α-gal-specific IgE > 0.10 kUA/L) is 5.5–8.1%.[62] In the southeastern regions of the US, α-gal sensitisation prevalence is as high as 34–37% (Viracor-IBT Laboratory, 7300 serum samples[63]). In Germany, of the 35.0% of forest workers and hunters who are sensitised to α-gal (α-gal-specific IgE > 0.10 kUA/L), only 8.6% have had mammalian meat anaphylaxis.[64]

Clinical features of tick anaphylaxis

In Australia, tick anaphylaxis has been reported since the 1940s,[3,65-69] and since 1991, there have been documented cases in the US,[24,25] France[26] and Spain.[27,29-31,70] Worldwide, *Ixodes* spp. (*Ixodes holocyclus*,[3] *Ixodes pacificus*,[24] *Ixodes ricinus*[26,27]), *Rhipicephalus bursa*,[29,31] *Rhipicephalus sangineus*[30] and *Hyalomma marginatum*[31] are causative of tick anaphylaxis, the clinical features of which are listed in Box 6.

Management of tick-induced allergies

Tick anaphylaxis

At present, the management of tick anaphylaxis relies on tick bite prevention and killing the tick in situ and removing it, if necessary, under medical supervision to prevent allergic reactions if a subsequent tick bite occurs.[3,71] The identification of tick proteins

5 Pitfalls in the diagnosis of tick bite-induced mammalian meat allergy

Characteristics	References
• Lack of awareness in doctor or patient of the existence of the condition (axiom: where certain tick species are endemic and humans are bitten, mammalian meat allergy will occur)	
• Interpreting the presence of α-gal-specific IgE (in the absence of a supportive clinical history) as indicating the patient has a clinical allergy to mammalian meat*	
• Mammalian meat allergy is an "any time" but not an "every time" allergy (ie, cofactors are very influential in its expression)	28,50,57
• Challenge design is difficult due to delayed reactions and the crucial role of cofactors	28,50,57

* The presence of allergen-specific IgE in serum or a positive skin test to any allergen does not equate to the patient having an allergy to that allergen, unless it can be established clinically that the allergen is causing the symptoms being experienced at this time in their life. α-Gal sensitisation may be present in the absence of clinical allergy to mammalian meats.[28] ◆

6 Clinical features of tick anaphylaxis

Tick anaphylaxis:	References
• is only seen with bites from adult ticks	1,2,3,39-42,45,68,69,71
• is becoming more commonly seen in tick-endemic areas in Australia	1,2,3,32,65-69
• is uncommon in countries other than Australia	24-31
• is usually severe (> 74% Mueller grade III or IV)	32,65-71
• may be fatal (four lethal reactions in Australia)	22,23
• may be provoked when the tick is disturbed or removed inappropriately	1,2,32,71
• is very unlikely to occur if the tick is killed in situ	71
• is more likely to occur in older individuals (> 50%, > 50 years of age)	71

likely responsible for anaphylaxis in patients,[31,40-42,72,73] however, offers the prospect of diagnostics and immunotherapy for tick-induced allergies.

Mammalian meat allergy

Dietary education. Avoidance of mammalian meat and meat products is necessitated when mammalian meat allergy is severe. An expert dietitian is required to help with avoidance of meat products and maintenance of iron stores and to ensure vitamin B12 adequacy (www.tiara.org.au). In the minority of patients with mammalian meat allergy who are also clinically allergic to cow's milk or mammalian gelatine, the identification of hidden sources of cow's milk and gelatine is essential for their safety (www.allergy.org.au, www.allergyfacts.org.au).

Therapeutic precautions. α-Gal is widely distributed in therapeutic agents, and several novel therapeutic opportunities may prove risky in people who are α-gal sensitised (eg, wound healing and tumour therapy advances):[74]

- cetuximab — due to its α-gal content, fatal reactions have occurred with its use;[75]
- vaccination — α-gal is measurable in some vaccines (eg, measles–mumps–rubella and zoster), and other vaccines may contain mammalian products.[76] Use of these vaccines may expose patients with α-gal-specific IgE to the risk of an allergic reaction;[76]
- gelatine — sources of gelatine may need flagging (eg, vaccines, capsules, tablets, suppositories and collagen-containing agents, including implants);[48]
- porcine heart valve prostheses — α-gal sensitisation has likely played a role in serious allergic events after porcine cardiac valve xenograft transplantation;[77-79] and
- antivenoms — snake,[80] redback and funnel web spider, box jellyfish and stonefish antivenoms plus scorpion and other antivenoms produced internationally (all made in mammals) may confer a risk of reaction.

Pharmaceutical and complementary medicine manufacturers, pharmacists and regulatory authorities need to be aware of therapeutic implications of mammalian meat allergy.

Prevention strategies in tick-induced allergies

Neither mammalian meat allergy nor tick anaphylaxis develops without a tick bite having occurred. Further tick bites recharge α-gal sensitisation levels and, in the absence of tick bites, the α-gal-specific IgE level reduces over time and some individuals lose their sensitivity to mammalian meat.[81]

Prevention of tick bites involves "dressing for the occasion" and ensuring your property is unfriendly to ticks (www.tiara.org.au). The available data, albeit limited, indicate that lifestyle changes targeting tick bite prevention may largely avert subsequent tick bites, and tick anaphylaxis may be prevented by using appropriate removal techniques.[71] Killing the tick in situ is crucial to preventing allergic reactions,[71,82] and is aimed at ensuring the tick does not regurgitate allergen into the host. The most practicable method of killing a tick on a human host is to use an ether-containing freezing agent.[71,82] The dead tick ideally should be left to detach.[83] If tick removal is undertaken, then the greatest care should be taken to avoid compressing its salivary glands. Fine-tipped forceps should be used by health care experts with resuscitation facilities at hand.[83,84] Using fine-tipped forceps requires excellent vision, but many patients with tick anaphylaxis report difficulty in visualising the tick. Moreover, household tweezers are tick squeezers and their use should be discouraged.[71] Patients who have had a tick anaphylaxis previously should not disturb the tick, should summon paramedics and be taken to the nearest emergency department for tick killing and removal (www.allergy.org.au).

Overall, there are limited data regarding the relative efficacy of tick removal methods in preventing tick-induced allergies, chiefly because these are emergent allergies, but such studies are in progress.[71]

Mechanisms in the development of mammalian meat allergy

Mammalian meat allergy after tick bites is a paradigm for the development of an allergy: a process driven by genetic predisposition (eg, three out of four people in a single family will have the condition), environmental change (more ticks, more people, microclimate changes) and parasite-induced host immune changes, and possibly even an effect of the co-existence of an infectious agent in the tick (eg, rickettsiosis).

The emergence of mammalian meat allergy after a tick bite commenced 20–28 million years ago, when the fossil record shows the extinction of almost all hominoids after a catastrophic epidemiological event. Our surviving progenitors (and Old World monkeys and apes) had inactivated the enzyme that produces α-gal (α-galactosyltransferase), so humans and the higher primates then recognised α-gal as a foreign substance and could therefore elaborate anti-gal IgG antibodies, thus conferring protection against pathogenic α-gal-containing Old World organisms (enveloped viruses, protozoa and bacteria).[74]

However, the fact that α-gal is a foreign substance to humans allows those so prone — after a tick bite, which likely promotes a "pro-allergy" T helper type 2 cell cytokine profile in the host[85] — to make a switch in production in B cells, making anti-gal antibodies from IgG manufacture to IgE production.[40-42] This is facilitated by the galactosylation of the tick proteins, which enhances their immunogenicity. When the class switch to IgE production to the tick proteins is generated in the host, α-gal-specific IgE is also made.[40-42] α-Gal is then a cross-reactive carbohydrate determinant, in that allergic reactions occur after mammalian meat is consumed because the host has become allergic to the α-gal injected by a tick and α-gal is present in non-primate mammal meats.

Previously documented instances of a cross-reactive carbohydrate determinant provoking anaphylaxis comprise those reported by Jyo and colleagues[86] in 1993 (galacto-oligosaccharides allergy in Japanese oyster farmers exposed to sea squirt body fluids) and Goh and colleagues[87] in 2001 (bird's nest soup anaphylaxis in Singaporean children).

Araujo and colleagues[88] generated an α-galactosyltransferase knockout mouse model for the development of mammalian meat allergy, and Commins and Karim[89] have now shown anaphylaxis occurs when α-galactosyltransferase knockout mice sensitised to α-gal by intradermal injection of tick saliva are fed mammalian meat.

The final unique element is the delay seen with the majority of mammalian meat allergic reactions. The delay is likely due to the time taken to transport the α-gal from the gut to the circulation. α-Gal is present on both glycoproteins and glycolipids (including chylomicrons). Fat digestion takes several hours; α-gal-containing chylomicrons are absorbed by the enterocytes, transported in the lymphatics and then enter the circulation via the thoracic duct, triggering basophil mediator release[61] when they reach the circulation.

Conclusion

Tick bite-induced allergies, mammalian meat allergy and tick anaphylaxis are often severe, should be largely avoidable and offer fascinating insights into allergy development and primary and secondary prevention of allergies in general. Avoidance of tick bites is key to preventing tick-induced allergies. If a tick bite does occur, then killing the tick in situ and avoiding any compression of the tick when it is removed significantly limit the possibility of tick-induced allergies occurring.

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