

## **Mammalian Meat Allergy Accompanied by Venom Allergy: A Review of 12 Cases**

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### **ABSTRACT**

There has recently been an increase in mammalian meat allergy (MMA) in the Black Sea Region of Turkey. It has been associated with the expansion of tick populations. Tick bites appear to result in sensitization to the carbohydrate allergen galactose- $\alpha$ -1, 3-galactose, which is present in many types of mammalian meats.

In this study, we have emphasized that *Ixodes ricinus* named tick type which is implicated in meat allergy, is found in domestic animals of Black Sea Region of Turkey. A new concept has been recently raised; suggesting that having an alpha-gal allergy is associated with an increased risk of sensitization to multiple venom specific immunoglobulin (Ig) E. Our aim is to evaluate the clinical characteristics of adult patients with MMA and its relationship with insect sting reactions in Turkey.

Patients referring to the allergy outpatient clinic with possible MMA were interviewed regarding reactions to a stinging insect. Demographic features and detailed histories of the patients were recorded. Skin prick test (SPT) with commercial beef extract and venom allergens, as well as prick to prick tests with raw beef and cooked beef were performed. Serum total IgE and beef meat specific IgE were measured.

Of 50 interviewed patients, 12 patients (4 male [33,3%] and 8 female [66,6%]) had a history of venom hypersensitivity reaction. The mean age was  $36.50 \pm 13.35$  years (range:18–61). History of other allergic diseases was present in 8 (66.6%) patients. Both venom and meat allergy were confirmed with SPT or prick to prick tests in these 12 patients. Among these patients sensitization to honey bee venom was more frequent (83%). MMA and venom allergy are influenced by the same environmental exposures. We believe that there may be shared immunologic factors and similar antigens; making venom allergic patients more susceptible to MMA.

**Keyword:** Allergy; Mammalian meat; Venom

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### **INTRODUCTION**

Mammalian meat allergy (MMA) is an allergic

reaction which is associated with immunoglobulin E (IgE) antibodies; directed against the mammalian oligosaccharide epitope galactose- $\alpha$ -1, 3-galactose ( $\alpha$ -gal).<sup>1</sup> Clinically, it is characterized by including symptoms as follows: urticaria, angioedema, abdominal pain, nausea, vomiting, cough, dyspnoea, and wheezing after consumption of red meat.<sup>2</sup> MMA is a common type of food allergy in tick endemic areas across the world. Studies suggest that being bitten by some groups of ticks is the significant cause of MMA. MMA following tick bite was first reported in 2007 by van Nunen et al<sup>1</sup> Later in 2009, Commins et al reported 24 patients with delayed onset red meat allergy. Accordingly, most of the patients (80%) were bitten by ticks before having symptoms.<sup>2</sup>

The most common tick species implicated in meat allergy includes *Amblyomma americanum* (ie, the lone star tick) in the southeastern United States and other species (*Ixodes ricinus*, *Ixodes holocyclus*, *Amblyomma cajennense*, *Amblyomma sculptum*, and *Haemaphysalis longicornis*) in other parts of the world.<sup>3</sup> Some tick species are limited to areas with high rainfall and intensive forest.<sup>4</sup> Eastern Black Sea region of Turkey has a wet and humid climate with a great amount of rainfall. The region is also important in the migration routes of tick bearing birds. In this study, we have emphasized that *Ixodes ricinus* name tick type which is implicated in MMA, is found in domestic animals of Black Sea Region of Turkey.<sup>4</sup>

A typical allergic reaction to  $\alpha$ -gal occurs 3 to 6 hours after mammalian meat consumption.<sup>2</sup> On the other hand, Mabelane T et al. reported that  $\alpha$ -gal allergy is associated with rapid onset of symptoms and a high prevalence of gastrointestinal manifestations. It was found to occur within 45 to 375 minutes after mammalian meat ingestion.<sup>5</sup>

In a recent study, Jerath MR et al suggested a new concept. They claimed that there may be a relationship between MMA and insect allergy. They evaluated 109 patients for specific IgE to  $\alpha$ -gal as well as venoms. They suggested that patients with MMA are also five times more likely to be sensitized to stinging insects compared to patients without red meat allergy. Finally, they suggested that patients with MMA were also 3.6 times more likely to be sensitized to venom.<sup>6</sup>

Our aim was to evaluate the clinical and demographic characteristics of adult patients with MMA in Turkey and its relationship with insect sting reactions.

## MATERIALS AND METHODS

### Study Design

Patients (n: 50) referring to the allergy outpatient clinic with possible MMA were interviewed regarding the reactions to stinging insects.

### Sensitization to Mammalian Meat and Venom Allergens

Demographic features and detailed histories of the patients were recorded. Skin prick tests (SPT) with commercial beef extract, venom allergens (ALK prick test diagnostic vespula spp and *Apis mellifera* 100 mcg/mL) and prick-prick skin tests (PPST) with raw beef and cooked beef were performed. Additionally, all patients underwent SPT with *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, Grass pollen, weed pollen, tree pollen, *Parietaria*, *Artemisia vulgaris*, *Aspergillus fumigatus*, *Alternaria alternata*, *Penicillium*, cat, and dog allergen extract (solutions from Allergopharma, Germany was used in the SPT). SPT and PPST were performed on the volar side of the forearm. It was considered positive if there was a wheal response with a mean diameter of 3 mm or greater.<sup>2</sup> Specific IgE levels were measured by ImmunoCAP (Thermo Fisher Scientific Inc., Phadia AB, Uppsala, Sweden). For immunoCAP, a positive result was defined as a value  $\geq 0.35$  kU/L.<sup>7</sup> All patients had history of allergic reactions to red meat for less than 4 years or even shorter than a year<sup>8</sup>. Since none of the patients signed the informed consent, oral provocation tests were not performed.

### Ethics Considerations.

Informed consent was obtained from all patients and the study was approved by the Ethical committee. (Approval identification number : 1080)

### Statistical Analysis

Statistical analysis was performed; using SPSS ver. 17 (SPSS Inc., Chicago, IL, USA). Data are presented as mean $\pm$ standard deviation (SD). Descriptive statistics were used to evaluate demographic and clinical characteristics.

## RESULTS

### Baseline Clinical Characteristics of Patients

Of 50 interviewed patients, 12 patients (4male

[33.3%] and 8 female [66,6%]) had a history of venom hypersensitivity reaction. The age range of these 12 patients was 18-61 years and the mean  $\pm$  SD age was  $36.50 \pm 13.35$  years. History of other allergic diseases was present in 8 (66.6%) patients (6 individuals with allergic asthma and 2 cases with allergic rhinitis). The median reported age meat allergy onset was 19 years (interquartile ranges, 14, 5; 20). Two patients were first-degree relative (Patient 7- patient 8, mother and son), and the rate of family history of meat allergy was 25 %. All patients were living in two cities (Giresun and Ordu) in the Eastern Black Sea region of Turkey. Five patients had experienced tick bites several times, 3 patients were not bitten by ticks and 4 patients were not aware of any tick bites. Angioedema, dyspnea, and gastrointestinal symptoms were the most frequent (58,3%) reported symptoms after meat consumption. MMA-related complaints were usually reported within the first hour. The median reported time for the onset of symptoms after meat consumption was 30 minutes (interquartile ranges, 15; 30). Most of the patients had a recent history of anaphylaxis (the mean  $\pm$  SD duration from the last reaction was  $9,5 \pm 12.16$  months). None of the patients reported allergic reactions to chicken, turkey, fish, cow's milk, and any other foods.

Considering the fact that pork consumption is not common due to religious rules, patients were not skin tested for pork.

Clinical and demographic characteristics of patients with MMA accompanied by venom allergy are shown in table 1

#### Skin Prick Test Response

SPT evaluation with commercial meat extract revealed sensitization in 9 out of 12 patients.

SPT with commercial meat extract was negative; while prick to prick test with cooked fresh meat revealed sensitization in other 3 patients. SPT evaluation revealed sensitization to bee venom in 5 patients, wasp venom in 2 patients, both wasp and bee venom in 5 patients that were in accordance with sting reaction. Patients with MMA reported being sensitized to venom allergens. Among mammalian meat allergic patients, honey bee venom sensitization was more frequent (83,3%). A patient's anamnesis revealed that red meat allergy occurred immediately after the bee sting. Interestingly, after one year of venom immunotherapy, she started to consume red meat without any problem.

**Table 1. Clinical and demographic characteristics of patients with meat allergy accompanying venom allergy**

	Age	Gender Female (F) Male (M)	Age of meat allergy (years)	Other Allergic Disease	Tick Bite	Symptoms after meat consumption.	Family history of meat allergy	Time of onset of symptoms	Last Reaction Time for Meat Allergy (Month)
1	38	F	18	Asthma	Positive	A,D	Negative	30 minute	6
2	46	F	16	AR	NS	A,D	Negative	15 minute	12
3	61	F	58	-	Positive	A,D, AP,N,V	Positive	2 hour	6
4	18	M	3	-	NS	U, A, D	Negative	15 minute	2
5	22	F	18	-	NS	A, D, AP,N,V	Negative	30 minute	7
6	35	F	30	AR	Negative	U,A,AP	Negative	15 minute	2
7	55	F	20	Asthma	Positive	A,D, AP,N,V	Positive	30 minute	36
8	29	M	6	AR	Positive	A,D, AP,N,V	Positive	30 minute	24
9	16	M	14	AR	Negative	A,D, AP,N,V	Negative	30 minute	24
10	32	M	18	-	NS	U,A, D	Negative	15 minute	24
11	43	F	18	AR	Negative	A,D, AP,N,V	Negative	30 minute	6
12	40	F	20	AR	Positive	A,D, AP,N,V	Negative	1 hour	36

AR: Allergic Rhinitis, NS: Not sure, A: angioedema, U: urticaria, AP: abdominal pain, C:cough; D: dyspnoea, N: nausea, V: vomiting; W: wheezing,

### DISCUSSION

There has recently been an increase in MMA cases; referring to our allergy outpatient clinic in the Black Sea Region, despite a relatively high level of seafood consumption. In some studies, the possible link between MMA and tick bites have been identified.<sup>1</sup> All patients included in the study were living in two cities (Giresun and Ordu) in the eastern Black Sea region of Turkey. Due to intensive livestock, beekeeping, and outdoor activities, people have a very high risk of being exposed to *Ixodes ricinus*. Accordingly, five patients of the current study had experienced tick bites several times. MMA may be developed at various ages.<sup>9</sup> It is commonly found among children in eastern Black Sea regions of Turkey and genetic factors may play an important role. In a study performed in Turkey, the estimated prevalence of IgE-mediated beef allergy in the pediatric population was 2.6%.<sup>10</sup> On the other hand, meat allergy seems to remain through adulthood.<sup>9</sup> To date, there has been no study on the evaluation of clinical characteristics of adult patients with MMA in Turkey. In our study, we evaluated the clinical characteristics of adult patients with MMA for the first time. The median reported onset age of meat allergy was 18 years (ranged from 3 to 58). In a study reported by Zik T et al., family history of meat allergy was found in 67% of the participants.<sup>10</sup> In our study, two patients were first-degree relative and the rate of family history of meat allergy was 25%. Data from the literature suggests that atopy may be the risk factor for the development of meat allergy. Fiocchi A et al reported that meat allergy is the most commonly reported allergy among children with atopic dermatitis or food allergies.<sup>11</sup> Similarly, in our study most of the patients (66,6%) were atopic (6 cases with allergic asthma and 2 patients with allergic rhinitis). Our study revealed that meat allergy-related complaints were usually reported within the first hour.

In our study, we evaluated venom hypersensitivity in patients who were referred to the outpatient allergy clinic with meat allergy complaints. To date little is known about having alpha-gal allergy and risk of sensitization to venom. In a study by Choudhary S et al., patients with alpha-gal allergy reported a higher rate of allergic reactions following insect stings and were five times more likely to be sensitized to the honey bee, white-faced hornet, common wasp, paper wasp or fire ant than patients without the allergy.

Additionally, wasp venom had the highest rate of venom sensitization among mammalian meat allergic patients (30%).<sup>6</sup> On the contrary, honey bee venom sensitization was more common (83%) among mammalian meat allergic patients of our study. While alpha-gal is a carbohydrate structure allergen, clinically important venom allergens are found in protein structure. Although the role of specific IgE to plant and insect venoms cross-reactive carbohydrate determinant (CCD) in patients with meat allergy is controversial, up to now, oligosaccharide alpha-gal sensitization has been reported in the ticks<sup>12-14</sup> and hymenoptera sting induce anti-CCD IgE antibodies that are clinically not relevant in anaphylaxis (15). Even if both alpha-gal and venom allergy are influenced by the same environmental exposures, we think that there may be shared immunologic factors and similar antigens that make venom allergy patients more susceptible to meat allergy.

To date, there has been no study on the evaluation of clinical characteristics of adult patients with MMA in Turkey. In this study, clinical characteristics of adult patients with MMA and venom sensitization was reported for the first time. It seems that there are different clinical aspects for meat allergy and the role of bees and ticks are questionable for this region.

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