

A case of alpha-gal syndrome: Recall urticaria and 10 years of measurements of IgE to galactose- α -1,3-galactose



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Alpha-gal IgE level can change rapidly. Reassessment of a patient's alpha-gal IgE level may be helpful in the patient's clinical follow-up. Pruritus related to the site of a previous tick bite strengthens the diagnosis of alpha-gal syndrome. (J Allergy Clin Immunol Global 2024;3:100280.)

Key words: Alpha-gal syndrome, delayed anaphylaxis to red meat, red meat allergy, recall urticaria, tick bite, natural history, IgE, galactose- α -1,3-galactose

In 2008, alpha-gal syndrome (AGS) was described as an IgE-mediated food allergy toward the oligosaccharide galactose- α -1,3-galactose (alpha-gal) present in nonprimate mammals and New World monkeys.¹ AGS is characterized by urticaria, angioedema, pruritus, gastrointestinal symptoms, and/or anaphylaxis developing 2 to 6 hours after consumption of mammalian meat or other alpha-gal-containing products. The diagnosis of AGS is usually made on the basis of these delayed symptoms and elevated level of serum-specific IgE to alpha-gal. The recognition of AGS started with a distinct geographic pattern of patients experiencing anaphylaxis after their first infusion with cetuximab, a novel mAb for treating cancer.¹ It was shown that the anaphylactic episodes occurred in patients with preexisting antibodies to alpha-gal in geographic areas with a high prevalence of ticks.¹ A strong link between tick bites and subsequent AGS has been established, and it has been indicated that levels of IgE to alpha-gal seem to decrease if the patient avoids new tick bites and, accordingly, that a new tick bite can yield a marked increase in the alpha-gal IgE level.^{2,3} Further, 2 recent case reports of AGS described

Abbreviations used

AGS: Alpha-gal syndrome
alpha-gal: Galactose- α -1,3-galactose

urticaria at the site of a previous tick bite, which was labeled as recall urticaria.^{4,5} In particular, recall urticaria has been described in case reports in relation to allergen-specific immunotherapy with a local reaction at the site of previous allergen injections after, for example, administration of a new allergen⁶ or environmental exposure to the allergen,⁷ drugs,⁸ or food.⁹ In this case, we have more than 10 years of repeated measurements of levels of IgE to alpha-gal, showing the first longitudinal data on how IgE level changes over the course of a decade. Additionally, this case highlights the potential importance of symptoms related to the tick bite.

In late 2012, a man in his 60s who was undergoing radiation therapy for prostate cancer started experiencing severe local pruritus at the site of the latest tick bite that he had received that year. He had previously undergone radical prostatectomy and was not treated with chemotherapy. The patient lived in a forest area and had a history of repeated tick bites and several instances of suspected Lyme disease with erythema migrans rash, which were treated with penicillin. Testing for IgG to *Borrelia burgdorferi* yielded a weakly positive result. After the patient completed radiation therapy, his pruritus worsened, with frequent episodes of generalized pruritus. There was severe illness in the patient's family; thus, attending to the symptoms was not prioritized. Still, the patient's medical record revealed at least 3 visits to a general practitioner for severe pruritus from April to May 2013. The patient had a typical Danish diet, including mammalian meat. However, because of the illness in the patient's family, cooking was limited to primarily rye bread, oats, potatoes, and chicken. A screening for food allergy in May 2013 revealed specific IgE to milk (f2) at a level of 0.37 kU_A/L and to egg white (f1) at 0.32 kU_A/L (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden). In June 2013, the results of skin prick tests using panels of aeroallergens (birch, grass, mugwort, horse, dog, cat, house dust mites, and molds) and food allergens (wheat flour, oat, egg, raw cow's milk, peanut, rye flour, soy, pork, and cod) conducted by a dermatologist were all negative. There are no known food allergies or instances of urticaria among the patient's first-degree relatives.

In August 2013, the patient consumed approximately 100 g of beef and/or pork in the evening, and at 2 AM he woke up with severe abdominal pain and respiratory distress. At that time,

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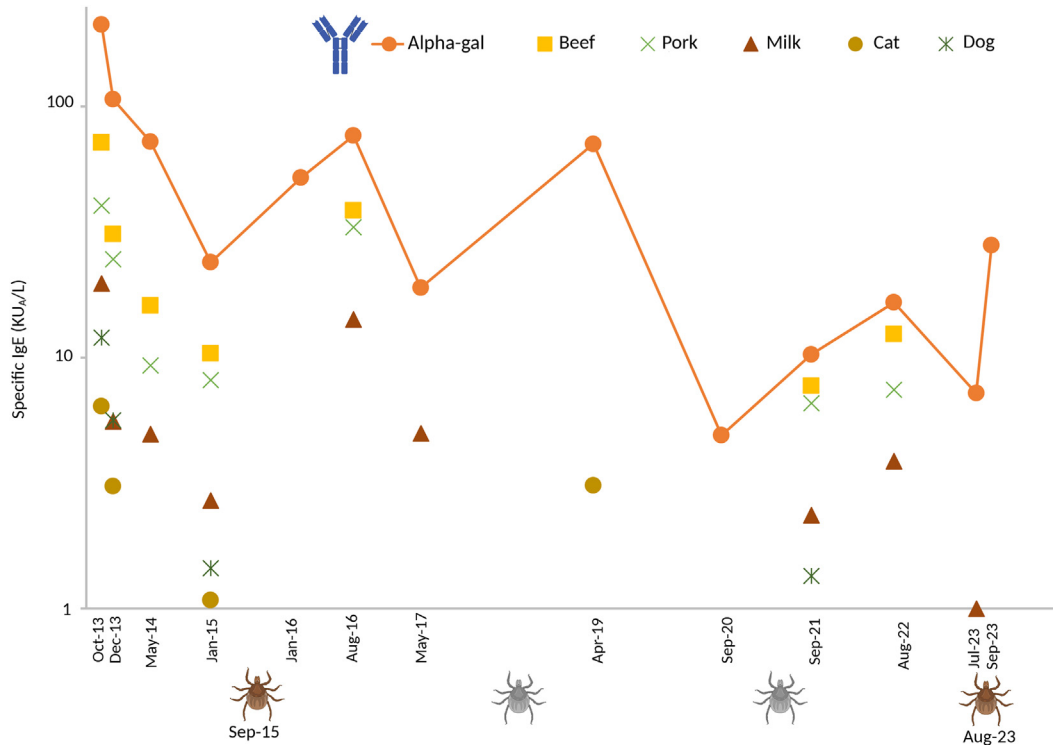


FIG 1. Levels of serum-specific IgE levels from 2013-2023. Brown ticks indicate known tick bites, and gray ticks indicate suspected tick bites. The IgE measurements are plotted on a logarithmic scale and were analyzed by ImmunoCAP. Figure created with [BioRender.com](https://www.biorender.com).

however, the patient did not connect the incident with meat intake. In late September 2013, a relative shared an article from a Danish newspaper describing the novel food allergy AGS and suggested it as a possible cause of the patient's symptoms. In October 2013, the patient's level of alpha-gal-specific IgE was determined to be 212 kU_A/L (72 kU_A/L in the case of beef, 40.4 kU_A/L in the case of pork, 19.7 kU_A/L in the case of milk, 6.4 kU_A/L in the case of cat, and 12 kU_A/L in the case of dog [Fig 1]). Further, the patient's total IgE level was determined to be 2832 kU/L, and his tryptase level was determined to be 3.6 µg/L. The patient initiated a mammalian meat- and milk-free diet, after which his pruritus ceased completely. In early 2014, the patient moved to an area with a low probability of ticks, although he occasionally identified a tick on his dog. He did not experience any tick bites until September 2015. The patient's alpha-gal-specific IgE levels decreased rapidly and in December 2013, his level of alpha-gal was determined to be 107 kU_A/L. After a tick bite in September 2015, the patient's level of alpha-gal increased (Fig 1). A similar pattern appeared for beef, pork, milk, cat, and dog, although at lower levels than for alpha-gal. The patient reported a tick bite in August 2023 and also reported having been bitten a few times in the intervening years. Unfortunately, the timing of these tick bites is unknown, but we hypothesize that they may correlate with the increasing levels of alpha-gal in April 2019 (71 kU_A/L) and August 2022 (16.6 kU_A/L). In August 2023, despite still adhering to a meat-free diet, the patient accidentally consumed pork (<20 g), and 3 hours later he experienced severe urticaria covering his arms. He reports that currently, if he is exposed to small amounts of milk or cheese,

he experiences local pruritus at the site of his latest tick bite in the months after the tick bite.

This case with more than 10 years of IgE measurements for alpha-gal highlights how rapidly IgE level can change and how the change appears to be dependent on exposure to tick bites. Several epidemiologic studies support tick bites being a strong risk factor for AGS, including in a dose-response relationship.^{1,2,10} Interestingly, some tick species have been linked to AGS, whereas others have not.¹⁰ Although the presence of alpha-gal has been demonstrated in some tick species, whether ticks can produce alpha-gal remains to be determined.¹⁰ Further, this case underlines the phenomenon of recall urticaria, which may be a useful clinical sign in the diagnosis of AGS.^{4,5} Future research should evaluate the proportion and clinical relevance of AGS cases with symptoms related to tick bites and potential recall urticaria.

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