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## Galactose- $\alpha$ -1,3-galactose syndrome: an Italian survey

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### KEY WORDS

$\alpha$ -Gal syndrome; red meat allergy;  
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### Summary

**Background.** The term of  $\alpha$ -Gal syndrome, which includes the delayed allergy to red meat and the allergic reactions following the administration of cetuximab, is associated to the presence of specific IgE to  $\alpha$ -Gal. In Italy, only anecdotal cases were reported so far. The Association of Italian Allergists (AAIITO) carried out a survey with the aim of evaluating presence, characteristics, clinical features, and distribution of the syndrome in Italy. **Methods.** A web structured questionnaire was made available on the website of AAIITO from July 2016 to January 2017. It included 31 multiple-choice questions concerning different items, including the site of physicians, the number of patients diagnosed as having cetuximab allergy and/or delayed red meat allergy, recall of tick bites, symptoms, time to reactions, elicitor foods, reactions with foods other than meat, and in-vivo and in-vitro tests used for the diagnosis. **Results.** Seventy-nine physicians completed the questionnaire. Nine cases of allergy to cetuximab and 40 cases of delayed red meat allergy were recorded across Italy. 22.5% of patients with cetuximab allergy and 62.5% of those with delayed red meat allergy recalled a tick bite. 75% of patients with delayed red meat allergy experienced symptoms after eating beef (butcher's cut in 72.5%). Urticaria was the most frequent clinical manifestation (65% of cases). In 60.6% of cases symptoms appeared 2 - 4 hours after meat ingestion, while in 7.9% symptoms appeared after > 4 hours. The most used diagnostic methods were the intradermal test for cetuximab allergy (88.9%) and the detection of IgE to  $\alpha$ -Gal (55.5%) for red meat allergy. Most case reports came from Northern Italy. **Conclusion.**  $\alpha$ -Gal syndrome is present in Italy and beef is the most frequent offending food. In most cases symptoms were not severe.

## Introduction

Galactose- $\alpha$ -1,3-galactose ( $\alpha$ -Gal) is a carbohydrate epitope that is abundantly expressed on glycoproteins of mammalian origin, including non-primates, prosimians and New World monkeys (1,2) and is produced by the enzyme  $\alpha$ -1,3-galactosyltransferase ( $\alpha$ -1,3 GT). In contrast,  $\alpha$ -Gal is not expressed in Old World monkeys, apes and humans, since the enzyme  $\alpha$ -1,3 GT is non-functional, as result of an evolutionary event that occurred possibly 28 million years ago (3). As a consequence, species not expressing the  $\alpha$ -Gal epitope produce large amounts of IgG antibodies to  $\alpha$ -Gal, due to the constant antigenic stimulation exerted by bacteria present in the intestinal flora (4). It is estimated that approximately 1% of all IgG antibodies in human subjects are directed against the  $\alpha$ -Gal epitope, representing the major immune barrier in xenotransplantation (5). IgE antibodies against the  $\alpha$ -Gal epitope were identified in a subset of patients treated with cetuximab, a chimeric mAb approved for use in patients with colorectal cancer and squamous cell carcinoma of the head and neck, who developed severe anaphylactic reactions upon the first administration, suggesting the presence of pre-existing IgE antibodies. Further investigations revealed that anaphylactic reactions were induced by pre-existing IgE antibodies against the  $\alpha$ -Gal epitope on the Fab portion of cetuximab (6). In addition, IgE antibodies to  $\alpha$ -Gal have resulted to be related also to delayed (from 3 to 6 hours) anaphylactic reactions following the ingestion of red meat (7,8). Intriguingly, both cetuximab and red meat allergies showed great variation depending on the geographic location, which led to hypothesize that the cross-reactivity could originate from locally occurring biting insect or other parasites (9). In the US, the development of IgE to  $\alpha$ -Gal was eventually linked to bites from ecto-parasitic ticks, especially the Lone Star tick, *Amblyomma americanum* (10), whereas in Europe and Australia it has been associated to bites of *Ixodes* species (9). Hamsten and coworkers (11) showed that the  $\alpha$ -Gal epitope is present in the gastrointestinal tract of *Ixodes ricinus*, which exposes the host to  $\alpha$ -Gal during the bite. Two other papers from Brazil (12) and Japan (13) demonstrated the presence of  $\alpha$ -Gal epitope in the saliva of other tick species, respectively *Amblyomma sculptum* and *Haemaphysalis longicornis*. The term " $\alpha$ -Gal syndrome" was recently proposed to better describe this novel disease that occurs worldwide (14,15) and is clinically defined by the three facets of this allergy: (a) an IgE mediated food allergy with a typically delayed onset following the ingestion of mammalian meat and innards; (b) a drug allergy to cetuximab or gelatin-based colloids, both containing many  $\alpha$ -Gal epitopes; and (c) allergic (generally local) reactions to tick bites (16).

Many cases of  $\alpha$ -Gal syndrome have been described in Europe, particularly in Sweden, Germany and France (16,17), whereas in Italy only anecdotal cases have been reported so far (18), al-

though a study carried out on a population living in pre-Alps area and largely exposed to bites of *Ixodes ricinus* showed a high prevalence of sensitization to  $\alpha$ -Gal (19). In this study we report the results of a survey on  $\alpha$ -Gal syndrome carried out among the members of the AAIITO (the Italian Association of Allergists and Immunologists working on the Territory) with the aim of evaluating the presence, clinical features, and distribution of  $\alpha$ -Gal syndrome in Italy.

## Methods

A web structured questionnaire was made available on the AAIITO website ([www.aaeito.it](http://www.aaeito.it)) for six months, from July 2016 to January 2017. An invitation to participate to the survey was sent twice by e-mail to all the 500 members of the association. The 31 multiple-choice questions covered the following items: geographical origin of the physicians involved in the survey; number of patients visited per year; number of patients with cetuximab and/or delayed red meat allergy diagnosed so far; memory of a tick bite (if positive, where and number); symptoms features; in the case of red meat allergy: kind of meat involved, dish preparation, latency of reactions, reactions with foods other than meat; in vivo and in vitro diagnostic tests commonly used (20-21); availability of tests to detect sIgE to  $\alpha$ -Gal.

In 44 centres, the diagnosis of  $\alpha$ -Gal sensitization was carried out by means of ImmunoCap to  $\alpha$ -Gal (Thermofisher diagnostics, Uppsala, Sweden).

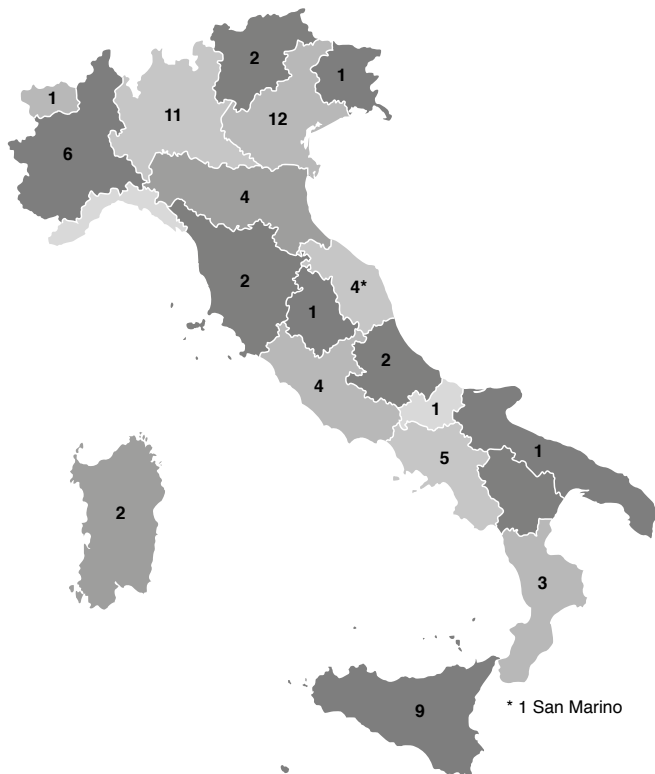
## Results

Seventy-nine physicians (79/500; 15.8%) from 20 of 21 Italian Regions (**Figure 1**) completed the questionnaire. They globally visit more than 150.000 patients per year (range 500 - > 2000 patients / centre).

Nine cases of allergy to the first injection of cetuximab were described in 5 centres (2 centres reported 3 cases) from 4 different regions (Toscana, Friuli Venezia Giulia, Lombardia and Lazio); specific features are shown in **Table I**. Only two patients recalled a previous tick bite. 4/9 (44.4%) experienced a severe reaction and the diagnosis was made by the intradermal test with cetuximab in the majority of patients (88.9%).

Forty cases of delayed red meat allergy were reported by 21 centres located in 11 different Italian Regions, with a higher prevalence in Northern Italy (**Figure 2**). The distribution of these cases in the 21 centres are shown in **Figure 3**, while their main features are reported in **Table II**. Twenty-five/40 (62.5% of patients) recalled a previous tick bite which, in the majority of cases, occurred in the hills (76%) or in the mountains (20%). 22/40 (55.3%) of patients experienced from two to four adverse reactions before the diagnosis, and 34.2% of pa-

**Figure 1** - Number of allergy centers distributed for the single Italian regions that answered the questionnaire.



tients more than four. 75% of the reactions were associated to the ingestion of beef, 17.5% of pork, and only few cases to the ingestion of sheep (5.0%) or game meat (2.5%). The majority of reactions (72.5%) were elicited by butcher's cut meat (i.e., muscle meat), whereas tripe (10%), sausages (5.0%), ham (2.5%), hamburger (2.5%) and liver / kidney (2.5) were the elicitors in the remaining cases. Nine out of 40 (22.5%) patients with delayed meat allergy reported adverse reactions also with other foods, in particular milk (4/9), gelatine containing sweet / toffee (4/9), and cakes (1/9), and one patient experienced an acute reaction during a gelatine plasma expander infusion. The most frequent clinical presentation was urticaria, and in 60.6% of patient the symptoms appeared between 2 and 4 hours after meat ingestion.

55% of the interviewed centres diagnosed  $\alpha$ -Gal sensitization by in vitro means (specific IgE to  $\alpha$ -Gal; Thermofisher diagnostics, Uppsala, Sweden); 55% by SPT with commercial beef and/or pork meat extracts, 42.5% by prick-prick with fresh meat, 27.5% by prick-prick with liver / kidney of pork or beef, 10% by SPT / intradermal test with cetuximab, and 5% by basophils activation test (BAT).  $\alpha$ -Gal-specific

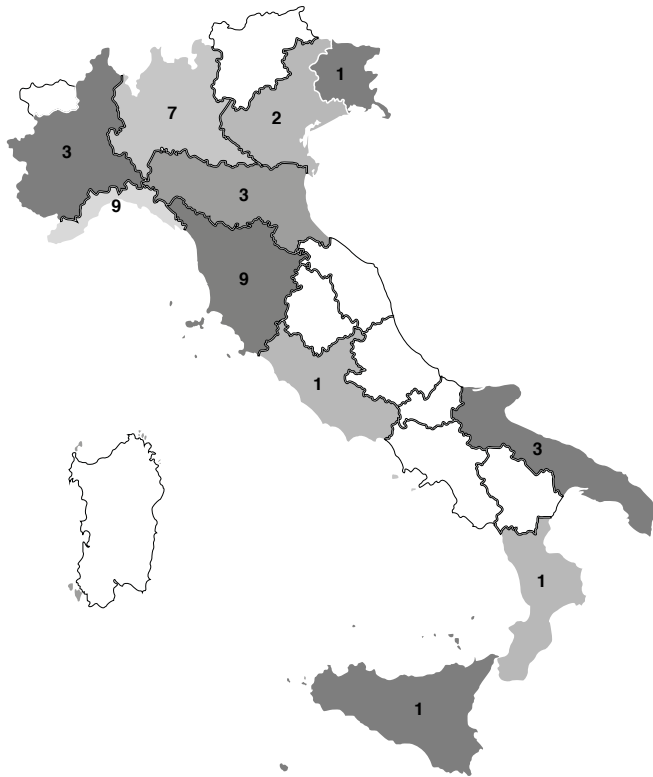
**Table I** - Features of patients with cetuximab allergy.

Question	N° (%)
1. Do the patient remember the tick bite	
yes	2/9 (22.2)
no	5/9 (55.6)
unknown	2/9 (22.2)
2. If yes, how many months before the adverse reaction?	
< 1	0/2 (0.0)
1-3	2/2 (100)
4-6	0/0 (0.0)
7-12	0/0 (0.0)
> 12	0/0 (0.0)
3. The patient was bitten	
in urban area	1/2 (50.0)
in rural area on the plain	1/2 (50.0)
in the hills	0/2 (0.0)
in the mountains	0/0 (0.0)
4. The adverse reaction was	
mild	2/9 (22.2)
moderate	3/9 (33.4)
severe	4/9 (44.4)
10. Methods used for the diagnosis	
SPT with cetuximab	6/9 (66.7)
Intradermal test with cetuximab	8/9 (88.9)
BAT	0/9 (0.0)
sIgE to $\alpha$ -Gal	3/9 (33.3)

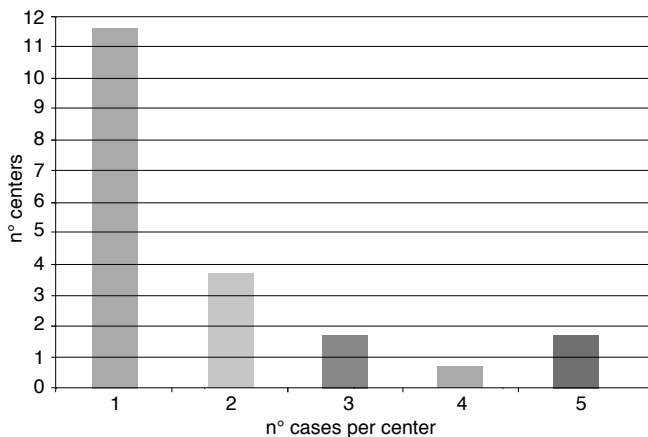
IgE levels were very high in most cases (> 100 kUA/L in 8/22 cases) (**Figure 4**).

Finally, physicians were asked whether they felt that they previously visited other patients with possible  $\alpha$ -Gal syndrome that remained undiagnosed, because at that time the syndrome was not yet known or because the diagnostic facilities were unavailable in their clinical setting. Nineteen physicians answered they met patients with symptoms possibly suggesting an  $\alpha$ -Gal syndrome (17 cases of delayed red meat allergy; 2 cases of cetuximab allergy). In these cases, the diagnosis made was: idiopathic anaphylaxis (38.1%); adverse reaction to red meat / cetuximab of possible allergic type (19.0%); not allergic adverse reaction to red meat / cetuximab (9.5%); other diagnoses (33.3%).

**Figure 2** - Distribution of the cases of delayed red meat allergy in Italy.



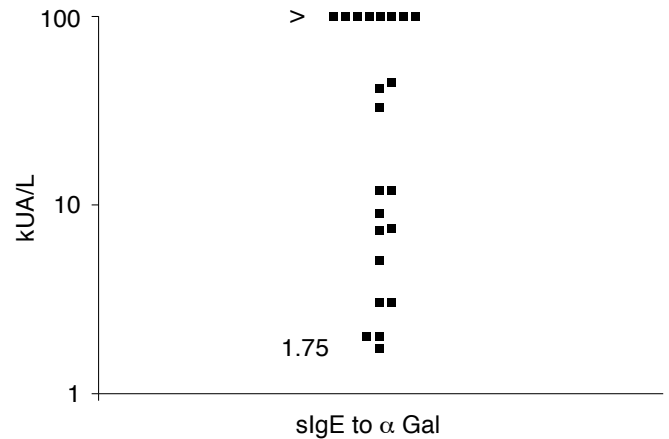
**Figure 3** - Number of cases reported for single center.



**Discussion**

This survey shows that the  $\alpha$ -Gal syndrome is present throughout all Italy, as expected in view of *Ixodes* spread in the country. Nonetheless, cases reported from Northern Italy exceed those

**Figure 4** - Values of specific IgE to  $\alpha$ -Gal in patients with  $\alpha$ -Gal syndrome.



reported from other regions. Whether this really reflects a higher prevalence, or it is due to a more widespread awareness of this syndrome and/or to a larger availability of the technology to detect specific IgE to  $\alpha$ -Gal, remains to be established.

Only a minority of patients with cetuximab allergy (22.2%) vs 62.5% of those with delayed red meat allergy recalled tick bites. These percentages are lower than those reported by Commins et al. (10), who found that more than 90% of subjects with serum IgE to  $\alpha$ -Gal had a history of tick bites, and by Kennedy et al. (22), who reported in a paediatric population with delayed anaphylaxis to red meat a tick exposure in 100% of cases. A possible explanation for this fact might be that, unlike subjects exposed to *Amblyomma americanum*, subjects exposed to *Ixodes ricinus* are not always aware of being bitten, as during the attachment and feeding process *Ixodes ricinus* injects a complex mixture of bioactive chemicals into the host, eventually resulting in a painless bite. Moreover, larval ticks are about 1 mm in diameter and are generally not seen or appear as small black dots, but still may cause sensitization through their bites (10). As expected, the majority of patients were bitten in the hills or mountains between one and twelve months before the appearance of symptoms (Table II).

An interesting finding of this survey is that reactions were most frequently reported with beef, which is in contrast with data from other European surveys, where beef and pork showed a similar importance as symptoms elicitors (16). Another important difference with the cases described in Germany and France, is that in Italy most of the reactions were seen after ingestion of butcher's cut meat, whereas in the other European countries mammalian kidney, innards, and sausages (frequently including innards), were the major elicitors (16,17, 23). Thus, the different food habits between European countries may play a relevant

**Table 2** - Features of patients with delayed red meat allergy

Question	N° (%)		
1. Do the patient remember the tick bite		tinned meat	0/40 (0.0)
yes	25/40 (62.5)	tripe	4/40 (10.0)
no	10/40 (25.0)	liver / kidney	1/40 (2.5)
unknown	5/40 (12.5)	other	2/40 (5.0)
2. If yes, how many months before the adverse reaction?		7. Adverse reaction with foods/products a part the meat	
< 1	0/22 (0.0)	no	31/40 (77.5)
1 - 3	5/22 (22.7)	yes	9/40 (22.5)
4 - 6	5/22 (22.7)	If yes	
7 - 12	6/22 (27.3)	milk	3/9 (33.3)
> 12	6/22 (27.3)	sweet / toffee	4/9 (44.4)
3. The patient was bitten		cakes	1/9 (11.1)
in urban area	0/25 (0.0)	vaccines	0/9 (0.0)
in rural area on the plain	1/25 (4.0)	gel infusion	1/9 (11.1)
in the hills	19/25 (76.0)	other	0/9 (0.0)
in the mountains	5/25 (20.0)	8. Symptoms	
4. How many adverse reactions the patient complained before the diagnosis?		urticaria	26/40 (65.0)
0 - 1	4/38 (10.5)	angioedema	1/40 (2.5)
2 - 4	21/38 (55.3)	oral / gastrointestinal	8/40 (20.0)
> 4	13/38 (34.2)	anaphylaxis	5/40 (12.5)
5. Which kind of meat caused the adverse reaction?		9. Symptom onset	
pork	7/40 (17.5)	< 30'	3/38 (7.9)
beef	30/40 (75.0)	30' - 1 h	4/38 (10.5)
horse	0/40 (0.0)	1 h - 2 h	5/38 (13.1)
lamb	2/40 (5.0)	2 h - 4 h	23/38 (60.6)
game	1/40 (2.5)	> 4 h	3/38 (7.9)
rabbit	0/40 (0.0)	10. Methods used for the diagnosis	
6. Which was the dish preparation?		SPT with commercial extracts	21/40 (52.5)
butcher's cut	29/40 (72.5)	prick to prick with meat	17/40 (42.5)
ham	1/40 (2.5)	prick to prick with liver/kidney	11/40 (27.5)
sausages	2/40 (5.0)	prick with cetuximab	4/40 (10.0)
würstel	0/40 (0.0)	BAT	2/40 (5.0)
hamburger	1/40 (2.5)	sIgE to $\alpha$ -Gal	22/40 (55.0)

role in the occurrence of the syndrome. In fact, in many regions of Europe innards are both consumed as local delicacies, and used in sausage products. Kidney, tripe, heart, sweetbread, lung, brain, and tongue from pork, beef, and lamb are processed in

such delicacies and consumed in Germany and France. Interestingly, time delay > 2-4 hours was seen in about 70% of Italian subjects, which is typically associated with muscle meat ingestion, whereas the allergic reaction occurs as short as 1 h follow-

ing the consumption of pork kidney (16,17,24), thus behaving like a classic immediate-type allergy probably due to the higher content of  $\alpha$ -Gal in kidney (17,25).

According to clinical histories, 65% of  $\alpha$ -Gal syndrome patients experienced urticaria, and only 12.5% had potentially dangerous systemic allergic reactions on at least one occasion (anaphylaxis > grade II according to Ring/Messmer) (26). The lower severity of reactions in Italian patients than in those described in American and other European series (16,20) remains an open question, although we cannot rule out a role played by the offending food (muscle meat vs kidney-innards) and the presence / absence of co-factors (that were not investigated in the present survey).

Finally, 22.5% of patients with delayed red meat allergy experienced adverse reactions after consuming foods other than meat, in almost all cases after ingesting milk or gelatin-containing sweets.

In conclusion,  $\alpha$ -Gal syndrome is present throughout Italy, although it is mostly diagnosed in the Northern part of the country. Beef meat is the most common offending food, symptoms are not extremely severe in most cases and develop 2-4 hour after the ingestion. Nearly 25% of patients react to foods other than meat, namely milk and gelatin-containing sweets.

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