Could cat flea bites contribute to alpha-gal serum IgE levels in humans?

Stenger F[1], Seidel P[1], Schricker T[2], Volc S[1], Fischer J[1,2]

[1]Department of Dermatology, University Hospital Tuebingen, Eberhard Karls University Tuebingen, Tuebingen, Germany
[2]Division of Experimental Allergy and Immunodermatology and University Clinics of Dermatology and Allergy, University of Oldenburg, Oldenburg, Germany

Corresponding author:
Dr. med. univ. Dr. med. Sebastian Volc
Eberhard Karls University
Universityhospital Tuebingen
Department of Dermatology
Liebermeisterstr. 25
72076 Tübingen
Germany
Email: sebastian.volc@med.uni-tuebingen.de

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0784

J Investig Allergol Clin Immunol 2022; Vol. 32(6)
doi: 10.18176/jiaci.0784

Key words: Alpha-gal. Cat flea. Ticks. Anaphylaxis. Alpha-gal syndrome.

Palabras clave: Alfa-gal. Pulga de gato. Garrapata. Anafilaxia. Síndrome de alfa-gal.

About 25 million years ago, in an evolutionary event, ancestral humanoids lost their ability to synthesize the carbohydrate galactose-α-1,3-galactose (alpha-gal) [1]. In contrast to other mammals, the alpha-gal epitope has become highly immunogenic to humans [1]. Consumption of mammalian meat or administration of drugs of mammalian origin (cetuximab, snake antivenom, gelatin containing vaccines or drugs) [1] can elicit anaphylaxis in individuals with specific IgE (sIgE) to alpha-gal. This novel allergy is termed alpha-gal syndrome (AGS). The induction of alpha-gal-specific IgE is considered to be environmentally induced by bites of ticks and mites. [1,2]. The following case report deals with the question of other possible bloodsucking parasites that could also potentially be involved with alpha-gal sIgE formation.

This is a 30-year-old biology student who presented to the allergy unit in October due to six bouts of nocturnal angioedema and urticaria in the last three months. These events occurred three to four hours after warm dinners with pork or beef meat. The patient had a medical history of allergic rhinitis but not for food allergy. The onset of this new health issue was temporally associated with infestation of his cat with cat fleas (*Ctenocephalides felis*). Since then, he suffered from itching urticarial papules due to flea bites. According to the patient's description some of these bites showed intense itching and local inflammatory reactions lasting for more than one week. A veterinarian had been consulted and treatment initiated but not yet completed at the time of presentation. Upon questioning, the patient recalled tick bites two years prior, but not during the last summer.

J Investig Allergol Clin Immunol 2022; Vol. 32(6)
doi: 10.18176/jiaci.0784

Prick-to-prick skin tests performed with fresh preparations of beef and pork meat, pork and beef kidney were positive. Intracutaneous testing with a 1:100 dilution of Gelatine polysuccinate infusion solution (Gelafundin^{TM} 4%) also was positive, while prick testing with commercially available and certified food and meat test solutions proved negative. Laboratory measures demonstrated an elevated total immunglobulin E (tIgE) of 137 kU/L and a sIgE to pork of 7.7 kU_A/L, to beef of 12.3 kU_A/L, and to alpha-gal (bovine thyroglobulin) of 57.2 kU_A/L (ImmunoCAP, Thermo Fisher Scientific, Germany). Serum basal tryptase was 4.8 µg/L (range <11.4 µg/L).

Based on the patient's history and diagnostic findings AGS was diagnosed.

At the follow-up appointment six weeks later, the patient, after changing his diet to poultry and fish, reported no further episodes of generalized urticaria. Efforts to control the cat's flea infestation were unsuccessful. In fact, the patient had suffered more flea bites in the meantime. Follow-up serological testing showed an increase in IgE levels, i.e. the tIgE concentration was 312 kU/L, sIgE to pork 20.2 kU_A/L, sIgE to beef 33.1 kU_A/L, and sIgE to alpha-Gal 115 kU_A/L. According to the patient, there had neither been tick bites nor a chiggers rash in the meantime and activities with high risk of bites had not taken place. Due to seasonally low daily temperatures in autumn (average local daytime temperature 8.4°C), activity for most frequent local tick, *Ixodes ricinus,* was low along with the combination of assumed low likelihood of unnoticed tick bites.

Herein, we present the first case with a significant increase in alpha-gal sIgE titers in the context of cat flea bites. There is strong scientific evidence advocating that bites of hard ticks (*Ixodidae*, subclass *Acari,* class *Arachnida*) can induce alpha-gal sIgE and increase sIgE titres [1]. Based on clinical observations, it is also possible that bites of chiggers (*Trombiculidae*, subclass *Acari*, class *Arachnida*) can contribute to

J Investig Allergol Clin Immunol 2022; Vol. 32(6)
doi: 10.18176/jiaci.0784

alpha-gal sensitization [2]. Ticks and mites are obligatory parasites requiring a blood meal from mammals or other vertebrates for each stage in their lifecycle [3]. Hence, blood meal constituents are absorbed during the process of hematophagy and stored in the hemolymph [3]. During the next bite various constituents of the previous host, including alpha-gal containing glycoproteins, are secreted into the wound with the tick's saliva [4,5]. In order to undermine the host's immune defense, a Th2-predominated wound milieu is being established creating immunological conditions which stimulate the production of sIgE to alpha-gal [5]. Following a tick bite, clinical signs of alpha-gal-sIgE positive individuals include long lasting and severe local pruritic eruptions along with the boostering of alpha-Gal sIgE titers [6].

Certain physiological similarities between ticks/mites and fleas (*Pulicidae*, class *Insecta*) exist. In the adult stage fleas are also obligatory hematophagous animals ingesting host related blood meal constituents [7]. Fleas, however, show greater mobility, more frequent host changes and can take blood with bites several times within the same individual (e.g. "breakfast, lunch and dinner sign" in humans) [7]. In Europe flea infestation of domestic cats by *Ctenocephalides felis* has been reported to be at approximately 15% and measures for pest control can be laborious [7,8]. Although their main hosts are cats and dogs, cat fleas may also affect humans as accidental hosts. Considering the large numbers of cats held as pets, the often intimate human cat flea infestation is assumed to be underreported [8]. It has been shown that cat fleas transmit various pathogens (e.g. *Rickettsia spp.*) with their saliva [9]. It is, therefore, likely that they, in a manner similar to ticks and mites (Figure 1), transfer traces of alpha-gal-carrying glycoprotein, and, in consequence, increase of alpha-gal-sIgE titres and onset of AGS. In addition, a previous epidemiological study on alpha-gal sensitization performed by Gonzalez-Quintela et al. described cat ownership as a risk

J Investig Allergol Clin Immunol 2022; Vol. 32(6)
doi: 10.18176/jiaci.0784

for alpha-gal sIgE-positivity, but could not provide an explanation for this relationship. Exposure to flea infested cats appears to be a plausible hypothetical explanation for this observed association [10].

Compared to the frequency and potentially associated health issues of tick and mite bites, cat flea bites certainly are a rare and special situation. However, this observation should encourage the curiosity of practitioners in finding other possible potential blood-sucking parasites that may play a decisive role in relevant increases or induction of alpha-gal sIgE in humans.

Funding

This work was supported with funding from the Deutsche Forschungsgemeinschaft (DFG; project FI 2226/2–1).

Conflict of Interest

The authors declare that they have no conflicts of interest.

J Investig Allergol Clin Immunol 2022; Vol. 32(6)
doi: 10.18176/jiaci.0784

References

1 Hilger C, Fischer J, Wölbing F, Biedermann T. Role and Mechanism of Galactose-Alpha-1,3-Galactose in the Elicitation of Delayed Anaphylactic Reactions to Red Meat. Curr Allergy Asthma Rep. 2019;19:3.

2 Stoltz LP, Cristiano LM, Dowling APG, Wilson JM, Platts-Mills TAE, Traister RS. Could chiggers be contributing to the prevalence of galactose-alpha-1,3-galactose sensitization and mammalian meat allergy? J Allergy Clin Immunol Pract. 2019;7:664-6.

3 Fischer J, Riel S, Fehrenbacher B, Frank A, Schaller M, Biedermann T, et al. Spatial distribution of alpha-gal in Ixodes ricinus - A histological study. Ticks Tick Borne Dis. 2020;11:101506.

4 Araujo RN, Franco PF, Rodrigues H, Santos LCB, McKay CS, Sanhueza CA, et al. Amblyomma sculptum tick saliva: α-Gal identification, antibody response and possible association with red meat allergy in Brazil. Int J Parasitol. 2016;46:213-20.

5 Kim TK, Tirloni L, Pinto AFM, Moresco J, Yates JR, da Silva Vaz I, et al. Ixodes scapularis Tick Saliva Proteins Sequentially Secreted Every 24 h during Blood Feeding. PLoS Negl Trop Dis. 2016;10:e0004323.

6 Fischer J, Lupberger E, Hebsaker J, Blumenstock G, Aichinger E, Yazdi AS, et al. Prevalence of type I sensitization to alpha-gal in forest service employees and hunters. Allergy. 2017;72:1540-7.

7 Rensch GP, Elston DM: What's eating you? cat flea (Ctenocephalides felis) revisited. Cutis. 2019;104:182-3.

J Investig Allergol Clin Immunol 2022; Vol. 32(6)
doi: 10.18176/jiaci.0784

8 Beugnet F, Bourdeau P, Chalvet-Monfray K, Cozma V, Farkas R, Guillot J, et al. Parasites of domestic owned cats in Europe: co-infestations and risk factors. Parasit Vectors. 2014;7:291.

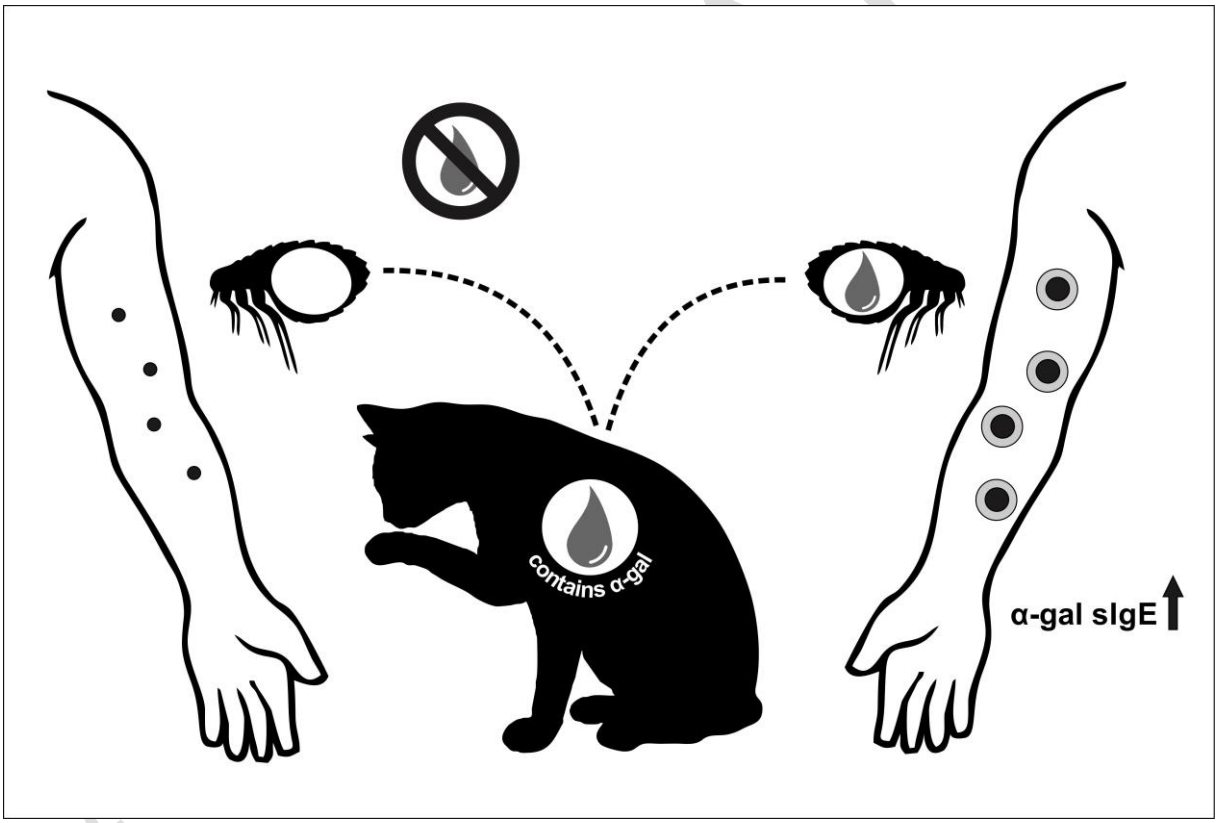
9 Oteo JA, Portillo A, Santibáñez S, Blanco JR, Pérez-Martínez L, Ibarra V. Cluster of cases of human Rickettsia felis infection from Southern Europe (Spain) diagnosed by PCR. J Clin Microbiol. 2006;44:2669-71.

10 Gonzalez-Quintela A, Dam Laursen AS, Vidal C, Skaaby T, Gude F, Linneberg A. IgE antibodies to alpha-gal in the general adult population: relationship with tick bites, atopy, and cat ownership. Clin Exp Allergy. 2014;44:1061-8.

doi: 10.18176/jiaci.0784

FIGURE

Figure 1. In contrast to adult female hard ticks feeding on a single host for several days, adult female cat fleas collect the blood required for laying eggs by multiple short termed bites on a singular or multiple hosts ("breakfast, lunch and dinner sign" in humans). According to this hypothesis, cat fleas can transfer traces of alpha-gal-carrying glycoprotein from a previous blood meal on a cat during a further bite to an accidental human host. This can result in persisting itching, local inflammation around the bite area and lead to increase of alpha-gal sIgE in susceptible individuals.



J Investig Allergol Clin Immunol 2022; Vol. 32(6)
doi: 10.18176/jiaci.0784