

TICK INDUCED MAMMALIAN MEAT & GELATIN ALLERGY

Introduction

Tick Induced Mammalian Meat Allergy (and gelatin) allergy is an interesting emerging allergy *increasingly* recognized in tick-endemic areas of Australia and the United States, but also occurring worldwide where ticks are endemic.

Sensitization to **galactose- α -1,3-galactose (α -Gal)** has been shown to be the mechanism of allergic reaction in mammalian meat allergy *following* a **tick bites**.

Mammalian meat allergy, therefore is essentially an acquired allergy to galactose- α -1,3-galactose.

It may manifest in patients previously bitten by a tick, following the subsequent ingestion of mammalian meat as:

1. Urticaria
2. Recurrent angioedema
3. GIT symptoms
4. Anaphylaxis

Correct killing and removal of ticks, plays an important role in the prevention of the development of mammalian meat and gelatin allergy.

Further tick bites recharge a-gal sensitisation levels and, in the absence of tick bites, the a-gal-specific IgE level reduces over time and some individuals lose their sensitivity to mammalian meat.

See also separate documents on:

- **Tick Allergy (in Allergy folder)**
- **Australian Paralysis Tick Envenomation (in Envenomation folder).**
- **Adrenaline (in Drugs folder)**
- **Anaphylaxis (in Allergy folder)**

History

The fossil record shows that in the **Oligocene epoch** around 20 - 28 million years ago, a catastrophic event occurred that almost led to the extinction of all hominoids.

It appears that the hominids that did survive had the ability to inactivate alpha-galactosyltransferase, the enzyme that produces alpha-gal. The majority of Hominids thereafter recognized alpha-Gal as a foreign carbohydrate and could produce anti-gal **IgG** antibodies.

It is intriguing to note that many old world pathogenic microorganisms, including enveloped viruses, protozoa and bacteria contain alpha-Gal. It is interesting to speculate that the nature of the near extinction event could have been a susceptibility to these microorganisms. ⁴

Perhaps the near hominid extinction event of the Oligocene epoch led to the evolution of hominids that recognized alpha-Gal as a foreign substance and in so doing they were protected against many virulent old world pathogenic microorganisms.

It is thought that after a tick bite, there is stimulation of “pro-allergy” T helper type 2 cells. These cells induce a change in B cell activity. Instead of producing anti-gal IgG antibodies they now produce anti-gal IgE antibodies; thus generating a state of alpha-Gal hypersensitivity.

Mammalian meat anaphylaxis following tick bite was first reported by the Australian Allergy specialist, **Sheryl A. van Nunen** and her team in 2007.

Her findings have since been confirmed by researchers in the USA and in Europe.

Biochemistry

Galactose- α -1,3-galactose (or **alpha-Gal**) is a **disaccharide carbohydrate** found in most mammalian cell membranes *except* in primates, including humans, great apes and Old World monkeys, where the immune system of these species recognize it as a *foreign* substance.

A **subgroup** (< 10 %) of these patients with mammalian meat allergy will *also* be allergic to **mammalian gelatin**.

Gelatin may be found in:

1. Mammalian milks
2. Mammalian-derived gelatin present in:
 - Some food products, (as a binding agent)
 - ♥ Jelly / meat extracts (e.g. Bonox) / some confectionaries such as jelly babies / Gravox / soup stocks.

- Some medications
 - ♥ Cetuximab

Exposures to **a-gal**-containing medications have proved lethal in a minority of people.

- Some intravenous blood substitutes known as gelatin colloids:
 - ♥ e.g. Haemaccel, Gelofusine.

In those with **Galactose- α -1,3-galactose allergy** the mammalian red meats which may be expected to be problematic include:

1. Beef
2. Pork / bacon / ham
3. Lamb / mutton.
4. Kangaroo
5. Venison
6. Buffalo
7. Some more exotic meats eaten in some countries (e.g. guinea pig) in South America and ethnic specialty restaurants in North America and even Australia; and probably even whale meat (e.g. in Japan) as well as gelatin.

Epidemiology

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

Pathophysiology

Mammalian meat allergy is due to an **IgE-mediated** reaction to a **carbohydrate moiety, a-gal (galactose- α -1,3-galactose)**, which is present in all mammals *except* humans, great apes and Old World monkeys.

Galactose- α -1,3-galactose is therefore in all mammalian meat (and mammalian products) that is eaten by humans.

Normally when **ingested** there is no problem, however when injected directly into the blood stream - via the bite of a tick - sensitization can occur.

The delay of **3 - 6 hours** in these allergic reactions is due not to immunological influences, but rather to factors **modulating the uptake of the allergen (a-gal) from the gut** and its subsequent presentation to the host circulation.

Risk factors in mammalian meat allergy:

As with all food allergens, (to a greater or lesser degree), *additional* risk or **modulating factors** both separately and collectively may confer an increased risk of an a-gal-sensitised individual having an allergic reaction to mammalian meat at any particular time.

Recognized concomitant risk factors for mammalian meat allergy include:

- 1 Ingesting greater **amounts** of allergen
2. The **actual meat** being consumed:
 - The concentration of a-gal *varies* between different mammalian meat products. Offal (e.g., pork kidney) has the highest a-gal concentration, thus increasing the likelihood of a reaction.
3. Co-ingestion of:
 - Alcohol
 - Spices (usually chilli or capsicum)
4. Eating post Exercise (particularly within 2 hours):
 - This effect is so striking in mammalian meat allergy that European authors have drawn parallels with food-dependent exercise-induced anaphylaxis.
5. The prior administration of non-steroidal anti-inflammatory agents
6. Being otherwise unwell
7. Being in the peri-menstrual phase
8. The method of cooking (slow cooking or reheating of the meat dish).
9. Genetic predisposition:
 - There is also genetic predisposition to the development of mammalian meat allergy.

In general terms, 3 out of 4 people in the same family will have the potential for the condition.

While cow's milk contains alpha-gal, **boiling** cow's milk will **abolish** its reactivity, and so pasteurized cow's milk is often tolerated.

Clinical features

Patients with mammalian meat allergy associated with tick bites present with allergic reactions after **ingesting mammalian meat (i.e red meat)** or **mammalian meat products**, which are typically delayed i.e. classically a “middle of the night” anaphylaxis.

This delay is typically around **3 - 6 hours**, but can range from **2 - 10 hours**, depending upon exposure to amplifying factors e.g. alcohol ingestion, exercise.

The spectrum of clinical manifestations includes:

1. Urticaria
2. Angioedema
3. GIT symptoms
4. **Anaphylaxis** (most seriously):
 - Anaphylaxis occurs in up to 60% of cases.

Almost invariably mammalian meat allergic patients have a history of previous tick bite

Occasionally, the evidence for such a tick bite can be subtle e.g., a recalled excoriated scalp lesion consistent with a tick bite after only a single visit to a tick endemic area.

Many others will have experienced a **local reaction** to a previous tick bite.

Note that bites from either **nymphs** *or* **adult** ticks may provoke the condition (as opposed to envenomation where just adult females are the problem).

Natural history:

Further tick bites recharge a-gal sensitisation levels.

In the *absence* of tick bites, the a-gal-specific IgE level reduces over time and some individuals can lose their sensitivity to mammalian meat.

Investigations

Blood tests:

Individuals with **mammalian meat allergy** will almost invariably have:

- **Alpha-gal-specific IgE** detectable in their serum

And/or:

- Positive skin tests to raw, organic mammalian meats and/or cetuximab

Researchers have identified that the following blood allergy tests are positive in the majority of those with serious allergic reactions to mammalian meat, and that testing (which can be ordered by any doctor) may assist in confirming the diagnosis:

1. Beef, lamb, pork “**Immunocap**”
2. **Alpha-galactose Immunocap** a sugar molecule present in mammalian meats (but not in humans, great apes or Old World monkeys), as well as the gut of ticks.
3. Elevation of **tryptase** (an enzyme that is increased in those with a condition called mastocytosis, which is associated with an increased risk and severity of allergic reactions to a number of allergic and non-allergic triggers including insect stings and tick bites).

By contrast, **blood** allergy testing to **gelatin** is usually **negative** (even in patients who have had clear allergic reactions to gelatin orally or by injection).

It is important to note that while positive red meat allergy tests are *frequently* seen in those with isolated tick bite allergy, **routine** avoidance of red meat and gelatin is **not** advised unless a patient **has an allergic reaction** to one of these foods **as well**.

Nonetheless, patients should be aware of this possibility and informed by their doctors of the potential risk.

Skin tests:

In contrast, **skin allergy testing** to commercially available mammalian meats is much less reliable unless performed with raw, organic mammalian meats for confirmation (and very occasionally, even using raw meats, the diagnosis may not be confirmed).

Gelatin skin testing results are highly variable, with often minor reactions on skin prick testing with gelatin, whilst intradermal injection skin testing is more reliable in diagnosing gelatin allergy.

Management

Prevention:

General Prevention:

General measures to reduce the risk of tick bite include:

1. Wearing long sleeved shirts and long trousers when walking in areas where ticks occur.
2. Tuck shirting into trousers and trouser legs into long socks.
3. Wearing a wide-brimmed hat.
4. Wear light-coloured clothes, (which makes it easier to see ticks).
5. Brushing clothing before coming inside to remove ticks.
6. After being out-doors clothing can be removed and placed in a hot dryer for 20 minutes. This will kill ticks left on clothing.
7. Undressing and checking for ticks daily, especially checking carefully in the neck and scalp
8. An insect repellent may help, particularly ones containing **diethyltoluamide** (also known as DEET)

Products include: RID, **Tropical RID**, **Tropical Aerogard** and Bushmans

9. Consider using **permethrin**-treated clothing when exposed to tick habitat (e.g. gardening in tick endemic areas).
10. In those with recurrent **dangerous allergic reactions** to tick bites, consideration should be given to relocating to an area where ticks are not endemic.

Dietary prevention:

Dietary education is important for those diagnosed mammalian meat allergy.

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** and **B12**.

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

Therapeutics precautions:

Alpha-Gal is widely distributed in therapeutic agents, and several novel therapeutic agents in particular may prove risky in people who are a-gal sensitised (e.g., wound healing and tumour therapy advances).

The following are potential hazards in those with Alpha-Gal allergy:

1. Cetuximab:

- Due to its a-gal content, fatal reactions have occurred with this agent used in Oncology.

2. Some vaccinations:

- Alpha-gal is measurable in some vaccines such as measles- mumps - rubella and zoster, and other vaccines that may contain mammalian products.

Use of these vaccines may expose patients with a-gal-specific IgE to the risk of an allergic reaction.

3. Gelatine:

- Sources of **gelatine** may need flagging (e.g., vaccines, capsules, tablets, suppositories and collagen-containing agents, including implants).

Some intravenous blood substitutes are gelatin based colloids:

- ♥ Haemaccel / Gelofusine.

4. Porcine heart valve prostheses:

- Alpha-gal sensitisation has likely played a role in serious allergic events after porcine cardiac valve xenograft transplantation.

5. Antivenoms:

- Snake / Redback / funnel web spider / box jellyfish / stonefish antivenoms 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.

[Immuno-prevention:](#)

Allergen immunotherapy (i.e desensitisation) is currently not available to “switch off” tick bite allergy.

Patients who are tick allergic, and in an endemic area for ticks should be supplied with an **EpiPen**.

[Medical Alert Bracelets:](#)

A medical alert bracelet can be worn, especially to avoid the administration of gelatin based colloids.

Killing the tick in-situ before removal:

The available data indicates that for the **prevention of a recurrence** of tick anaphylaxis the tick should be killed in situ before removal.

Killing the tick may also reduce the possibility of the person *becoming* allergic to ticks in the first place.

This can be achieved by the use of **ether-containing agents** to **freeze the tick** where it is embedded. This method has the advantage of being easy to use and the sprays are readily available.

For adult ticks “freeze don’t squeeze”

Once the tick is dead it should be left to drop off the host.

If this is not feasible, it should be removed **without compressing the salivary glands** which can inject allergen, venom (or rickettsia) into the person (see **Australian Paralysis Tick Envenomation in Envenomation folder**).

Ether-containing aerosol sprays are currently recommended for killing ticks.

“**Aerostart**” (and other similar products) have been used extensively to kill ticks in allergic patients.

It should be noted that these products are not registered for use in humans and contain **benzene** but there is long term experience with these products which have been shown to be very effective in treating those with **serious tick allergies**.

The use of *other* ether-containing sprays (e.g. Wart-Off Freeze, Elastoplast Cold Spray) have also been effective but still require further study.

If available, **liquid nitrogen** should also (in theory) be effective.

Freezing the tick (regardless of whether one is concerned about transmission of infection, tick venom or tick allergens) may also have the advantage of reducing the risk of tick sensitization and later development of tick allergy or related allergic syndromes, as discussed below.

Pending future studies of the effectiveness of various tick removal and killing methods, current advice is based on a consensus of “expert opinion” rather than derived from results of formal clinical studies.

Note that for the very small **larval stage nymphs** - these can be killed by the use of **Permethrin** based creams (such as the anti-scabies product “Lyclear”)

For larval stage nymphs - “dab don’t grab”

Tick Removal:

Traditional advice has been to insert fine forceps or tweezers between the skin and the tick mouthpiece and lever the tick out, without killing the tick first.

This method, however, **does not prevent anaphylaxis in tick allergic individuals** and current advice from **ASCIA** specifically advises **against** this method, **before the tick is killed.**

If you find a tick, do **not** forcibly remove it, but rather **kill it first** by using a product to rapidly **freeze** the tick to **prevent it from injecting more allergen-containing saliva.**

Ideally, once killed the tick should be left to fall off naturally (usually within 24 hours) - if it doesn’t fall off, then careful removal with fine tweezers will be necessary. Note that most **household tweezers** are too blunt for safe removal - **“Household tweezers are tick squeezers”**

If tweezers are used then they should be **very fine pointed** so as to ensure that the mouthpiece is being grabbed and not the body of the tick (see **Appendix 1 below**)

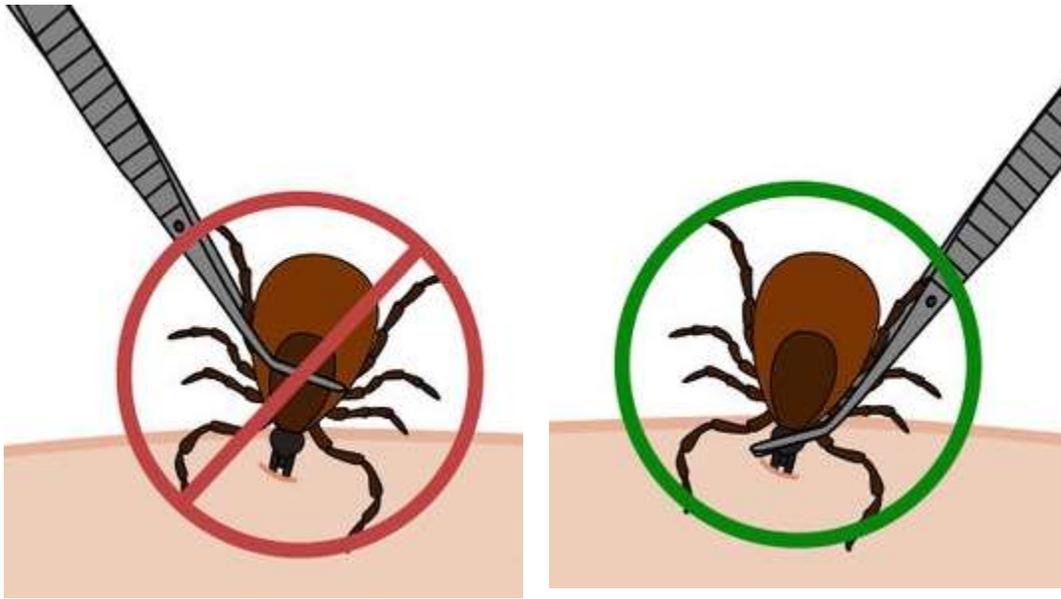
Patients who have had a **tick anaphylaxis previously** should not disturb the tick, but rather should summon paramedics and be taken to the nearest **emergency department** for tick killing and removal by Emergency department staff.

Anaphylaxis:

Anaphylaxis is treated according to standard protocols

See Anaphylaxis (in Allergy folder).

Appendix 1



Tick removal must be done by fine tweezers (as opposed to the usual blunt household tweezers). The mouthpiece may be grabbed - not the body of the tick!

References

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Further resources:

Tick-induced Allergies Research and Awareness (TiARA) at:

- www.tiara.org.au

Dr. J. Hayes

Acknowledgments:

Dr Andrew Ratchford

Reviewed May 2018