HEALTH ADVISORY

Missouri Department of Health and Senior Services

Paula F. Nickelson, Director **14 May 2024**

Alpha-gal Syndrome: Important Information for Missouri Healthcare and Public Health Professionals

The Missouri Department of Health & Senior Services (DHSS) uses four types of documents to provide important information to medical and public health professionals, and to other interested persons:

Health Alerts convey information of the highest level of importance which warrants immediate action or attention from Missouri health providers, emergency responders, public health agencies, and/or the public.

Health Advisories provide important information for a specific incident or situation, including that impacting neighboring states; may not require immediate action.

Health Guidances contain comprehensive information pertaining to a particular disease or condition, and include recommendations, guidelines, etc. endorsed by DHSS.

Health Updates provide new or updated information on an incident or situation; can also provide information to update a previously sent Health Alert, Health Advisory, or Health Guidance; unlikely to require immediate action.

Phone: 800-392-0272
Fax: 573-751-6041
Web: health.mo.gov

Summary

Alpha-gal Syndrome (AGS) is an emerging, tick bite-associated allergic condition characterized by an immunoglobulin E (IgE)-mediated hypersensitivity to galactose-alpha-1,3-galactose (alpha-gal), a sugar molecule found in most non-primate mammalian meat and products derived from these mammals. It is also known as mammalian meat allergy, alpha-gal allergy, red meat allergy, and tick bite meat allergy. AGS is a serious and potentially life-threatening allergic condition, with symptoms and severity varying among persons. Symptoms generally appear 2-6 hours after eating foods or exposures to other products containing alpha-gal. Persons with AGS may have reactions that range from mild hives to severe and life-threatening anaphylaxis. Evidence suggests that AGS is primarily associated with the bite of the lone star tick, *Amblyomma americanum* in the United States. No cure is currently available; therefore, early identification and preventive efforts are the mainstay of addressing AGS.

A recent national survey of mostly primary care physicians in the U.S. found 78% of providers have little to no knowledge of AGS, and only 5% felt “very confident” in their ability to diagnose or manage patients with AGS.[1] The survey findings raised concerns for a delayed or missed diagnosis and incorrect patient management. Nearly 10% of patients diagnosed with idiopathic anaphylaxis were later found to have AGS.[2] Alpha-gal-specific IgE (sIgE) antibody testing results processed by the commercial laboratory responsible for nearly all testing in the United States before 2022 suggested that suspect cases predominantly occurred in counties in states located within the southern, midwestern, and mid-Atlantic U.S. regions, including Missouri.[3] Therefore, the Missouri Department of Health and Senior Services (DHSS) is issuing this Health Advisory to raise awareness of AGS and provide up to date information and resources to Missouri’s healthcare providers.

Background

AGS is not caused by an infection, but rather an (IgE)-mediated allergic condition which has been reported worldwide since 2007. People can get AGS after being bitten by a tick. The lone star tick (Fig 1.) can transmit alpha-gal to people through its saliva, which can trigger the immune system to produce IgE antibodies against alpha-gal causing AGS.[4, 5]

As a result, affected persons become very sensitive to an alpha-gal sugar molecule found in red meat and dairy products. A recent study found substantial epidemiologic evidence implicating a tick bite as a risk factor for AGS.[5] Patients with AGS were more likely than controls to report a tick bite, to have more ticks found on their bodies, and to have found more embedded ticks on their bodies before developing AGS.[5]

The exact mechanism, causal relationship, and risk factors associated with the development of AGS are currently unknown. The induction of alpha-gal sIgE by a tick bite is thought to be a key event in the development of AGS. In some persons, tick bites result in the development of sIgE antibodies in the absence of clinically apparent AGS resulting in a state referred to as **sensitization**. It is not known why some people develop alpha-gal sIgE but do not present with AGS, so other intrinsic factors may also play a role. It is also possible a single tick bite may result in sensitization, but that repeated tick bites could be required for some persons to develop AGS.[5]

Figure 1. Lone star Tick.[4]

The lone star tick is thought to be the most likely culprit related to AGS in the U.S., but a link to other kinds of ticks has not been ruled out. A temporal and geographic alignment of the onset of AGS and state of residence with the seasonal timing of the lone star tick activity and the known geographic distribution of the lone start tick respectively has also been reported.[3,5] The lone star tick is a well-known vector for tickborne illnesses in the U.S. including ehrlichiosis and tularemia. Missouri is among the states with the highest rates of ehrlichiosis and tularemia cases. Consequently, it is not unexpected that Missouri is among the states with the highest prevalence of sIgE-positive persons and AGS (Fig 2).[3]

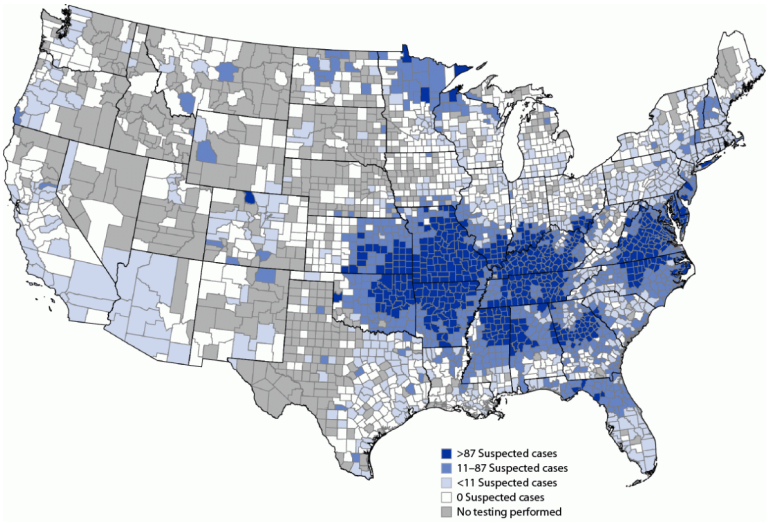

Figure 2. Geographic distribution of suspected alpha-gal syndrome cases per 1 million population per year — United States, 2017–2022.[3]

Clinical Presentation

AGS is characterized by a delayed onset allergic reaction following ingestion of mammalian meat or its derivatives. Unlike other food allergies, the symptoms often appear delayed for 2-6 hours after eating or other exposures to products containing alpha-gal.[6] Exposures to alpha-gal commonly include beef, pork, lamb, or meat from other mammals, as well as many other foods, including dairy products, medications, and medical products made using materials from mammals. Some foods and medications contain gelatin, which is often made from mammal-derived collagen or other materials from animals. Symptom onset is more rapid with intramuscular or intravenous exposures, such as from some medical products (e.g., certain monoclonal antibodies, heparin, antivenom).[6]

The clinical spectrum of AGS is broad with symptoms ranging from urticaria and gastrointestinal distress to angioedema and life-threatening anaphylaxis. The mucocutaneous signs and symptoms were found to be the most common, with hives/urticaria being most frequently reported followed by gastrointestinal symptoms.[6] Respiratory or cardiovascular symptoms were less frequently reported. AGS reactions can vary from person to

person and in some persons may not occur after every alpha-gal exposure. Approximately 75% of patients identified as having AGS met the criteria for anaphylaxis with a symptom profile that was distinct from other food allergies.[6]

The symptoms of AGS reaction can include[4]:

- Hives or itchy rash
- Nausea or vomiting
- Heartburn or indigestion
- Diarrhea
- Cough, shortness of breath, or difficulty breathing
- Drop in blood pressure
- Swelling of the lips, throat, tongue, or eye lids
- Dizziness or faintness
- Severe stomach pain

Diagnosis

AGS is diagnosed by an allergy specialist or other healthcare provider through a detailed patient history, physical examination, a blood test that looks for specific antibodies, and follow-up evaluation after the AGS exposure has been removed. There is no definitive sIgE level that confirms AGS diagnosis. Tested persons can have sensitization to alpha-gal without clinical reactivity, and only a fraction of patients with alpha-gal sIgE experience symptoms with meat ingestion.[8] Currently, blood test levels of alpha-gal sIgE of ≥ 0.1 kU/L are considered positive.[3,5,6] The clinical relevance of the higher proposed cut-off value of 0.35 kU/L remains unclear.[8] Tests for alpha-gal sIgE are available at several large commercial laboratories and may be available at certain academic institutions. Even though the presence of alpha-gal sIgE is an established diagnostic criterion, levels do not correlate directly with symptoms or disease severity.[6,7,9] Even more challenging is that **asymptomatic alpha-gal sensitization is known to occur, so not all patients who test positive for alpha-gal sIgE will have AGS**. For example, the sensitization rate was found to be 22% among a cohort of patients undergoing endoscopy without a history of AGS in North Carolina,[10] while an asymptomatic cohort in Tennessee showed a sensitization rate of 20.8%.[11] Additionally, a study conducted in Germany to characterize the prevalence of alpha-gal sIgE positivity among forest service employees and hunters found that 35% were sensitized to alpha-gal, but only 8.6% reported clinical symptoms of AGS.[12] Published data also demonstrated that among random cohorts of subjects in TN, VA, and NC 15% or more of the population have IgE to alpha-gal.[13] In such populations with high alpha-gal sensitization rates, the alpha-gal sIgE ≥2 IU/ml or >2% of the total IgE makes the AGS diagnosis more likely.[13] Measuring total IgE is helpful because some cases are non-atopic and have low total IgE.

The anti-alpha-gal IgE diagnostic assay can lead to false-positive results in those individuals where alpha-gal IgE sensitization may be related to bee and wasp stings, parasitism, atopy, or cat ownership, creating cases where these antibodies do not match the clinically pathognomonic history of AGS.[8] Thus, the alpha-gal sIgE testing is a helpful diagnostic tool but cannot be relied on solely for a diagnosis. Skin tests documenting a reaction to certain allergens (such as pork or beef) may also be used to diagnose AGS.[4,7]

Management

The management of patients with AGS generally requires a multi-faceted, patient-centered approach, including prevention of additional tick bites, antihistamine use, a diet void of mammalian meat and products derived from mammals to avoid allergic reactions, and follow-up visits with a healthcare provider. Patients experiencing an anaphylactic reaction require emergent medical care.

Not all patients with AGS have reactions to every ingredient containing alpha-gal. Mammalian meat (such as beef, pork, lamb, venison, rabbit, etc.) can contain high amounts of alpha-gal. Certain cuts of meat may contain more

than others. Because around 5% to 29% of people with AGS may have allergic reactions to dairy products (which contain alpha-gal, though at lower levels than meat), food products that contain milk and milk products may need to be avoided.[6] Some patients with AGS may be able tolerate milk products. Although very rare, some people with severe AGS may react to ingredients in certain vaccine types/brands (lists of additives to specific vaccines, called vaccine excipients, are available through CDC's Pink Book[14]) and medications/products that contain gelatin, glycerin, magnesium stearate, and bovine extract. Other medical products such as heart valves from pigs or cows, monoclonal antibodies, heparin, and certain antivenoms are animal-derived and may also contain alpha-gal. Persons suspected for AGS should read food and medicine product labels carefully.[15]

People with AGS who need to avoid eating meat from mammals can continue to eat chicken, turkey, fish, and other non-mammalian meats because those meats do not contain alpha-gal. It is important to consider that many varieties of sausages use casings derived from pork gut, such as chicken and turkey sausages, and consumption may induce anaphylactic or other reactions.[13] As with any severe allergy, patients with AGS should work with their healthcare providers to make decisions about individual risks and benefits from specific medications/vaccines. There is no clear evidence to indicate how long patients must maintain avoidance before adding back alpha-gal-containing products, but many report having to avoid alpha-gal for years. Over time, in the absence of repeated tick-bite exposures, the level of IgE antibodies against alpha-gal may decrease, and, as a result, some people with AGS may again be able to consume beef, pork, and other mammalian meats and other products that contain alpha-gal without having an allergic reaction. Spontaneous resolution of AGS is more likely in those who avoid additional tick bites and experience a decline in alpha-gal sIgE levels over time. All patients should receive personalized guidance on management of their AGS under the direct supervision of their qualified healthcare provider.

Prevention

Taking steps to prevent tick bites is crucial to reduce the risk of the development and persistence of AGS. For patients with a history of AGS, additional tick bites may heighten or reactivate allergic reactions to alpha-gal. Repeated lone star tick bites (or bites from other species of ticks associated with AGS in other parts of the world) can cause IgE antibody levels to rise or prevent them from decreasing. **Preventing tick bites is also an important measure to reduce the risk of other tickborne illnesses diagnosed in Missouri including ehrlichiosis, Rocky Mountain spotted fever, tularemia, Heartland virus, Bourbon virus, and Lyme disease.** Additional information regarding tickborne illnesses in Missouri is available on Missouri's Tickborne Disease Story Map.[16]

It is important to consider the following information and guidance for the prevention of tick bites.

- Whenever possible, avoid grassy, brushy, and wooded areas, where ticks may be found.
- When hiking, walk in the center of trails.
- Use Environmental Protection Agency (EPA)-registered insect repellents[17] on any exposed skin. EPA-registered active ingredients such as DEET and picaridin are widely available.
- Treat clothing and gear with products containing 0.5% permethrin. Treated items will remain protective through several washings. Alternatively, you can buy pre-treated clothing and gear.
- After being outdoors, carefully check your clothing, gear, and pets for ticks.
- Whenever possible, shower and change clothes soon after spending time outdoors.
- If you see an attached tick, remove it immediately.

Surveillance and Reporting

In 2022, a national surveillance case definition was developed for AGS to provide a set of uniform criteria for public health surveillance.[18] Surveillance case definitions enable public health officials to classify and count cases consistently across reporting jurisdictions. Surveillance case definitions are not intended to be used for the purposes of making a diagnosis or for decisions regarding treatment. AGS is not included on the Nationally

Notifiable Condition List and is not a reportable disease/condition in Missouri. AGS is however, an important public health concern that is impacting Missourians. In addition to increasing awareness and information regarding AGS to medical providers, DHSS continues to be active participants in the national discussion regarding AGS. Missouri DHSS is also monitoring developments in AGS research and continues to evaluate the feasibility of heightening surveillance efforts for AGS in Missouri.

Additional Information

For additional information on AGS, visit CDC's AGS website[4], the references provided, and/or seek consultation with a healthcare provider specializing in Allergy and Immunology. Missouri healthcare providers can contact their local public health agency or the DHSS's Bureau of Communicable Disease Control and Prevention at 573-751-6113 with questions regarding this Health Advisory.

References

1. Carpenter A, Drexler NA, McCormick DW, et al. Health care provider knowledge regarding alpha-gal syndrome—United States, March–May 2022. MMWR. 2023 July;72(30):809-814.
2. M.C.Carter, K.N. Ruiz-Esteves, L.Workman, et al. Identification of alph-gal sensitivity in patients with a diagnosis of idiopathic anaphylaxis. *Allergy*. 2018 May; 73(5): 1131-1134.
3. Thompson JM, Carpenter A, Kersh GJ, et al. Geographic distribution of suspected alpha-gal syndrome cases—United States, January 2017–December 2022. MMWR. 2023 July;72(30):815-820.
4. CDC. Alpha-gal Syndrome website. Visited April 2024.
5. Kersh GJ, Salzer J, Jones E, et al. Tick bite as a risk factor for alpha-gal-specific immunoglobulin E antibodies and development of alpha-gal syndrome. Ann Allergy Asthma Immunol. 2022 130(4): 472-478.
6. Binder A, Cherry-Brown D, Biggerstaff B, et al. Clinical and laboratory features of patients diagnosed with alpha-gal syndrome – 2010-2019. *Allergy*. 2023;78:477-487.
7. Commins S.P. Diagnosis and Management of Alpha-gal Syndrome: Lessons from 2,500 Patients. *Expert Rev Clin Immunol*. 2020;16:667-77.
8. Vaz-Rodrigues R, Mazuecos L, Fuente J. Current and Future Strategies for the Diagnosis and Treatment of the Alpha-Gal Syndrome (AGS). *J Asthma Allergy*. 2022 Jul 18;15:957-970.
9. Binder A, Cumins, M, Altrich, M, et al. Diagnostic testing for galactose-alpha-1,3-galactose, United States, 2010 to 2018. *Ann Allergy Asthma Immunol*. 126(2021) 411-416.
10. Burk CM, Beitia R, Lund PK, et al. High rate of galactose-alpha-1,3-galactose sensitization in both eosinophilic esophagitis and patients undergoing upper endoscopy. *Dis Esophagus*. 2016 Aug;29(6):558-62.
11. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 2008;358(11):1109–17.
12. Fischer J, Lupberger E, Hebsaker J. Prevalence of Type I Sensitization to Alpha-gal in Forest Service Employees and Hunters. *Allergy.* 2017 Oct;72(10):1540-1547.
13. Platts-Mills TAE, Li R, Keshavarz B, et al. Diagnosis and Management of Patients with the α-Gal Syndrome. The Journal of Allergy and Clinical Immunology: In Practice 2020;8(1):15-23.e1.
14. CDC Epidemiology and prevention of Vaccine-Preventable Diseases (The Pink Book). Appendix B Vaccine Excipient Table.
15. U.S. Food and Drug Administration's Have Food Allergies? Read the Label webpage.
16. Missouri Department of Health and Senior Services "Missouri Tickborne Disease Story Map".
17. U.S. Environmental Protection Agency's Repellents: Protection against Mosquitoes, Ticks, and Other Arthropods webpage.
18. Council of State and Territorial Epidemiologists Alpha-gal Syndrome (AGS) 2022 Case Definition accessed on CDC Nationally Notifiable Diseases Surveillance System webpage
19. CDC List of Alpha-gal Syndrome Publications, Training, and Resources