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Red meat allergy in Sweden: Association with tick sensitization and B-negative blood groups

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Over the past few years, allergy to mammalian meat has been identified as a new syndrome of food allergy presenting as symptoms of delayed severe allergic reactions after consumption of red meat (beef, lamb, or pork).¹⁻⁴ These allergic reactions are directed against the carbohydrate galactose- α -1,3-galactose (α -Gal). In the initial studies on red meat allergy, Commins et al⁵ observed that the geographic distribution of IgE antibodies to α -Gal in the United States overlapped the region where the tick *Amblyomma americanum* is common, suggesting that tick bites might be relevant to these reactions. Since then, several reports have confirmed a relationship between tick bites and red meat allergy.^{6,7} We have recently identified α -Gal in the gastrointestinal tract of the European tick *Ixodes ricinus*, which provides further evidence of the tick as an initiator of red meat allergy.⁷

In this study we have identified 39 patients with a history of allergic reactions after consumption of mammalian meat and IgE against α -Gal (ImmunoCAP; Thermo Fisher Scientific, Uppsala, Sweden; median, 20 kU_A/L; range, 1.3-130 kU_A/L; Table I). With the exception of 2 patients, they all described delayed symptoms in which urticaria was dominant, but as many as 45% had experienced anaphylaxis (Table I). All patients had IgE

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against α -Gal-containing allergen sources, such as beef and pork, and the majority also had IgE to cow's milk, dog, cat, and moose (see Table E1 in this article's Online Repository at www.jacionline.org). Significant correlations between IgE to α -Gal and the different mammalian allergens were noted (see Fig E1 in this article's Online Repository at www.jacionline.org). Because the medical investigation revealed that all patients had been bitten by ticks, the majority more than 10 times (Table I), we investigated whether our patients were sensitized to the European tick *I ricinus* and whether they also recognized IgE epitopes in *A americanum* (described in the Methods section in this article's Online Repository at www.jacionline.org). We found that all but 2 patients had IgE antibodies to *I ricinus* (Table I). Although the IgE levels to *I ricinus* were less than those to α -Gal, we observed a strong correlation, supporting the association between tick bites and sensitization to α -Gal (Fig 1, A). This is in line with the results by Commins et al,⁵ who reported an equally strong correlation between IgE to α -Gal and the tick *A americanum* among patients presenting with allergic reactions from the southeastern United States. More than 35% of the patients with red meat allergy reported here were also sensitized to *A americanum*, but the IgE levels were much lower than those to *I ricinus*, suggesting that *I ricinus* is the species to which they were primarily sensitized. However, the IgE antibody levels against both tick species correlated significantly (Fig 1, B).

We were also interested in examining the allergenic cross-reactivity between *I ricinus* and *A americanum*. A serum pool of 4 Swedish patients with meat allergy (25 kU_A/L to *I ricinus* and 8.5 kU_A/L to *A americanum*) was preincubated with *I ricinus* or *A americanum* tick extract before measurement of *I ricinus*-specific IgE by mean of ImmunoCAP. The results revealed that the *A americanum* extract was only able to inhibit 37% of IgE binding to *I ricinus* at the highest concentration (81 μ g/mL). In contrast, the *I ricinus* extract almost completely inhibited the IgE binding to *I ricinus* (91%) at the same concentration. The results indicate that the 2 tick species share similar allergen epitopes but that they also have species-specific epitopes.

To investigate how common IgE antibodies against α -Gal are in the general population, we screened 143 healthy blood donors from the greater Stockholm area. We found that as many as 10% had IgE antibodies to α -Gal (see Table E2 in this article's Online Repository at www.jacionline.org) compared with 0.7% (1/150) of teenagers from a prospective study on asthma in northern Sweden, where tick bites are rare.^{5,8} We also screened 207 patients with Lyme disease as a confirmed recently tick-bitten population and found 22% to have positive IgE levels to α -Gal (see Table E3 in this article's Online Repository at Fig 1, C). These low levels probably reflect sensitization only and are not predictive of an allergic reaction. However, the frequency of α -Gal-sensitized subjects was significantly higher in the group with Lyme disease compared with the healthy blood donors (46/207 vs 5/143; Fig 1, D; χ^2 25.8.09; $P < .005$), which strengthens the role of tick bites for the induction of IgE to α -Gal. When comparing the patients with red meat allergy with the α -Gal-positive patients with Lyme disease, we found that their median IgE titer to α -Gal was significantly higher and that the correlations between α -Gal and total IgE, as well as *I ricinus*, were significantly stronger. Similarly, IgE responses to *I ricinus* were significantly higher in both frequency (37/39 vs 21/46, $\chi^2 = 23.59$, $P < .001$) and median levels (1.49 vs <0.10 kU_A/L, $P < .001$) in

patients with red meat allergy compared with those seen in α -Gal-positive patients with Lyme disease. For both groups, the responses to *I ricinus* correlated with total IgE levels ($r = 0.65$ and $r = 0.52$, respectively; $P < .001$, see Fig E2 in this article's Online Repository at www.jacionline.org).

Because the α -Gal epitope is a major blood group substance of nonprimate mammals and structurally related to blood group B, we investigated the blood type of our population with meat allergy. We found that all but 2 patients belonged to the B-negative blood groups (A or O, 5%) which is significantly less compared with the expected number in the Swedish population (18%; www.geblod.nu). Also, 86% of the healthy blood donors and 78% of the patients with Lyme disease who had positive IgE levels to α -Gal were B-negative, and in the majority the IgE levels to α -Gal were very low. Taken together, we here report that there is a strong relationship with tick bites for the production of IgE to α -Gal and, for the first time, that red meat allergy is strongly associated with the B-negative blood groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIG 1.

A and **B**, Correlations between IgE responses to α -Gal and *I. ricinus* (Fig 1, A) and *I. ricinus* and *A. americanum* (Fig 1, B) in Swedish patients with red meat allergy. **C**, IgE reactivity to α -Gal in patients with red meat allergy compared with that in healthy blood donors and patients with Lyme disease expressed as kilounits of allergen per liter. Mann-Whitney U tests were performed to assess statistical significance: $*P < .001$. Solid bars denote median values. **D**, Prevalence of IgE reactivity to α -Gal in healthy blood donors compared with that in patients with Lyme disease.

TABLE I

Characteristics of patients with meat allergy

Patient no.	Age (y)/sex	Reaction	Time to reaction [†]	IgE [*]					Tick bites [‡]	Blood group
				Total	α-Gal	Beef	<i>I ricinus</i>	<i>A americanum</i>		
1	67/M	AE, GI, U	6	260	54	5.0	30	5.2	+++	A
2	40/F	ANA, GI, U	3-4	120	16	3.5	0.46	<0.10	11	A
3	63/F	GI, U	2	20	13	5.5	0.60	<0.10	++	A
4	69/M	AE, GI, U	4	280	23	11	40	6.0	111	A
5	39/M	AE, GI, U	4-5	33	6.4	4.4	0.72	<0.10	11	A
6	74/M	U	3-4	210	30	10	1.9	<0.10	1	A
7	51/M	ANA, U	4-5	25	2.2	1.4	0.17	<0.10	111	A
8	48/F	AE, ANA, GI, U	0.25-1	150	16	7.9	4.7	<0.10	111	O
9	43/M	AE, ANA, GI, U	8	320	88	11	3.1	0.15	111	O
10	69/M	GI, U	6	87	18	4.9	1.5	<0.10	1	A
11	46/M	GI	2	90	4.4	2.2	0.35	<0.10	1	O
12	70/M	AE, U	6	420	130	16	37	1.5	111	O
13	48/F	GI, U	2-6	870	6.2	11	2.8	0.87	11	A
14	44/M	AE, ANA, GI, U	4-7	1800	24	4.5	10	2.6	11	O
15	33/F	AE, ANA, GI, U	6-7	270	46	7.2	0.34	<0.10	1	O
16	65/F	AE, ANA, U	6	550	31	22	13	11	1	O
17	69/M	AE, U	10-12	130	25	20	8.1	0.13	1	A
18	63/F	AE, ANA, GI, U	3-4	140	20	3.0	0.17	<0.10	1	A
19	38/F	GI, U	6	140	19	3.2	2.3	0.23	11	A
20	54/M	ANA, GI, U	2	20	3.6	1.1	0.27	<0.10	1	O
21	74/F	AE, GI, U	8	30	1.6	0.53	0.3	<0.10	11	A
22	36/M	GI, U	6-7	80	22	3.3	2.1	0.11	111	O
23	60/M	AE, ANA, U	6-7	2200	76	6.2	54	5.9	111	O
24	54/F	ANA, U	5-6	130	19	3.8	2.9	<0.10	111	A
25	37/F	AE, ANA, GI, U	6-7	110	12	2.8	1.2	<0.10	1	O
26	57/F	GI, U	2-8	50	29	6.3	0.61	<0.10	1	A
27	69/M	AE, ANA, GI, U	6	48	6.6	0.49	<0.10	<0.10	111	O

Patient no.	Age (y)/sex	Reaction	Time to reaction [†]	IgE [*]					Tick bites [‡]	Blood group
				Total	α-Gal	Beef	<i>I ricinus</i>	<i>A. americanum</i>		
28	49/M	ANA, U	7	48	10	1.8	0.36	<0.10	11	A
29	57/M	U	3	33	2.4	0.25	0.11	<0.10	11	O
30	52/F	AE, ANA, U	1-2	87	12	5.4	2.7	<0.10	11	O
31	73/M	GI	ND	340	37	6.0	1.4	1.3	1	O
32	45/F	AE, U	5	44	5.0	0.3	<0.10	<0.10	11	AB
33	36/F	AE, GI, U	4-5	120	37	9.9	6.9	0.32	111	O
34	44/F	U	2-7	240	110	9.7	0.26	<0.10	11	O
35	40/M	GI, U	6	270	84	28	3.3	<0.10	11	O
36	41/F	GI, U	3	360	61	12	1.5	<0.10	1	A
37	18/F	AE, ANA, GI, U	4-8	180	1.3	0.93	0.56	0.64	1	O
38	55/M	GI, U	4-12	150	22	1.9	4.4	<0.10	111	B
39	70/M	AE, ANA, GI, U	0.25-3	150	23	1.9	3.6	<0.10	11	O

AE, Angioedema; ANA, anaphylaxis; F, female; GI, gastrointestinal symptoms; M, male; ND, not determined; U, urticaria.

* ImmunoCAP IgE results: total IgE levels are expressed in kilounits per liter, and allergen-specific IgE levels are expressed in kilounits of allergen per liter.

[†] Reported time to reaction expressed in hours.

[‡] Estimated total number of tick bites: 1, 1 to 10; 11, 10 to 50; and + + +, 50 to 100.