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Red meat desensitization in a child with delayed anaphylaxis due to alpha-Gal allergy

To the Editor,

Alpha-Gal allergy is a recently described phenomenon in food allergy field caused by IgE antibodies directed against galactose-α-1,3-galactose (alpha-Gal) in red meat, which is reportedly induced by tick bites.[1] Severe delayed-onset systemic reactions within 2-6 hours of exposure to red meat may be presented as symptoms of urticaria-angioedema and life-threatening anaphylaxis in alpha-Gal allergy. Until now, there are a limited number of cases with alpha-Gal allergy in children.[2,3]

Avoidance is the mainstay management of food allergies; nevertheless, exclusion of red meat from the diet may be difficult, and the risk of accidental exposure can be high. Satisfying outcomes with oral immunotherapy in several food allergies such as peanut, cow's milk, and hen's egg have been reported.[4] Red meat desensitization may be proposed to serve as a promising treatment of alpha-Gal allergy. Recently, successful desensitization to red meat in adults with alpha-Gal allergy was reported.[5] Hereby, we present the treatment of first pediatric case of alpha-Gal allergy with desensitization to red meat.

A 10-year-old girl, without previous food allergy, was admitted to our clinic with a history of two anaphylaxis episodes. In her first episode, angioedema, nausea, vomiting, and respiratory distress had started nearly 4 hours after eating meatballs. Subsequently, 2 weeks later, she had the same delayed type of reaction after beef consumption. After that episode, she never consumed red meat until oral provocation test with red meat was performed. In her detailed history, 10 days before her first episode a tick bite in Black Sea region of Turkey was noted.

Her serum total IgE was 92.5 IU/L, beef-specific IgE (spIgE) was 3.82 kU/L, and spIgE levels for cow's milk and lamb were negative. Prick-to-prick skin tests with both cooked and raw beef and lamb were all negative. Also, skin prick tests (SPTs) with cow's milk and hen's egg were found negative.

A single-blind oral provocation test was performed with an initial dose of 2 g of cooked beef followed by a doubling dose of 4 g After 2 hours of the second dose, itchiness and redness on the ears, flushing of the face, and angioedema at the left eyelid and forehead appeared. The provocation test was considered to be positive and terminated.

Serum alpha-Gal spIgE level was 5.2 kU/L. A 3-mm wheal reaction was measured with cetuximab and was considered as positive in SPT, as well.

Written consent was obtained for desensitization to red meat, due to the eagerness of the patient to consume red meat. A 24-step red meat desensitization protocol modified from Unal D. et al[5] was performed (Table 1).

We started desensitization with 10 drops of 1% diluted boiled beef extract (0.00005 mg beef) as per protocol, and no reaction was observed during initial two doses of 10 drops, which were given in 4 hours of intervals in the first 3 days. However, we needed to treat a reaction of itching and urticarial lesions, which was observed after 3 hours of the first dose on the 4th day with a single dose of oral cetirizine.[6] Subsequently, the second dose of 20 drops was tolerated without any symptoms. On the 7th day of the desensitization, 2 mg of cooked beef was given twice daily and the total dose was increased every following day.

Our case had no symptoms throughout the rest of the desensitization protocol. At the end of day 24, she was able to tolerate a serving size of 120 g of beef without any complaints. Correspondingly, she was advised to consume daily 120 g of cooked red meat to maintain desensitization and she was able to do that continuously within the last 6 months until now.

TABLE 1 Red meat desensitization protocol

Days	First dose	Second dose	Daily cumulative dose
1	10 drops[a]	10 drops	20 drops
2	10 drops	20 drops	30 drops
3-5	20 drops	20 drops	40 drops
6	40 drops	40 drops	80 drops
7	2 mg[b]	2 mg	4 mg
8	4 mg	8 mg	12 mg
9	16 mg	32 mg	48 mg
10-12	32 mg	32 mg	64 mg
13	40 mg	40 mg	80 mg
14	60 mg	80 mg	140 mg
15	80 mg	160 mg	240 mg
16	160 mg	320 mg	480 mg
17	320 mg	640 mg	960 mg
18	640 mg	1280 mg	1920 mg
19	1280 mg	2560 mg	3840 mg
20	5600 mg	10 g	15.6 g
21	10 g	20 g	30 g
22	20 g	40 g	60 g
23	40 g	80 g	120 g
24	60 g	60 g	120 g

[a]Beef extract solution: %1 diluted solution, 6 mg of beef boiled in 600 mL water for 15 min.
[b]Cooked beef introduced to protocol instead of beef extract solution.

Alpha-Gal allergy is a recently defined clinical entity, which is associated with a tick bite. Delayed-onset IgE-mediated hypersensitivity reactions after red meat ingestion and immediate IgE-mediated hypersensitivity reactions to cetuximab infusions are the two distinct clinical presentations of alpha-Gal allergy. Cetuximab is a chimeric monoclonal antibody to epidermal growth factor receptor (EGFR), which contains oligosaccharide alpha-Gal residues on the heavy chain of the Fab part.[1,7]

Alpha-Gal allergy has been diagnosed by a story of late-onset anaphylaxis after red meat consumption followed by a previous tick bite in our case. Mabelane et al[8] have recently reported that spIgE alpha-Gal levels above >5.5 kU/L indicate red meat allergy with 95% probability. In this case, the diagnosis has been confirmed by positive oral provocation test and high serum spIgE alpha-Gal level, in addition to SPT positivity to cetuximab. Generally, SPTs with raw and cooked red meats and their extracts give negative results and spIgE of beef, lamb, and pork exerts low sensitivity in alpha-Gal allergy. SpIgE assay to alpha-Gal is a sensitive and commercially available diagnostic tool. Also, SPT with cetuximab provides a sensitive diagnostic option to evaluate alpha-Gal allergy.

There is a single case series report of 45 children and a report with a limited number of pediatric cases with several adult cases with alpha-Gal allergy.[1,3,9,10] It has been presumed that tick bites are the main cause of sensitization to alpha-Gal. Alpha-Gal has been identified in the gastrointestinal tract of the tick species *Ixodes Ricinus* that appears to be responsible for alpha-Gal allergy in Europe and in our region.[10,11]

In general, desensitization to red meat is not recommended in the routine clinical practice in alpha-Gal allergy. The decisive point in considering the indication for desensitization to red meat needs to be individualized based on the impact and importance of red meat in the patient's family diet and culture, as well as general health outcomes of the diet for the patient. Our main indication for desensitization to red meat in this case was eagerness of the patient to eat red meat, the major dietary component of the Turkish Cuisine, and to prevent the risk of accidental exposures.

Awareness of alpha-Gal allergy has increased after an association has been linked in between tick bite and red meat allergy. Due to delayed-onset nature of reactions in alpha-Gal allergy, it is possible to misdiagnose as idiopathic anaphylaxis, and true alpha-Gal allergy prevalence is underestimated. It is utmost important to take a detailed history of tick bite, especially in those who traveled into rural areas and are developing hypersensitivity reactions to red meat.

Delay in diagnosis could lead to repeated accidental consumptions, which may increase possible life-threatening anaphylactic reactions. As strict avoidance affects patients' and their family's qualities of lives, red meat desensitization may provide management of alpha-Gal allergy.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

Clinical implications

Development of red meat allergy after a tick bite is a recently described phenomenon related to sensitization to alpha-Gal. Delayed-onset IgE-mediated hypersensitivity reactions after red meat consumption are the cardinal features seen in alpha-Gal allergy.

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REFERENCES

1. Commins SP, Platts-Mills TA. Tick bites and red meat allergy. *Curr Opin Allergy Clin Immunol*. 2013;13(4):354-359.
2. Kennedy JL, Stallings AP, Platts-Mills TA, et al. Galactose-alpha-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. *Pediatrics*. 2013;131(5):e1545-e1552.
3. Wilson JM, Schuyler AJ, Workman L, et al. Investigation into the alpha-gal syndrome: characteristics of 261 children and adults reporting red meat allergy. *J Allergy Clin Immunol Pract*. 2019. https://doi/10.1016/j.jaip.2019.03.031

4. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73(4):799-815.
5. Unal D, Coskun R, Demir S, Gelincik A, Colakoglu B, Buyukozturk S. Successful beef desensitization in 2 adult patients with a delayed-type reaction to red meat. *J Allergy Clin Immunol Pract*. 2017;5(2):502-503.
6. Barbi E, Longo G, Berti I, et al. Adverse effects during specific oral tolerance induction: in-hospital "rush" phase. *Eur Ann Allergy Clin Immunol*. 2012;44(1):18-25.
7. 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):1109-1117.
8. Mabelane T, Basera W, Botha M, Thomas HF, Ramjith J, Levin ME. 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.
9. Bircher AJ, Hofmeier KS, Link S, Heijnen I. Food allergy to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal): four case reports and a review. *Eur J Dermatol*. 2017;27(1):3-9.
10. Hamsten C, Starkhammar M, Tran TA, et al. Identification of galactose-alpha-1,3-galactose in the gastrointestinal tract of the tick Ixodes ricinus; possible relationship with red meat allergy. *Allergy*. 2013;68(4):549-552.
11. Uzunoglu E, Polat E, Oguz ID, et al. Tick bite cases among hazelnut farm workers in Giresun. *Cumhuriyet Med J*. 2017;39(2):473-478.

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Accidental ingestion of food allergens: A nationwide survey of Japanese nursery schools

To the Editor,

The accidental ingestion of food allergens is an important problem in preschool-aged children with food allergy (FA).[1] However, reports regarding accidental ingestion in nursery school children are limited. This nationwide questionnaire-based survey determined the incidence of accidental ingestion in this population and identified the associated risk factors.

Data were gathered using a nationwide questionnaire survey[2] dispatched by post to all childcare facilities in Japan (Table S1).

Accidental ingestion was defined as unintended accidental allergen exposure leading to allergy symptoms. Data were expressed as n (%) or means (standard deviation). This study was approved by the ethics committee of Jikei University. The detailed methods of the survey administered to nursery schools, and the regulations in Japan are described in Appendix S1.

Questionnaire responses were received from 15 722 (48.8%) of 32 210 institutions. A total of 1 390 481 children were enrolled in the survey (Figure S1). Among 51 531 children with FA, 408 and 5317 were excluded owing to missing data and nursery center information, respectively. Finally, 45 806 children with FA met the inclusion criteria; their characteristics are shown in Table 1. The mean age of the children was 2.3 ± 1.6 years (median: 2.0 years). Egg allergy was the most common FA (74.8%). A person accountable for FA was identified in 65.6% of nursery schools. Adrenaline auto-injectors (AAIs) were prescribed to 5123 (11.2%) children, 1154 (2.5%) of whom brought them to their nursery school. Of 4853 children with a history of anaphylaxis, 1450 (29.9%) had been prescribed AAIs, 784 (16.2%) of whom brought them to their nursery school. Overall, 3497 (7.6%) children had experienced accidental ingestion with symptoms in the current fiscal year, 44 (0.1%) of whom required hospitalization. Only, 11 children (0.02%) had used an AAI in their nursery school. Data on symptom severity were obtained from 2113 children, but were unknown in 2155 children. Severe (requiring hospitalization), moderate (requiring doctor treatment), and mild symptoms (not requiring treatment) were observed in 44, 303 and 1766 children, respectively. There were no cases of mortality.

Significant associations with accidental ingestion were observed for sex, age, history of anaphylaxis to causative food, milk allergy, wheat allergy, fish allergy, number of eliminated foods, number of children in the nursery center, and the absence of a person accountable for FA (Table 1). The incidence of accidental ingestion was highest in children younger than one year of age (9.7%) and gradually decreased with age (*P*-value for trend: <0.001; Figure S2). Larger facilities with more children had a lower incidence of accidental ingestion, while the incidence increased in smaller nursery schools (*P*-value for trend: <0.001; Figure S3).

The factors significantly associated with accidental ingestion were assessed for crude odds ratios (ORs) and adjusted ORs (aORs; Table 2). These factors were categorized as related to either children or nursery centers. The significant risk factors in children were male sex (male; aOR: 1.115), younger age (per one-year increase; aOR: 0.893), history of anaphylaxis to causative foods (aOR: 2.199), current milk allergy (aOR: 1.239), current wheat allergy (aOR: 1.266), and current fish allergy (aOR: 1.191). The number of eliminated foods was significant only in univariate analysis (crude OR: 1.126). The significant factors associated with accidental ingestion in nursery centers were fewer children (per 10-fold increase; aOR: 0.703)