

EDITORIAL

Clinical & Experimental Allergy

IgE antibodies specific to alpha-gal: an example of clinically relevant cross-reactive anti-carbohydrate antibodies

This editorial discusses the findings of the paper in this issue by A. Gonzalez-Quintela et al. [9], pp. 1061–1068.

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Red meat allergy is an unusual, novel form of allergy with delayed onset of reactions (anaphylaxis, angioedema or urticaria) several hours after meat consumption and is thought to be primarily mediated by IgE antibodies to gal- α -1,3-gal- β -1,4-GlcNAc (α -gal) [1–4]. The α -gal epitope is a carbohydrate structure that is abundantly expressed on many proteins and cellular structures of many mammalian species. Notable exceptions are humans as well as several other primates that lost the ability to express α -gal. Consequently, many individuals make IgG antibodies to α -gal, which were first described in 1984 and found to be abundant in the general population [5]. These antibodies are predominantly IgG2 and are presumably formed in response to gut microorganisms that can also express α -gal [6]. In recent years, IgE antibodies to α -gal were found in some individuals and linked to hypersensitivity reactions following consumption of red meat, which contains abundant amounts of α -gal. Rather unusually, there is no evidence that these IgE antibodies are formed in response to exposure to red meat [7]. A different type of exposure is required for these antibodies to be elicited, and both parasite infections and tick bites have been implicated as described below. At the same time, anaphylactic reactions to subsequent tick bites appear not to occur [7]. Therefore, sensitization and symptom

elicitation seem to require different agents for this syndrome, which, together with the delayed onset of reactions, makes it a relatively complicated syndrome to study and recognize. Furthermore, it raises questions about the antigen processing and recognition by the immune system leading to IgE production, or effector cell activation. In a recent study, open food challenge has now confirmed earlier patients' descriptions of the delayed reactions starting between 3 and 7 h after ingestion of mammalian meat, with *in vivo* basophil activation occurring in the same time frame [1][†]. Glycolipids containing the α -gal epitope have been suggested to be the main actors responsible for the symptoms, because these would be consistent with the requirements for digestion, absorption and uptake into the circulation. However, the exact nature of the presumed antigen(s) and the way they elicit reactions are not yet known.

IgE antibodies to α -gal were first described following cases of cetuximab-induced anaphylaxis [8]. As pre-dose samples contained IgE anti- α -gal antibodies, they were not elicited by the drug. Subsequently, it was observed that the prevalence of these antibodies profoundly varied between different regions in the United States. In a number of studies, a link with exposure to the lone star tick *Amblyomma americanum* has been made [2, 7]. It has been suggested that IgE to α -gal represents an emerging phenomenon resulting in an increasing number of cases of hypersensitivity to red meat [2].

Obviously, these findings raise the question about the prevalence of IgE anti- α -gal and red meat allergy in regions outside of the United States. By now, a number

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[†]Curiously, several control subjects negative for IgE anti- α -gal also showed signs of delayed basophil activation while not reporting symptoms.

of studies have been undertaken to investigate the prevalence of IgE anti- α -gal antibodies across different populations from different regions as well as selected subjects with either a history of Lyme's disease, or being infected with parasites, or having experienced hypersensitivity reactions following consumption of red meat (Table 1; Fig. 1). In Sweden, prevalence of IgE anti- α -gal (> 0.35 kU/L) was previously found to be almost 9% amongst subjects with a history of Lyme's disease, but this was not significantly different from a general population from the same region [10]. However, tick bites have now been associated with IgE anti- α -gal in Denmark. A recent study published elsewhere in this journal investigated the prevalence of IgE anti- α -gal in this country [9]. The results indicate that about 1–2% of the population has IgE anti- α -gal above the threshold of 0.35 kU/L, with 0.35% expressing levels exceeding 3.5 kU/L. This study reports that the presence of IgE anti- α -gal is associated with a history of tick bites. Moreover, in Australia, 24 of 25 cases of red meat allergy reported previous tick bites [11]. Therefore, evi-

dence that several different types of ticks may be able to induce IgE anti- α -gal is accumulating.

Furthermore, in populations from tropical regions, IgE anti- α -gal was reported to be potentially induced by a parasite infection, although a direct relationship has not been demonstrated. Nevertheless, 40 of 47 subjects from Zimbabwe with a confirmed schistosomiasis or geohelminth infection were found to be positive for IgE anti- α -gal [13].

In addition, the study by Gonzalez-Quintela reported a significant correlation between IgE anti- α -gal and cat ownership [9]. This, however, does not prove a causal relationship between cat exposure and formation of IgE anti- α -gal and will need to be further examined. In this context, it is of interest to note that while cat IgA was found to express α -gal, IgE antibodies to α -gal are a poor predictor of cat allergy, probably because the α -gal-containing IgA (and IgM) does not get airborne [12]. Taken together, there are probably multiple species of ticks, helminths and other (ecto)parasites that may elicit an IgE antibody response to α -gal.

Table 1. Populations in which the prevalence of IgE anti- α -gal antibodies has been evaluated

Region	Population	Demographics	IgE anti- α -gal > 0.35 kU/L	%	Notes	References
Stockholm, Sweden	Red meat allergy	Ticks (<i>I. ricinus</i>) common	39/39	100	(a)	[10]
Stockholm, Sweden	Healthy blood donors	Ticks (<i>I. ricinus</i>) common	5/143	3.5		[10]
Stockholm, Sweden	History of Lyme disease	Ticks (<i>I. ricinus</i>) common	18/207	8.7		[10]
Norbotton, Sweden	Healthy teenagers	Ticks/parasites uncommon	1/150	0.7		[7]
Tennessee, USA	Random subjects	Ticks (<i>A. americanum</i>) common	24/107	22		[7, 8]
California, USA	Cancer patients	Ticks/parasites uncommon	3/49	6.1		[8]
Boston, USA	Woman	Ticks/parasites uncommon	2/341	0.6		[8]
Virginia, USA	Red meat allergy	Ticks (<i>A. americanum</i>) common	117/121	97		[7]
Virginia, USA	Asthma	Ticks (<i>A. americanum</i>) common	10/68	15		[7, 12]
Virginia, USA	Random subjects	Ticks (<i>A. americanum</i>) common	42/217	19		[7, 12]
California, USA	Asthma & control subjects	Ticks/parasites uncommon	1/117	0.8		[7]
California, USA	Asthma & control subjects	Ticks/parasites uncommon	3/136	2.2		[7]
Kabati, Kenya	Random subjects (rural)	Tick bites and parasite infections common	100/131	76	(b)	[7]
Kabati, Kenya	Random subjects (urban)	Tick bites and parasite infections less common	36/123	29		[7]
Ecuador	School children	Parasite infections common	110/295	37		[7]
Spain	Random subjects	Ticks/parasites uncommon	41/2297	1.8	(c)	[9]
Denmark	Random subjects	Ticks/parasites uncommon	10/444	2.2	(d)	[9]
Zimbabwe	Parasite infection	Parasite infections common	40/47	85	(e)	[13]
Zimbabwe	Cat allergy	Parasite infections common	6/31	19	(e)	[13]
Australia	Red meat allergy				(f)	[11]
Spain	Red meat allergy		5/5	100		[14]
France	Red meat allergy		14/14	100		[15]
Flanders, Belgium	Red meat allergy		9/10	90		[16]

(a) correlation between IgE anti- α -gal and anti-*I. ricinus*.

(b) correlation between IgE anti- α -gal and anti-cat epithelium.

(c) IgE to α -gal correlated with cat ownership.

(d) IgE anti- α -gal correlated with reported history of tick bites and cat ownership.

(e) IgE not expressed in international units, positivity based on O.D (italics).

(f) 24/25 patients history of tick bites (*I. holocyclus*).

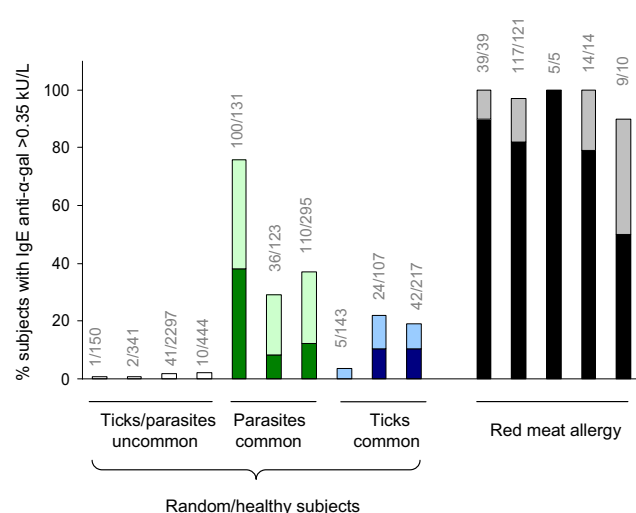


Fig. 1. Percentages of subjects that test positive for IgE anti- α -gal in various cohorts (light shade: > 0.35 kU/L; dark shade: > 3.5 kU/L).

It would be of interest to investigate which factors are responsible for the apparently potent induction of IgE anti- α -gal following tick bites, while many individuals already make IgG antibodies to α -gal and therefore have been exposed to α -gal in different ways, (including red meat consumption and abundant exposure via gut micro-organisms). Of note, prolonged periods of prior meat consumption may not have resulted in the development of tolerance. Apparently, the route by which the antigen is presented to the immune system can profoundly influ-

ence the type of response that is elicited. Moreover, a high level of IgG2 anti- α -gal, present in many individuals, does not appear to offer any protection against IgE production in response to tick bites [2, 6].

Selected subjects that reported hypersensitivity reactions following consumption of pork, beef, or other types of α -gal-containing meat generally make substantial amounts of IgE anti- α -gal, with a prevalence (> 0.35 kU/L) close to 100% (Table 1; Fig. 1), but often expressing much higher levels [1]. The relatively high titres of IgE generally found in these subjects suggest that individuals with low titres of IgE anti- α -gal may experience no or only mild symptoms. Antibodies to carbohydrate structures are often of low affinity, which may be one explanation why only high titres of IgE anti- α -gal may induce hypersensitivity reactions. Furthermore, fine specificities of the anti- α -gal antibodies may vary, and the carbohydrate structures that contain α -gal may differ in their ability to be recognized by the anti- α -gal antibodies [6, 17, 18]. As the precise nature of the antigen(s) leading to hypersensitivity is not yet known, an optimal test strategy (i.e. which antigen/carbohydrate structure should be used for testing) has yet to be developed. Therefore, what remains to be investigated is the possibility of developing allergic symptoms upon red meat consumption with respect to the titre and fine specificity of IgE anti- α -gal.

Conflict of interests: The authors declare no conflict of interest.

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