Original Research

IgE TESTING FOR MEAT, CAT AND ASCARIS IN PATIENTS WITH AND WITHOUT ALPHA-GAL ALLERGY

Michael E Levin,[1]
Wisdom Basera,[2,3]
Maresa Botha,[1]
Heidi Facey Thomas,[1]
Tshegofatso Mabelane[4]

[1] *Department of Paediatric Allergology, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa*
[2] *School of Public Health and Family Medicine, University of Cape Town, South Africa*
[3] *Burden of Disease Research Unit, South African Medical Research Council, South Africa*
[4] *Department of Family Medicine, Sefako Makgato Health Science University, South Africa*

Email | Michael.levin@uct.ac.za

ABSTRACT

Background: Severe meat allergy with anaphylaxis may be caused by sensitisation to alpha-gal. Although a wide range of variation in alpha-gal-specific IgE is found in both subjects with and without alpha-gal-induced meat anaphylaxis, the level of alpha-gal sensitisation correlates with the likelihood of meat allergy. Other laboratory tests have been implicated to be affected by alpha-gal sensitisation. Correlations between alpha-gal sensitisation and sensitisation to certain animals or parasites may provide further clues about potential sensitisers, apart from ticks, in alpha-gal allergy.

Methods: In this study we assessed 131 participants who reported adverse reactions to meat, and 26 control subjects, by means of questionnaires, IgE sensitisation to alpha-gal and oral food challenge to beef sausage. Specific IgE to alpha-gal, beef, pork, lamb, cat, cat serum albumin and ascaris in those participants with challenge-proven meat allergy were compared with control subjects from the same environment.

Results: 84 participants were diagnosed with alpha-gal allergy. Alpha-gal IgE ranged between 0.7 and 344.5 kU/L. Beef, pork and lamb IgE were strongly correlated with alpha-gal IgE in both cases and controls. Cat IgE was significantly associated with alpha-gal sIgE, with a strong correlation in cases but a moderate correlation in controls. There was no association between cat serum albumin and alpha-gal IgE. Ascaris sIgE was significantly associated with alpha-gal sIgE.

Conclusion: Cross-sensitisation between alpha-gal and beef, pork, lamb and cat can be explained by the presence of alpha-gal-containing epitopes on the ImmunoCAP reagents. The absence of cross-sensitisation to cat serum albumin is due to the pure nature of the reagent used. Cross-sensitisation between alpha-gal and ascaris could be explained by the presence of significant amounts of alpha-gal-containing epitopes within the helminth. However, the absence of binding to ascaris IgE in some patients with significant levels of alpha-gal IgE argues against this being the sole or main factor, thus the possibility of a causative role in helminths causing sensitisation to alpha-gal.

Keywords: alpha-gal, galactose-alpha-1,3-galactose, anaphylaxis, food allergy, meat allergy, oral food challenge, red meat allergy, ascaris

INTRODUCTION

Galactose-alpha-1,3-galactose (alpha-gal) has been identified as a novel food allergen causing delayed reactions 1–4 hours after ingestion of non-primate mammalian meat products.[1] Bites by ticks of specific, region-dependent species have widely been held responsible as the initial sensitising event to alpha-gal.

Cross-reactivity between tests for IgE specific to meat and to alpha-gal itself is postulated to occur because of the content of alpha-gal-containing epitopes in the mammalian meat reagents used.[2–4] Primary sensitisation to alpha-gal-containing epitopes in some cat-allergic individuals is postulated to result in the low-level detection of alpha-gal antibodies, not associated with meat

allergy.[5,6] Laboratory evidence of sensitisation to cat dander can be primary or through cross-reacting with alpha-gal-containing epitopes present in helminths and schistosome.[7] Sera from patients with documented helminth infections, however, do not consistently contain IgE antibodies to alpha-gal.[8]

METHODS

PARTICIPANTS AND CONTROLS

Subjects with alpha-gal allergy and controls were identified in the Mqanduli district of the Eastern Cape province of South Africa, as previously described.[9] In brief, participants with a history of symptoms of adverse reaction to red meat were enrolled along with participants with no history of adverse reaction to red meat and who were regularly consuming meat. A questionnaire was completed assessing the demographics of the participants, clinical symptoms, and a history of exposure to tick bite, scabies or parasite infection. Blood samples were collected from all the participants to test total IgE and specific IgE antibodies (ImmunoCAP® Phadia) to alpha-gal, beef, pork, lamb, cat, cat serum albumin (CSA) and ascaris. Serum was analysed using the ImmunoCAP100 instrument (Thermo Fisher) and the results were expressed as kilounits per litre. Participants with a history of adverse reactions to meat and who were sensitised to alpha-gal were invited for an open food challenge (OFC) to cooked beef sausage, performed as described previously.[9] Both subjective and objective symptoms were recorded as the participants were observed for at least eight hours from ingestion and, if a reaction occurred, for at least two hours after the reaction resolved. The study was approved by the Human Research Ethics Committee of the University of Cape Town (174/2017) and informed consent, parental consent and assent were obtained from all the participants.

STATISTICAL ANALYSIS

Data were entered in Microsoft Access and exported for statistical analysis using R Core Team (2020). Graphical presentation of the serum IgE levels between alpha-gal and the different meats and organisms was done using R Core Team (2020) and by using a log base 10 transformation to exclude all the zero values. Kendall's Tau coefficients were used to measure the linear correlation between the specific and the total serum IgE values of alpha-gal, beef, pork, lamb, cat, CSA and ascaris. All the comparisons were stratified by cases and controls and a p-value of less than or equal to 0.05 eliminated chance correlation between the reported values. Kendall's Tau correlations were interpreted as follows: between 0 and + or -0.10: very weak; + or -0.10 to 0.19: weak; + or -0.20 to 0.29: moderate, and + or -0.30 or above: strong.

RESULTS

Of the subjects, 84 were diagnosed with alpha-gal allergy, 81 with positive OFC and three with extremely high levels of alpha-gal-specific IgE > 150 kU/L, with a history of recent severe reaction. Alpha-gal IgE ranged between 0.7 and 344.5 kU/L. Of 26 control participants who were regularly consuming red meat, half had no alpha-gal sensitisation and did not undergo an OFC. Half of them had a positive alpha-gal IgE and underwent an oral food challenge, showing no reaction.

Beef, pork and lamb IgE were strongly correlated with alpha-gal IgE (and each other) in both cases and controls. Although beef, pork and lamb IgE were also raised in subjects with alpha-gal allergy, the values were lower than that of alpha-gal IgE. Beef IgE typically achieved values of 50–60% of that of alpha-gal IgE, with the others being lower. Cat IgE was significantly associated with alpha-gal specific IgE (sIgE), with a strong correlation in cases (τ = 0.62) but only a moderate correlation in controls (τ = 0.21). There was no association between CSA and alpha-gal IgE. Ascaris sIgE was significantly associated with alpha-gal sIgE, with a strong correlation in cases (τ = 0.32) but a weak correlation in controls (τ = 0.16). There was no binding to ascaris IgE in some meat allergic patients with significant levels of alpha-gal sensitisation.

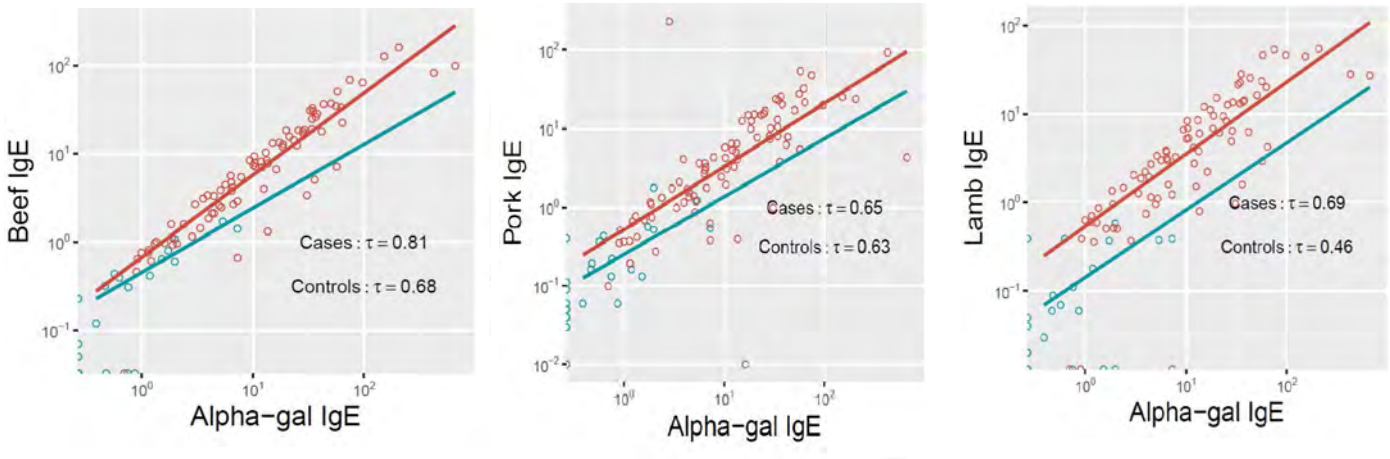

Figure 1: Correlations between alpha-gal IgE and IgE to mammalian meats in cases (red) and controls (blue)

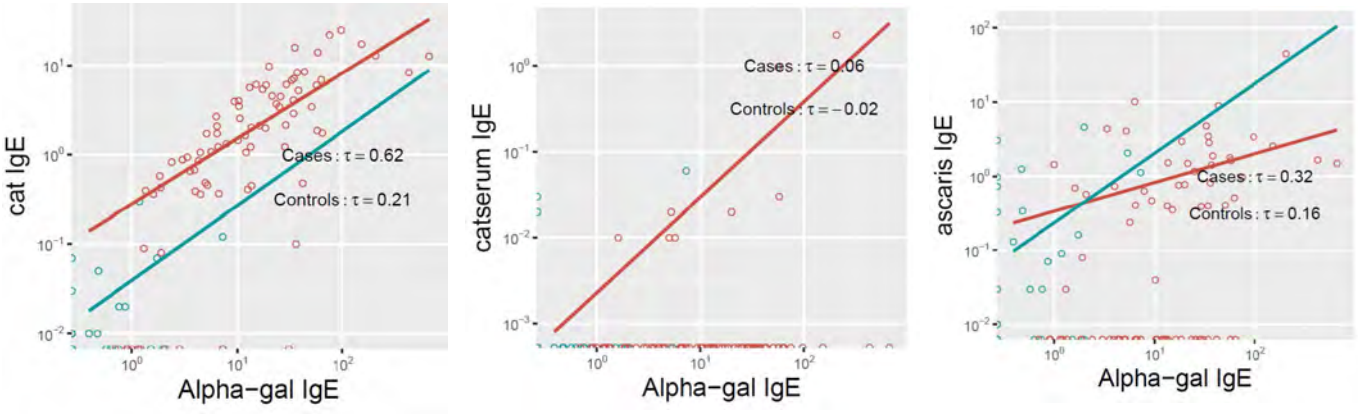

Figure 2: Correlations between alpha-gal IgE and IgE to cat (dander and CSA) and ascaris in cases (red) and controls (blue)

DISCUSSION

This study confirmed the close association seen in the literature between levels of sIgE to beef, pork and lamb with sIgE to alpha-gal; this is presumably due to the presence of alpha-gal-containing epitopes in the mammalian meat laboratory reagents. A similar explanation can be attributed to the correlation between IgE to cat (dander) and sIgE to alpha-gal. This would explain why individuals without cat allergy in areas with high alpha-gal sensitisation may test falsely positive to IgE against cat on ImmunoCAP testing. Because the purified CSA reagent used in ImmunoCAP tests does not contain alpha-gal epitopes, there is no cross-sensitisation between CSA and alpha-gal. There could be two different explanations for the relationship between sensitisation to ascaris and alpha-gal, different explanations which require further investigation. First, if there are alpha-gal-containing epitopes in the ascaris ImmunoCAP, it implies that ascaris contains significant amounts of alpha-gal. If this is the case, then the presence of those epitopes in the ImmunoCAP might be solely responsible for the correlation seen. This could account for the correlation in both cases and controls, but does not explain why the correlation is stronger in cases than controls, nor does it explain the presence of subjects with high-level alpha-gal sensitisation who do not have raised anti-ascaris IgE. Second, there is a possibility that infestation with ascaris could in turn induce IgE sensitisation to alpha-gal, with or without clinical reactivity. In this cohort there was high self-reported exposure to scabies and worm infestation, and some exposure to bilharzia in both alpha-gal and control participants, with no significant differences noted in cases and controls.

CONCLUSION

The relationship between sensitisation to ascaris and alpha-gal remains unclear and the importance of helminthic exposures as possible sensitising vectors for alpha-gal allergy is unknown. The stronger correlation between alpha-gal IgE and ascaris IgE in cases than in controls raises the possibility of a causative role in helminths causing sensitisation to alpha-gal.

DECLARATIONS OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Levin M, Apostolovic D, Biedermann T, et al. Galactose α-1,3-galactose phenotypes: Lessons from various patient populations. Ann Allergy, Asthma Immunol 2019;122(6):598-602. https://doi.org/10.1016/j.anai.2019.03.021.
2. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-α-1,3-galactose. N Engl J Med 2008;358(11):1109-1117. https://doi.org/10.1056/NEJMoa074943.
3. Commins SP, Platts-Mills TAE. Delayed anaphylaxis to red meat in patients with ige specific for galactose alpha-1,3-galactose (alpha-gal). Curr Allergy Asthma Rep 2013;13(1):72-77. https://doi.org/10.1007/s11882-012-0315-y.
4. Apostolovic D, Tran TAT, Hamsten C, Starkhammar M, Cirkovic Velickovic T, Van Hage M. Immunoproteomics of processed beef proteins reveal novel galactose-α-1,3-galactose-containing allergens. Allergy Eur J Allergy Clin Immunol 2014;69(10):1308-1315. https://doi.org/10.1111/all.12462.
5. Gonzalez-Quintela A, Dam Laursen AS, Vidal C, et al. IgE antibodies to alpha-gal in the general adult population: Relationship with tick bites, atopy, and cat ownership. Clin Exp Allergy 2014;44(8):1061-1068. https://doi.org/10.1111/cea.12326.
6. Commins SP, Platts-Mills TAE. Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. J Allergy Clin Immunol 2009;124(4):652-657. https://doi.org/10.1016/j.jaci.2009.08.026.
7. Arkestl K, Sibanda E, Thors C, et al. Impaired allergy diagnostics among parasite-infected patients caused by IgE antibodies to the carbohydrate epitope galactose-α1,3-galactose. J Allergy Clin Immunol 2011;127(4):1024-1028. https://doi.org/10.1016/j.jaci.2011.01.033.
8. Okano M, Satoskar a R, Nishizaki K, Abe M, Harn D. Induction of Th2 responses and IgE is largely due to carbohydrates functioning as adjuvants on Schistosoma mansoni egg antigens. J Immunol 1999;163(12):6712-6717.
9. Mabelane T, Basera W, Botha M, et al. Predictive values of alpha-gal IgE levels and alpha-gal IgE: Total IgE ratio and oral food challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. Pediatr Allergy Immunol 2018;29(8):841-849. https://doi.org/10.1111/pai.12969.