Update on alpha-gal allergy



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Learning Objectives

- Upon completion of this learning activity, participants should be able to recognize a clinical history consistent with alpha-gal syndrome
- Upon completion of this learning activity, participants should be able to diagnose alpha-gal syndrome
- Upon completion of this learning activity, participants should be able to name the risk factors that may lead to a patient developing alpha-gal syndrome
- Upon completion of this learning activity, participants should be able to design management options and proper avoidance diet for patients with alpha-gal syndrome



THANKS TO SCIENTIFIC CONTRIBUTORS

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Wesley Burks Erin McGintee Shawna Pochan Walter Oliveira Hayley James Whitney Stevens Charles J. Lane Johanna Smeekins Joanne Jordan Ron Falk Barrett Lewis Michael Land Scott Boyd Tho Pham Kelly Cox



In mid-2000s, we started to hear a similar history from a few adult patients: "Hey Doc, I might be allergic to beef" "but it's weird..."

- The reactions do not happen right away
- The reactions do not happen every time
- Sometimes it's really bad, other times just itching
- I might be bothered by pork now too...maybe lamb

Skin Testing Results: Often <4mm SPT







INTRADERMAL

Prick test performed using lancette and intradermal testing with 25 gauge needle in the same patient on a single clinic visit.



Serum tests in patients reporting reactions to red meat - 2009

Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-α-1,3-galactose

Scott P. Commins, MD, PhD,^a Shama M. Satinover, MS,^a Jacob Hosen, BS,^a Jonathan Mozena, MD,^b Larry Borish, MD,^a Barrett D. Lewis, MD,^c Judith A. Woodfolk, MBChB, PhD,^a and Thomas A. E. Platts-Mills, MD, PhD^a Charlottesville and Fredericksburg, Va, and Springfield, Mo

JACI, February 2009

- -24 patients
- -Virginia & Missouri
- Symptoms delayed 3-6 hours after eating mammalian meat
- Prick skin test often less than 4mm

Pork sausage challenge

Each patty ~25-30 grams with 10g fat/patty



Approximately 8.25 hours after eating sausage





-FC03 - slgE to alpha-gal = 17.6 IU/mL; Total lgE = 184

-3:54 after consuming meat, symptoms began as itching, flushing and progressed: ultimately requiring epinephrine





Basophil CD63 expression in individual subjects positive for IgE Ab over the course of a mammalian meat challenge



Commins et al. JACI, 2014

Distribution of known cases of delayed anaphylaxis to mammalian meat (2011)



Commins SP, James HR, Kelly LA...Platts-Mills TAE. The relevance of tick bites to the production of IgE ab to the mammalian oligosaccharide galactose- α -1,3-galactose. J Allergy Clin Immunol 2011

Patient-reported cases of alpha-gal allergy in the US



Downloaded July 20, 2019



AGS CLINICAL PRESENTATION

- 1) "Original" signs/symptoms from red meat (fatty) ingestion; tolerate dairy including pizza & ice cream
 - Itching, hives, swelling, N/V/D, hypotension, anaphylaxis



AGS CLINICAL PRESENTATION

55 yo woman awoken from sleep at 1am due to itching of her palms. She noted her palms were "red and swollen" and when she turned on bedside lamp her torso was "covered in hives." She reported feeling "intense" gastrointestinal cramping develop and collapsed on the way to the bathroom; the noise awakened her husband who called 911.

- She had leg of lamb at a restaurant for dinner earlier that evening
- And they enjoyed a "particularly good" bottle of wine with dinner

MANAGEMENT

• Avoidance diet:

- Mammalian meat, esp fatty cuts (ice cream)
- > Dairy and cheese often tolerated
- > Few issues with gelatin
- Caution re: exercise, alcohol
- Monitor IgE to alpha-gal over time
 - Pork sausage (3) challenge when level declines significantly



"Nearly all of the remaining weight is recovered as by-products"



Avoidance of red meat can be just the beginning



Compiled by Alyssa Auer (2009)

IUNC

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MEDICINE

Frabose, D., G. Bowman et al (2001) Swine Resource Handbook. The Ohio State University Extension.



AGS PHENOTYPES & CLINICAL PRESENTATION

 Original – signs/symptoms from red meat (fatty) ingestion; tolerate dairy including pizza & ice cream
Itching, hives, swelling, N/V/D, hypotension, anaphylaxis

2) GI only – exclusive gastrointestinal symptoms from red meat / dairy; occasionally symptoms are not as delayed



AGS CLINICAL PRESENTATION - "GI ONLY"

48 yo man from a rural area presented to the ED with "life-ending" abdominal pain. This was his 3rd acute care episode for abdominal pain in the past 6 months. An abdominal ultrasound was performed and several non-obstructing gallstones were noted. A cholecystectomy was performed.

- Two months later he returned to the ED with the same complaint
- He was referred to GI for further work-up; alpha-gal IgE =1.45
- Trial of red meat avoidance has resulted in no additional episodes over past 6 months



MANAGEMENT - GI

Isolated Gastrointestinal Alpha-gal Meat Allergy Is a Cause for Gastrointestinal Distress Without Anaphylaxis Michael Croglio & Sarah McGill. *Gastroenterology*, In press

- Abdominal pain (87.5%), nausea (75%), and diarrhea (68.75%), mainly episodic (68.8%) vs chronic (31.25%), were the most common symptoms

- Nine patients (56.2%) met the criteria for diarrhea-predominant IBS

- Patients reported awakening at night with GI distress and did not report a response to every exposure

- No patient related GI symptoms to mammalian meat ingestion before diagnosis, and 75% recalled a tick bite

- The median time from symptom onset to diagnosis was 21 months



MANAGEMENT - GI

• Pancreatic enzymes Stone CA et al. J Allergy Clin Immunol Pract. 2020



IBS – how much of non-specific GI distress is AGS?
And does geography matter?

WUNC SCHOOL OF MANAGEMENT - CARDIOLOGY

Then a patient with AGS had anaphylaxis following mitral valve replacement



How deep are the implications?

- Pericardial patches
- Premature failure





WUNC SCHOOL OF MANAGEMENT - CARDIOLOGY

Then a patient with AGS had anaphylaxis during cardiac catheterization



MANAGEMENT - ENDOCRINOLOGY



Rx only

Armour® Thyroid (thyroid tablets, USP)

Rev. August 2012

DESCRIPTION

Armour® Thyroid (thyroid tablets, USP)* for oral use is a natural preparation derived from porcine thyroid glands and has a strong, characteristic odor. (T3 liothyronine is approximately four times as potent as T4 levothyroxine on a microgram for microgram basis.) They provide 38 mcg levothyroxine (T4) and 9 mcg liothyronine (T3) per grain of thyroid. The inactive ingredients are calcium stearate, dextrose, microcrystalline cellulose, sodium starch glycolate and opadry white.

WUNC MEDICINE MANAGEMENT - GENERAL EXPOSURES

- $\circ~$ Gelatin-based plasma expanders, such as Gelafundin, Gelofusine, Haemaccel
- Many vaccines, including those that contain gelatin or other mammalian byproducts. In the U.S., these include Zostavax, MMR, TDaP (Boostrix)
- Antivenom, such as crotalidae polyvalent immune Fab (CroFab)
- $\circ~$ Other products that contain gelatin, such as:
 - Hemostatic agents, such as Surgiflo, Floseal hemostatic matrix and Surgifoam powder
 - Absorbable gelatin sponge, like Gelfoam
 - Gabapentin oral solution
 - Lidocaine patch
 - Gummy supplements
 - Vaginal capsules
 - Suppositories
 - Collagen-containing agents, including implants

TICKS. REALLY?





Early and Late Responses to Tick Bite in Patient with IgE Ab to alpha-Gal



Bites from larval ticks and IgE to alpha-Gal



Test	5/21/09	10/9/09	11/6/09*
Alpha-Gal	negative	48.3	130
Total IgE	199	350	532

•Multiple bites by seed ticks are not uncommon in the Southeast.

*Titers: Beef 19.2, Pork 10.1, Cat 17.5, Dog 19.8 IU/ml. Chicken, Turkey, Roach, Dust Mite and Ragweed all <0.35 IU/ml (undetectable).

Photograph: August 23, 2009.

Total IgE versus IgE to Alpha-Gal





IgE to Alpha-gal and Total IgE Rise Following Tick Bites



Different ticks, same allergy

> Med J Aust. 2009 May 4;190(9):510-1.

An association between tick bite reactions and red meat allergy in humans

Sheryl A Van Nunen ¹, Kate S O'Connor, Lesley R Clarke, Richard X Boyle, Suran L Fernando Affiliations + expand

PMID: 19413526

Abstract

Twenty-five patients living in a tick-endemic region of Sydney, New South Wales developed red meat allergy after experiencing large local reactions to tick bites. This represents a potentially novel cross-reaction between an arthropod and a food protein. (MJA 2009; 190: 510-511).

Implicated tick: Ixodes holocyclus

Different ticks. same allergy

Review > Allergo J Int. 2016;25(2):49-54. doi: 10.1007/s40629-016-0098-0.

Epub 2016 Mar 23.

The red meat allergy syndrome in Sweden

Danijela Apostolovic ¹, Thi Anh Thu Tran ², Maria Starkhammar ³, Sara Sánchez-Vidaurre ⁴, Carl Hamsten ⁴, Marianne Van Hage ⁵

Affiliations + expand PMID: 27656352 PMCID: PMC5016537 DOI: 10.1007/s40629-016-0098-0





Implicated tick: Ixodes ricinus



Different ticks, same allergy

short report Open Access Published: 13 May 2019

Alpha-gal allergy after a tick bite in Austria

Veronika Pisazka, Georg Duscher, Adnan Hodžić, Norbert Reider & Franz Allerberger MD 🖂

Wiener klinische Wochenschrift 131, 385–388(2019) Cite this article

> J Investig Allergol Clin Immunol. 2018;28(2):106-112. doi: 10.18176/jiaci.0218. Epub 2017 Dec 13.

IgE to α -Gal in Foresters and Forest Workers From La Rioja, North of Spain

M Venturini ¹, T Lobera ¹, A Sebastián ², A Portillo ³, J A Oteo ³

Affiliations + expand PMID: 29235434 DOI: 10.18176/jiaci.0218 Case Reports > Ann Allergy Asthma Immunol. 2019 Dec;123(6):616-618. doi: 10.1016/j.anai.2019.09.018. Epub 2019 Sep 28.

Allergy in frequent travelers: the alpha-gal story and the first UK case series

Verah Harper ¹, Annette Wagner ², Pawel Sowa ³, Krzysztof Rutkowski ⁴

Implicated tick: Ixodes ricinus

Alpha-gal IgE response to tick bites

- IgE to alpha-gal increased with time following one or more tick bites
- IgE to alpha-gal (kU/L) increased in patients with increasing numbers of tick bites

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Number of new tick bites

Hashizume H, et al. Repeated Amblyomma testudinarium tick bites are associated with increased galactose- α -1,3-galactose carbohydrate IgE antibody levels: A retrospective cohort study in a single institution. *J Am Acad Dermatol.* 2018

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- Kersh GJ, 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. 2023 Apr;130:472-478.
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"It is better to know some of the questions than all of the answers." - James Thurber

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