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Tick Associated Syndrome: The Alpha-Gal Meat Allergy, Identification, Treatment and Prevention

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ABSTRACT

The incidence of tick-borne diseases has increased in the US and the world, becoming a significant public health challenge. Health care providers need to increase their awareness of tick-borne diseases to include clinical manifestations, treatment and prevention. Tick borne diseases include those transmitted by the lone star tick (Amblyomma americanum) which include Ehrlichiosis, Rocky Mountain Spotted Fever (RMSF), Spotted Fever Rickettsiosis, Southern Tick Associated Rash Illness (STARI), Tularemia, Heartland Virus as well as transmitting the alpha gal meat allergy [1].The alpha gal epitope is not naturally present in humans (or apes) but is present in all other mammals. Exposure to lone star tick bites are associated with a delayed allergic reaction to mammalian meat due to development of antibodies to Galactose-alpha-1, 3-galactose or commonly known as alpha gal [1]. Although Lyme disease is the predominant tick- borne disease in the US which is transmitted by the Black Legged tick (Ixodes scalpularis), the alpha gal meat allergy sensitization caused by the lone star tick is increasing. This is attributed to the increased number of lone star ticks and their expansion into new geographic locations. It is important to educate the public on signs of this allergy, treatment and how to mitigate exposure to tick bites [2,3].

Keywords: Tick-borne diseases, Galactose-alpha-1, 3-galactose, Alpha-gal, IgE, Lone star tick (Amblyomma americanum)

INTRODUCTION

The increase of tick-borne diseases results in larger numbers of persons who become ill and who are also at risk for a delay in being diagnosed. This disease burden creates a significant impact on the healthcare system as well as for individual patients. Early diagnosis, treatment, and mitigation of tick exposure needs to be at the forefront of public health efforts [1, 2].

The association between tick bites and development of an emerging IgE mediated response to alpha-gal has been reported in many countries. Hard bodied ticks which are arthropods are in various parts of the world (Australia, France, Germany, Sweden, Spain, Italy, Korea and Japan) and have been associated with sensitization to the alpha-gal antigen [4, 5]. The alpha-gal epitope (a carbohydrate) is abundant on glycolipids and glycoproteins of mammals except for humans, apes and Old-World monkeys. As alpha gal is present in non-primate mammalian tissues, it is a novel target in food allergy [4].

Exposure to lone star tick bites are associated with a delayed allergic reaction to mammalian meat (beef, pork, lamb) due to an oligosaccharide antigen known as galactose-alpha-1,3-galactose or commonly known as alpha gal [4,5]. Humans and higher primates cannot produce alpha-gal, which makes it possible for antibodies to be produced when exposed to the alpha-gal antigen. Alpha-gal is a major transplant barrier between primates and other mammals [6, 7].

The lone star tick (Ambylomma americanum), a hard-bodied tick can inoculate the alpha-gal antigen into a person's skin during feeding, which in turn will cause the immune system to release a flood of IgE antibodies to fight off the foreign carbohydrate [4,5]. Alpha-gal, a carbohydrate is found on non-primate mammals and lone star tick glycoproteins but is not made by humans. Unlike other food allergies, this condition elicits a delayed onset of anaphylactic symptoms 3-6 hours after ingestion of mammalian or red meat [7].

BACKGROUND

The prevalence of the alpha-gal meat allergy is drastically increasing and although not all patients who are sensitive o alpha gal will experience symptoms, it is estimated that 10% of the US population may have increased IgE titers against

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the alpha-gal carbohydrate. This allergy is often misdiagnosed or there is a delay in diagnosis which places patients at increased risk for life threatening anaphylaxis. The delayed onset of symptoms makes alpha-gal diagnosis challenging. A meat allergy due to alpha- gal is often overlooked [7, 8].

Patients with undiagnosed alpha-gal meat allergy typically present to their health care provider, allergist or emergency department complaining of recurrent or worsening allergic reactions that may include an urticarial rash, abdominal pain or life-threatening anaphylaxis. Of note, classic food allergies such as milk, egg, wheat, soy, peanuts, tree nut, fish and shellfish are allergies to proteins. Alpha gal is unique as it is a carbohydrate, not a protein that is recognized by IgE antibodies [7].

The relationship between tick bites and subsequent meat allergies has come to the forefront in 2005. There were increased incidences of anaphylaxis in patients receiving the drug, cetuximab (a monoclonal antibody made from mouse cell lines) used for treating colorectal and head and neck cancers. Patients who unknowingly were exposed to alpha gal from previous tick bites, developed anaphylaxis within minutes after receiving intravenous cetuximab. Interestingly, these patients often had a history of tick bites and allergy symptoms after ingesting red meat. At the time, this connection was not immediately made [7].

In the US, the IgE antibodies are caused predominately by the bites of larval, nymph or adult lone star ticks. The IgE response triggers a histamine release which initiates the allergic reaction. Patients with the alpha gal allergy develop symptoms 4-6 h after ingesting mammalian meat [1,3]. This is often referred to as "midnight anaphylaxis" as patients will have an evening meal containing mammalian meat and awake hours later with alarm symptoms. After eating red meat, oligosaccharides are absorbed from the gut in a form that enters the circulation slowly. Part of this delay may be a result of conversion of fats to chylomicrons and then further to low density lipoproteins [4]. Symptoms include hives, shortness of breath, abdominal pain and angioedema. Patients experiencing only abdominal pain and/or diarrhea often attributed symptoms with food poisoning [5, 7].

In other countries, other tick species such as the Ixodes ricinus and Ixodes holocyclus are implicated with the transmission of alpha-gal. The Ixodes scapularis in the US which transmits Lyme disease does not induce IgE antibodies to alpha gal. The Lone Star tick (Amblyomma americanum) has another characteristic as it often produces a bite that causes more local site itching than the bite of the Ixodes scapularis tick [7].

Lone star tick larval are most active (after hatching from eggs) at the end of summer to early fall. They are very aggressive in seeking their first blood meal. Unsuspecting individuals traversing in geographic habitats where eggs have been hatched will experience multiple larval bites [7]. An individual can experience hundreds of larval bites in a very short time frame, most often with bites on the ankles and feet. This large exposure of multiple tick bites increases the likely hood of developing alpha-gal allergy. Larvae are not easily seen as they are translucent in color and extremely small (equivalent in size to celery salt). These bites are very irritating to the skin and associated with severe pruritus [7].

The Lone Star larval tick bites are often confused with chiggers. Many individuals refer to lone star larval bites as chigger bites. Chiggers which are the larval form of the Trombiculid mite are mostly found in the south, southeast and Midwest of the US. As they are not known to be in the temperate regions US Northeast [7].

Life Cycle of Hard Ticks

Lone star ticks (Ambylomma americanum) go through three stages which include larval, nymph, and adult stages throughout their two-year life cycle. This cycle is similar for other hard bodied ticks such as black legged ticks (Ixodes scapularis) and dog ticks (Dermacentor variabilis). Ticks require a blood meal at each of these three stages to survive (**Figures 1 and 2**).

Ticks also require a humid environment to survive. In very arid or dry hot environments ticks will desiccate and die. They prefer to be in moist ground covers or leaf litters shaded from the sun. Ticks quest and wait in vegetation such as in grasses or shrubs to find their hosts (mammals, rodents or birds). They sense animals by their heat, vibration and carbon dioxide plume. If their host harbors bacteria, parasites or viruses, the tick may become infected during feeding. At their next feeding, they can then inoculate the host with the infectious agent. Ticks are vectors for disease transmission to humans [1, 2].

Lone star ticks are vectors for Ehrlichiosis, Rocky Mountain Spotted Fever, Spotted Fever Rickettsiosis, Southern Tick Associated Rash Illness (STARI), Tularemia and Heartland Virus as well as transmitting alpha-gal. The Lone Star tick including larvae, contain the alpha-gal epitope in their saliva and gastrointestinal system. Preferred hosts for larval ticks consist of mice, voles, squirrels, birds and chipmunks. Larval ticks also feed on larger animals such as deer and humans. Nymphal and adult ticks will feed again on the next available host, increasing the chance of transmitting disease. White tailed deer (Odocoileus virginianus) are reservoirs for Ehrlichiosis and STARI in the US. The organism associated with STARI is still unknown. Rabbits are a common reservoir for tularemia (F. tularensis). The preferred host for lone star ticks are deer, however, they will feed on other animals such as horses, dogs and humans [1, 8].

It is unusual for Lone Star ticks to carry the Rickettsia rickettsii organism which causes Rocky Mountain Spotted

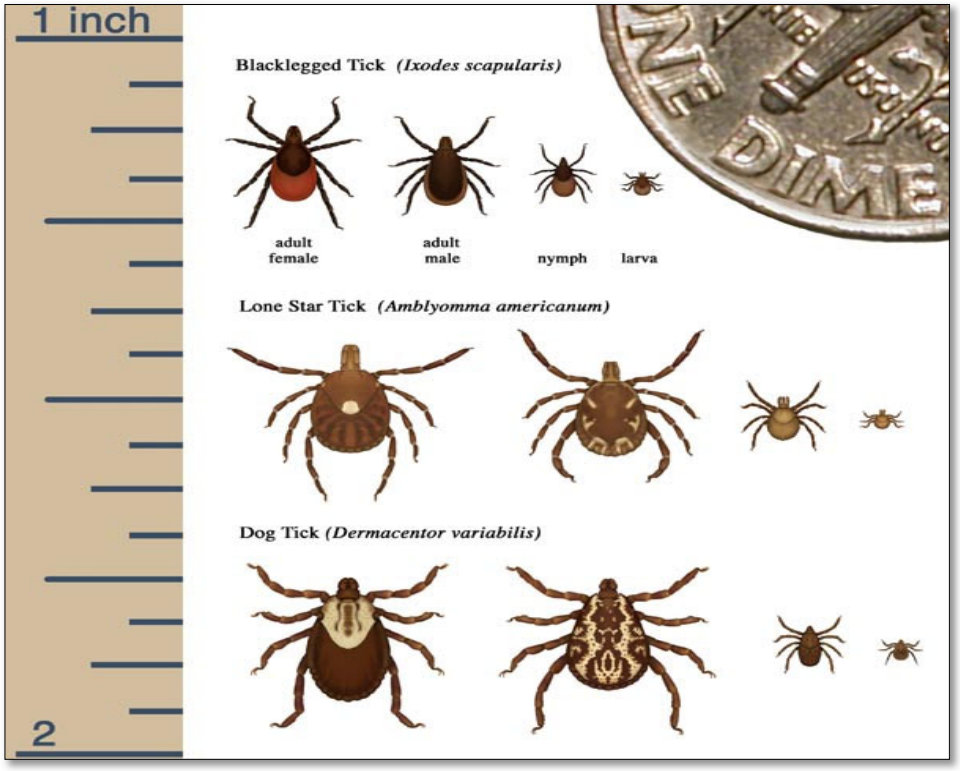

Figure 1. Tick species and size courtesy of the CDC.

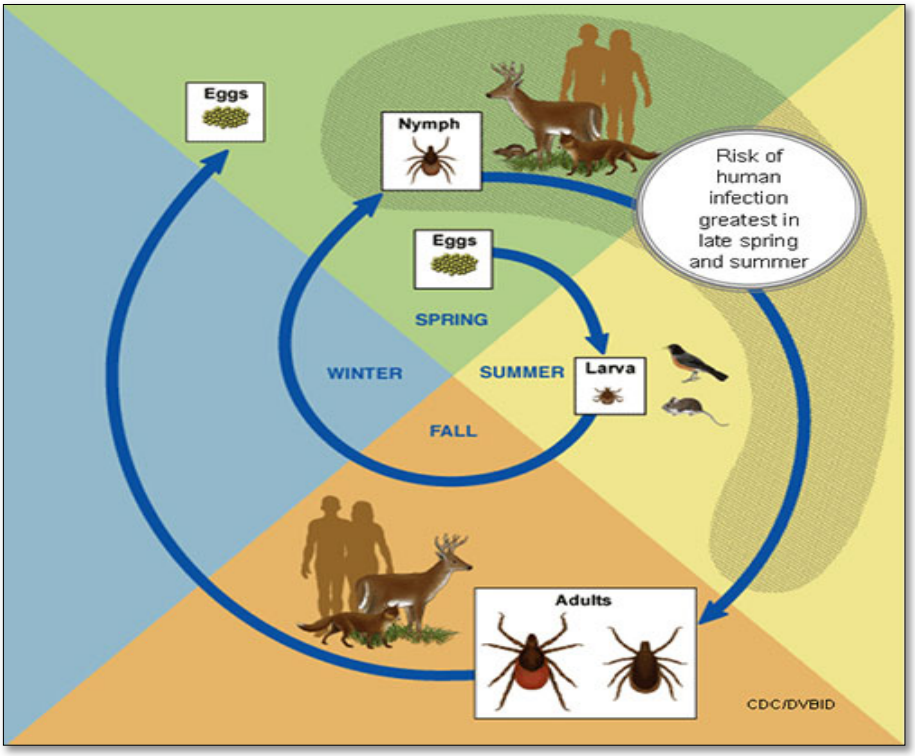

Figure 2. Life cycle of ticks courtesy of the CDC.

Fever (RMSF). Patients exposed to Lone Star ticks rarely report severe febrile illness like the classic presentation of Rocky Mountain Spotted Fever which is transmitted by the Dermacentor variabilis or dog tick. However, Lone Star ticks carry another member of the spotted fever group called Rickettsia amblyommatis, which causes positive rickettsia serology for Rocky Mountain Spotted Fever [9]. A more specific serology test is needed to differentiate these Rickettsia diseases. It is unknown if there is a symbiotic relationship of alpha gal and these new rickettsia species found in Lone star ticks [9].

Ticks wait with hind legs attached to vegetation known as "questing". When an animal brushes by the waiting tick it quickly attaches to the host. If there is no host, the ticks move back down to the ground to rehydrate and then return upward to quest once again. A unique characteristic of the lone star tick is they can withstand longer periods without hydration compared to the Black-legged tick (Ixodes scapularis). Also, the lone star ticks are very aggressive. The adult female lone star ticks are considered hunters that can travel longer distances in order to obtain a blood meal [1, 7].

Ticks attach onto their hosts with their barbs that anchor into skin and can feed for up to several days. Ticks also secrete cement like substance to further secure their anchor along with an anesthetic chemical in their saliva so their presence can go unnoticed by the host [1, 2]. The longer an infected tick is attached during its blood meal, the chance of disease transmission increases. Ticks that feed on humans, especially nymphal ticks can become attached, feed and then fall off without any awareness by the individual. This is especially true if ticks are attached in areas such as the groin, axillae, back or behind the knees [1, 2].

Tick eggs molt into larva prior to their first required blood meal. If they feed on an infected rodent such as a mouse, then the tick may become infected. The larval tick then molts into a nymph; the infected nymphs seek a blood meal which can be a deer (or other mammals) or human and then transmits the infection during the feeding process. In the US, adult ticks prefer to feed and mate on white tailed deer (Odocoileus virginianus), with females then falling off to lay their eggs before they die. Nymphal ticks can also feed on deer as they are often adjacent to them. The more substantial the blood meal for the female, the larger their egg clutch will become. A single female tick typically lays one to three thousand eggs. White-tailed deer are the principal host for the adult ticks; an important means of transport and tick abundance is closely linked to the abundance of these animals. A frost does not kill ticks and they often become active as soon as it is above freezing [1, 2].

ENVIRONMENTAL FACTORS

Factors that foster disease prevalence in ticks include environmental influences such as availability of hosts, precipitation and required habitats. The supply of acorns influences the proliferation of white-footed mice (Peromyscus leucopus) and deer populations, especially in the Northeastern US [5]. Disruptions of habitats caused by humans has set the stage in the ecology of Lyme disease and other tick-borne diseases. When farming moved to the Midwestern US, farms in the northeast became mixed hard wood forests. Suburban development changed landscapes pushing white-tailed deer and other animals out of their habitats. Also, deer populations have increased as they were no longer hunted for food and are now closer to residential areas [5, 6]. These environmental changes have drastically reduced medium sized predators who rely on small prey for food, resulting in increased numbers of rodent reservoirs [1, 8].

White tailed deer are heavily covered with ticks in the late fall and early spring. The use of roller applicators such as the "four posters" which apply insecticides to the deer while they are eating corn placed into bins. The pesticides will kill the adult ticks on the deer which subsequently halts those ticks from laying eggs, therefore reducing tick populations [1].

The epidemiological evidence about this recent migration of Lone Star ticks to the US northeast is complex and not clear (**Figure 3**).

Figure 3. Courtesy of the CDC.

The increase in deer populations which commonly carry these ticks along with climate change, bird migrations and peri domestic disruptions has most likely contributed to this phenomenon. The deer habitat has been pushed out of their woodland habitats due to increased development of houses, expansion of farms (with higher fencing), towns and villages [1, 6].

CLINICAL PRESENTATION

Alpha-gal mammalian meat allergy affects patients of all ages. An affected individual with alpha gal allergy typically experiences an allergic reaction 3-6 h after ingesting

mammalian meat such as beef, pork or lamb. This is also known as "Midnight Anaphylaxis". Allergy symptoms may be worse with consumption of fattier meats. Symptoms range from pruritus, localized hives, GI upset (abdominal pain, diarrhea, nausea or vomiting), and nasal congestion, wheezing, to angioedema or anaphylaxis (swelling of the lips, face, tongue and throat). Anaphylactic reactions require emergency hospital care. Patients report more severe reactions after eating large, fatty amounts of red meat or organ meat such as liver or kidney [5].

Histamine is a fundamental mediator in the pathophysiology of the allergic response which affects smooth muscle, mucosa and skin. Upon exposure, an antigen cross-links specific immunoglobin E (IgE) bound to the surface of mast cells and basophils. This leads to the release of histamine and other pro-inflammatory mediators. Histamine, then binds to receptors on a wide variety of cells within the surrounding tissues and vasculature [10].

Histamine receptors have varying degrees of responsibility for mediating an allergic response. H1 and H2 receptors are present on a wide range of cells to include endothelial, epithelial, smooth muscle, neurons and cells of the innate and acquired immune system. When these receptors are activated, they stimulate both the early phase of an allergic response (vasodilatation, swelling and hypotension) and the late-phase response, by upregulating cytokine production and cell-adhesion molecules, causing worsening symptoms caused by this pro-inflammatory state [10].

DIAGNOSIS

Patients who reside or travel to endemic areas where lone star ticks are abundant are at higher risk of developing the alpha-gal meat allergy. A detailed history needs to focus on symptoms in relation to types of food ingested and how food was prepared. Additional factors need to be ascertained such as recent exercise, ingestion of alcohol, use of nonsteroidal anti-inflammatory medications which often make allergy symptoms worse [6]. When making the diagnosis of alpha-gal it is important to note if onset of symptoms occur 3 to 6 hours after eating mammalian meat. Ascertain if symptoms started as an adult with no prior history of allergies [5].

The diagnosis is confirmed by obtaining patient serum and testing for this allergy using serum IgE immunoassays to galactose-alpha-1.3-galactose (alpha gal) [6]. Diagnosis is most likely if antibodies are greater to 2 IU/ml, or more than 2% of the total IgE [9]. This specific IgE antibody level of 0.35 kU/L are commonly considered the cut off point for sensitization for the allergen. High levels of antibodies to this allergen show strong correlation with clinical disease but not severity. Patients with alpha-gal allergy may test positive to cat IgA due to cross sensitization [6].

It is recommended that patients with this allergy be under the care of an allergist, avoid meat, meat products including gelatin. An epinephrine auto injector is also needed to treat potential anaphylactic reactions. This allergy can wane over time if there is no re-exposure to Lone star tick bites [4, 8].

TREATMENT

An avoidance diet of mammalian meat is the mainstay of treatment for alpha-gal. In most areas of the US, this means beef, pork, lamb, venison, and organ meat (kidneys, liver, heart, intestines or tripe). In some parts of the US, venison, rabbit and bear meat may be eaten. In other parts of the world, this may include horse, goat or other small mammals. Some patients may need to avoid dairy and gelatin [9].

Patients need to be educated and mindful of the food that they are eating. This is especially important when dining out, as they need to inquire about meal ingredients. Patients with alpha-gal do not have reactions to poultry or fish. However, there have been reports of reactions to canned tuna that was contaminated with dolphin which is a mammal. For example, if a patient is eating commercially made fish chowder, they need to be sure that there is no added meat such as bacon or lard [9].

Gelatin derived from beef and/or pork, is a concern as it is contained in many foods and candy. Gelatin is also present in medication or vitamin gel caps, as well as in some vaccines, such as the MMR (measles, mumps and rubella), varicella and Zoster. Gelatin is present in some plasma expander products (UK and Australia) [9]. It is important for affected patients to diligently read ingredient labels on food products.

Other concerns for patients with alpha gal sensitivity include medications that contain mammalian proteins, fat or alpha gal epitopes such as in pancreatic enzymes, heparin, magnesium stearate and anti-venom. Bovine or porcine heart valve replacements have been known to cause reactions or degrade more rapidly in patients with alpha-gal sensitivity [9].

Patients and their families may experience anxiety due to fear of anaphylaxis. After the diagnosis of alpha-gal a written plan may be helpful for patients with an outline of symptoms and instructions for treating allergic reactions. Patients that cannot tolerate any mammalian products, such as gelatin and dairy need to have a complete avoidance strategy. It may be helpful to refer patients and their families to a dietician knowledgeable about the alpha-gal allergy. Patients may require iron and vitamin B12 supplementation to prevent deficiencies in patients [5].

Patients experiencing mild reaction may be treated with an oral histamine H1-receptor antagonist which block histamine such as cetirizine. Patients need to be aware of worsening symptoms that require epinephrine and immediate medical attention [5].

The first line treatment for severe allergic reactions after calling for emergency services (911), especially if there is airway involvement is epinephrine. Epinephrine can be

administered undiluted or by auto injector. The epinephrine or adrenaline dose for children is 1:1000 (1mg/mL) 0.01 mL/kg, administered by subcutaneous or intramuscular injection (maximum dose 0.3 mL). For adults, the dose 0.5 mL administered by subcutaneous or intramuscular injection. For pediatric patients using an auto injector pen (EpiPen Jr. prefilled syringe or its authorized generic), the dose is 0.15 mg given for patients between 15-30 kg administered subcutaneous or intramuscularly. For adults using an autoinjector pen (EpiPen prefilled syringe or its authorized generic), the dose is 0.3 mg for patients >30 kg administered subcutaneous or intramuscular injection. A second dose may be required after 5-15 min if there is a suboptimal response to the first injection or experiences a bi-phasic reaction (reoccurrence of initial symptoms develops after an apparent resolution of the initial reaction) [5].

Prevention of tick exposure

It is also important for patients to be educated about preventing tick exposure and how to safely remove ticks. Patients need to be informed that further tick bites will lead to increases in IgE titers to alpha gal [8]. In the event of a lapse in implementing effective tick avoidance measures, preventing the transmission of significant quantities of the alpha-gal allergen is achieved by appropriate tick removal techniques. Tick removal needs to be done as soon as a tick is noticed. Tick removal techniques for adults and children should be the same for domestic animals such as cats, dogs and horses [8].

It is important for the public to be educated in taking preventive measures against ticks year-round and to be especially vigilant in warmer months when ticks are most active. Avoidance of wooded and brushy areas with high grass and leaf litter will reduce exposure risk [2]. Alpha-gal blood levels of IgE often drops over time in patients who avoid recurrent tick bites [11].

In the US, White tailed deer are heavily covered with ticks. The “Four Posters” program has been successful in the reduction of tick populations by applying Insecticides onto deer while they are eating corn from dedicated bins. The pesticide kills ticks feeding on the deer including the adult female ticks. Without the adult females’ eggs, the tick life cycle is halted [1].

Education should include

- Walking in the center of trails, avoiding brushing against tall grass and shrubs.
- Use of repellents that contain 20 to 30% DEET (N, N-diethyl-mtoluamide) on exposed skin for protection that lasts up to several hours. Always follow product instructions. Parents should apply this product to their children, avoiding hands, eyes, and mouth.
- Use products that contain permethrin on clothing. Treat clothing and gear, such as boots, sneakers, pants, socks and tents with products containing 0.5% permethrin. It remains protective through several washings. Pre-treated clothing is available and may provide longer-lasting protection.
- Bathing or showering soon after returning indoors (preferably within 2 h) to wash off and more easily find ticks.
- Conduct a full-body tick check using a hand-held or full-length mirror to view all parts of body upon returning from tick infested areas.
- Parents should check their children for ticks under the arms, in and around the ears, inside the umbilicus, behind the knees, between the legs, around the waist, and especially in their hair.
- Examine gear and pets. Ticks can ride into the home on clothing and pets, then attach to a person later, so carefully examine pets, coats, and day packs.
- Tumble dry clothes in a dryer on high heat for 10-20 min to kill ticks on dry clothing after returning indoors. If the clothes are damp, additional time may be needed. If the clothes require washing first, hot water is recommended. Cold and medium temperature water will not kill ticks effectively. If the clothes cannot be washed in hot water, tumble dry on low heat for 90 min or high heat for 60 min.

To reduce tick exposure near home environments, it is helpful to:

- Clear tall grasses and brush around home and at the edge of lawns.
- Maintain a three-foot barrier of wood chips or gravel between lawns and wooded areas and around patios and play equipment. This will restrict tick migration into recreational areas.
- Frequent mowing of lawns: grass should be kept at three inches or less in height.
- Remove leaf litter (ticks do not survive in dry, hot, low humid conditions; they prefer to stay in shaded, damp areas such as in leaf litter).
- Keep wood neatly stacked in a dry area as this discourages rodents.
- Keep playground equipment, decks, and patios away from yard edges and trees and place them in a sunny location, if possible. Remove trash from the yard that may give ticks a place to hide.
- The use of acaricides (tick pesticides) can reduce the number of ticks in treated areas of outdoor living spaces and yards. It is recommended application of acaricides be applied by a professional specialist.
- The Environmental Protection Agency (EPA) and state (US) determine the availability of pesticides.

There are professional pesticide companies that can apply appropriate pesticides [2, 3].

Education for proper tick removal should include (Figure 4)

- Use of fine-tipped tweezers to grasp the tick as close to the skin's surface as soon as possible.
- Pull tick upward with steady, even pressure.
- Don't twist or jerk the tick; this can cause the mouthparts to break off and remain in the skin. If this happens, remove the mouthparts with tweezers.
- If unable to remove the head easily with clean tweezers, area can be left alone to let the skin heal. Transmissions of pathogens do not occur if head of tick remains in skin, however this can result in skin irritation and inflammation.
- After removing the tick, thoroughly clean the bite area and hands with rubbing alcohol, an iodine scrub, or soap and water.
- Avoid following folklore remedies such as the use of hot matches; petroleum jelly or nail polish remover. These interventions are not effective can cause injury or infection.
- Dispose of a live tick by submersing it in alcohol, placing it in a sealed bag/container, wrapping it tightly in tape, or flushing it down the toilet [2, 3].

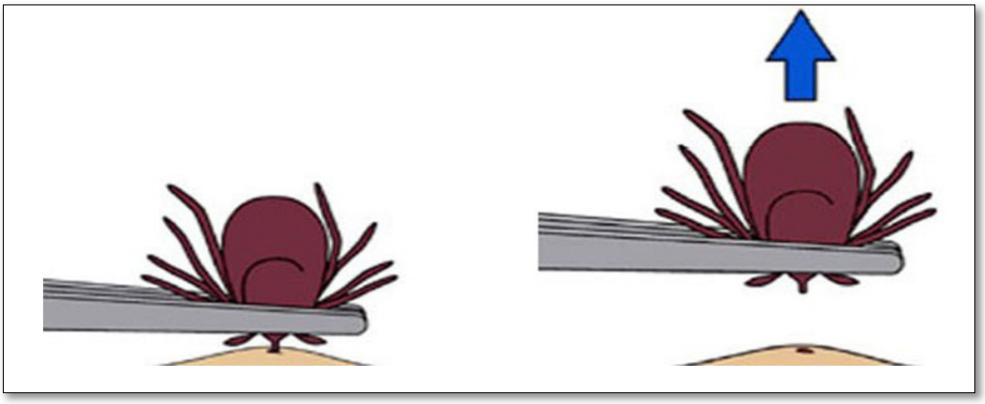

Figure 4. Courtesy of the CDC.

CONCLUSION

Tick induced alpha gal meat allergies are becoming increasingly prevalent in tick endemic areas in the US and worldwide. The lone star tick remains an important vector for tick-borne illnesses to include transmission of the alpha-gal meat allergy. It is important that health care providers recognize and manage patients who have the alpha-gal meat allergy [4, 5]. Patients need education about treatment, abstinence from mammalian meat and food products along with avoidance of tick exposures. Environmental interventions are needed to control animal reservoir populations. Reduction in deer and tick populations need to be implemented and expanded. Research about the alpha-gall allergy with best evidence-based practices need to be continued [1].

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