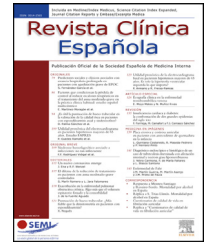




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BRIEF ORIGINAL

Alpha-gal syndrome. Allergy to red meat and gelatin[☆]

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KEYWORDS

Anaphylaxis;
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Abstract

Introduction: Alpha-gal syndrome is a potentially severe food allergy caused by the presence of alpha-gal-specific IgE. The aim of this study is to describe our series of 13 patients.

Material and methods: This work is a retrospective study of patients diagnosed in 2016 and 2017. Skin tests were performed with commercial extract and gelaspan as well as specific IgE determination for alpha-gal and different types of meat.

Results: Thirteen patients diagnosed with alpha-gal syndrome were analyzed; 9 of them had anaphylaxis, 6 of whom had been diagnosed with idiopathic anaphylaxis. All had a positive skin test with gelaspan, though this was not true with the commercial extracts, whose results were less conclusive.

Conclusions: We believe that a diagnosis of idiopathic anaphylaxis may prevent the identification of patients with alpha-gal syndrome. The gelaspan skin test is more useful than commercial extracts.

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PALABRAS CLAVE

Anafilaxia;
Carne roja;
Alfa-gal;
Gelatina

Síndrome de alfa-gal. Alergia a carne roja y gelatina

Resumen

Introducción: El síndrome de alfa-gal es una alergia alimentaria potencialmente grave producido por la presencia de IgE específica para alfa-gal. El objetivo de este estudio es describir nuestra serie de 13 pacientes.

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Material y métodos: Estudio retrospectivo de pacientes diagnosticados entre 2016 y 2017. Se realizaron pruebas cutáneas con extracto comercial y gelaspán así como determinación de IgE específica para alfa-gal y diferentes tipos de carne.

Resultados: Se analizó a 13 pacientes diagnosticados de síndrome de alfa-gal, 9 de ellos con anafilaxia, de los cuales 6 habían sido diagnosticados de anafilaxia idiopática. Todos presentaron prueba cutánea con gelaspán positiva, y no así con los extractos comerciales, cuyos resultados fueron menos concluyentes.

Conclusiones: Creemos que la anafilaxia idiopática puede esconder pacientes con síndrome de alfa-gal. La prueba cutánea con gelaspán es más útil que los extractos comerciales.

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Introduction

Allergy to galactose- α -1,3-galactose (alpha-gal) is a food allergy with different characteristics than other types of allergies. It manifests as urticaria, angioedema, or anaphylaxis hours after eating the meat of mammals. It is a delayed, IgE-mediated allergic reaction to an oligosaccharide, both of which are curious, exceptional aspects.

In a 2008 study on patients treated with cetuximab, Chung et al.¹ found 25 patients with a hypersensitivity reaction and of them, 17 had IgE antibodies against cetuximab that were present in the pretreatment samples. It was demonstrated that these antibodies were specific for galactose- α -1,3-galactose, which is present in the Fab portion of the heavy chain of cetuximab.

In 2009, Commins et al.² described a novel, severe food allergy related to IgE antibodies against alpha-gal. It was noteworthy that the reaction due to IgE had a delayed onset and was caused by a carbohydrate.

Alpha-gal is an oligosaccharide found in the cells of non-primate mammals; in cow, pig, and lamb organs and meat; and in cat epithelium. It is absent in chicken and fish^{3,4}.

In 2011, it was observed that tick bites could induce both IgE antibodies against tick proteins and IgE antibodies against alpha-gal. It was believed that tick bites could be the cause of the IgE antibody response to alpha-gal⁵.

Mullins et al.⁶ described that the majority of patients who are allergic to red meat are sensitized to gelatin, a component of plasma expanders, and confirmed the detection of alpha-gal in gelatin.

In Spain, five cases of patients allergic to alpha-gal were published in 2011⁷ and a series of 39 patients was published in 2020, which included the first case of an alpha-gal allergy in a child⁸. Below, we present our series of 13 patients with alpha-gal syndrome.

The aim of this study is to review the case histories and clinical characteristics of these patients.

Materials and methods

We conducted a retrospective study by means of a review of the medical histories of patients diagnosed with alpha-

gal syndrome between 2016 and 2017 in two hospitals—a first-level and a second-level hospital—which attend to a population of 600,000 residents.

Patients were considered to be allergic to red meat when they presented with compatible symptoms and an alpha-gal-specific IgE value in blood of greater than 0.35 kUA/L.

Clinical and demographic data were gathered. Skin tests were performed with a commercial extract (Roxal, Bilbao, Spain) of pork, lamb, and beef. An intradermal test with gelaspán (B. Braun Melsungen AG, Germany) and a determination of total IgE and IgE specific to pork, lamb, beef, and alpha-gal (Thermo Fisher Scientific, Uppsala, Sweden) were performed.

We used 10 mg/mL of histamine as a positive control and saline solution as a negative control.

Results

We present a series of 13 patients who are allergic to red meat: nine were diagnosed based on anaphylaxis, three based on urticaria, and one based on urticaria and recurrent angioedema. Of them, ten are men and three are women. Their ages range from 25 to 65 years. Ten patients live in a rural area and three live in an urban area. Three patients had a medical history of allergies. Of them, one presented with anaphylaxis to gelaspán and had a medical history of urticaria/angioedema following meat intake; nine of them recalled tick bites among their history.

The clinical manifestations that led to consultation were anaphylaxis in nine cases, urticaria in three, and urticaria with angioedema in one. Out of all patients, seven had a delay in diagnosis. The time between the start of manifestations and diagnosis was between two and ten years. The majority of patients with delayed diagnosis had urticaria, although some with recurrent idiopathic anaphylaxis also had delayed diagnoses. There was no diagnostic delay among the remaining six (Table 1). All reported a delay of between two and six hours between intake and symptoms onset.

All 13 of our patients had a positive skin test with gelaspán (Table 2). However, three patients with anaphylaxis and one with urticaria presented with a negative skin test for the commercial extract. All patients except for three we do not

Table 1 Demographic and clinical data.

Patient	Age (years)	Sex	Population	Reason for the study/year	Medical history	Diagnostic delay
1	42	Man	Rural	A /2016	A 2016 U recurrence 2013	A No U 3 years
2	26	Man	Urban	U 2016	U recurrence 2012	U 4 years
3	46	Woman	Rural	U/AE 2016	U recurrence 2015	U 1 year
4	48	Woman	Rural	A 2017	No	A No
5	51	Man	Rural	A 2016	A 2011 U 2011	A 5 years U 5 years
6	54	Man	Urban	U 2017	U recurrence 2013	U 4 years
7	37	Man	Rural	A 2016	RIA 2016	A 3 months
8	27	Man	Rural	A 2016	RIA 2014	A 2 years
9	47	Man	Rural	A 2016	RIA 2006	A 10 years
10	56	Woman	Urban	A 2017	ARI 2007	A 10 years
11	65	Man	Rural	U 2017	U recurrence 2017	U 1 year
12	25	Man	Rural	A 2017	RIA 2013	A 4 years
13	56	Man	Rural	A 2017	A 2017 U/AE 2012	A No U/AE 5 years

A: anaphylaxis; AE: angioedema; RIA: recurrent idiopathic anaphylaxis U: urticaria.

Table 2 Allergy study.

Patient/symptoms	Skin test in mm commercial extract	Skin test in mm gelaspan	IgE total	IgE beef	IgE lamb	IgE pork	IgE alpha-gal
1/Anaphylaxis	Beef 7 × 7 Pork 5 × 4 Lamb 5 × 5	10 × 10	468	17.7			>100
2/Urticaria	Beef 4 × 4 Lamb 5 × 4	10 × 10					7.05
3/Urticaria + angioedema	Beef 0 Lamb 0	10 × 6	144	8.67	1.64		34.6
4/Anaphylaxis	Beef 0	8 × 8	37.8	1.32	0.69	1.26	3.13
5/Anaphylaxis	Beef 0 Pork 0 Lamb 0	6 × 5	23.5	0.46	0.41	0.41	0.63
6/Urticaria	Beef 0 Pork 0 Lamb 0	15 × 15					>100
7/Anaphylaxis	Beef 0 Pork 0 Lamb 5 × 4	10 × 10	354	6.8		7.89	20
8/Anaphylaxis	Beef 3 × 3 Pork 3 × 3 Lamb 0	8 × 7	1414	43.0	28.7	18.3	>100
9/Anaphylaxis	Beef 0 Pork 0 Lamb 0	10 × 7	254	11.6	2.17	9.04	48.8
10/Anaphylaxis	Beef 3 × 3	10 × 10	737	48.0	22.7	41.1	>100
11/Urticaria	Beef 5 × 5 Pork 4 × 4 Lamb 5 × 5	16 × 16	127				10.1
12/Anaphylaxis	Beef 0 Pork 4 × 4 Lamb 3 × 3	10 × 10	422	48.8	13.2	35.7	>100
13/Urticaria + angioedema	Not performed	12 × 10	945	79.1	34.2	61.8	>100

have data on presented with positive IgE specific to lamb, beef, or pork.

Following diagnosis, all were recommended a diet free of red meat and to avoid gelatins. They were provided with and advised on the use of rescue medications, antihistamines, steroids, and adrenaline.

These patients were followed-up on annually and the alpha-gal IgE test was repeated; none had a test which negativized.

Discussion

Anaphylaxis is a severe allergic reaction with a rapid onset that is potentially fatal. It tends to manifest as skin symptoms such as urticaria and angioedema along with the involvement of other systems, such as the respiratory, cardiovascular, gastrointestinal, or neurological systems. Patients are considered severe if they present with hypoxemia, hypotension, or loss of consciousness.

Alpha-gal syndrome has been known for a little more than ten years and since then, the number of publications on it has increased considerably. Its prevalence remains to be determined. The main publications on food allergy prevalence that have recently been published in the USA and Europe did not discuss a red meat allergy in children or adults⁹.

In Spain, a prevalence of alpha-gal sensitivity of 15% has been reported in a select at-risk population (forestry workers) compared to 4% of sensitized individuals in the control group¹⁰. In a publication on the evolution of anaphylaxis etiology over time in a single center, Pattanaik et al.¹¹ reported a very significant decline in the percentage of cases attributed to idiopathic anaphylaxis (35%) with respect to the previous report (59%) and this decline could be explained by the number of cases of alpha-gal allergies diagnosed.

In our region (581,000 residents), 13 cases were diagnosed in two years, which indicates that it is an important cause of anaphylaxis in our population. Of them, five had previously been diagnosed with recurrent idiopathic anaphylaxis and another five with recurrent idiopathic urticaria. The clinical manifestations include urticaria, angioedema, and anaphylaxis. It has a long latency period—three to six hours following intake—which hinders suspicion of the trigger that causes the reaction; this was true in our series.

Recently, cases of early manifestations in less than two hours have been reported¹². A greater proportion of women was observed with this phenomenon and it has been related to the quantity and quality of the food and the presence of cofactors.

A significant percentage of patients have a history of tick bites. These bites could give rise to an IgE response to both the proteins derived from the ticks, which cause an immediate reaction, and to carbohydrates, specifically alpha-gal, which lead to delayed or food-induced reactions^{5,13}.

The majority of patients who are allergic to red meat are also sensitized to gelatin; a subgroup is allergic to both⁶. In our series, 13 patients were sensitized to gelatin. However, five of them (41%) had negative skin tests to all commercial extracts, which is in contrast to ten patients (25%) with a negative skin test in other series⁸. In addition, in our series, the diagnostic yield of the skin test with gelaspan was much

higher than that of commercial extracts, which it could substitute.

The figures of IgE specific to alpha-gal were very high: six (46%) were above 100 kUA/L, which is in contrast what has been published in other series⁸; seven of 39 (18%) were above 100 kUA/L, and would indicate greater sensitization.

Anaphylactic reactions to gelatin colloid used as plasma expanders have been described¹⁴. In our series, one patient presented with symptoms of anaphylaxis during the administration of gelaspan in the post-operative period of a hip operation. The incidence of allergic reactions to these solutions ranges from 3% to 4% and the most frequent is gelatin. There are also reactions to stabilizers or components of some vaccines, such as varicella, MMR, DTaP/ITV¹⁵, or herpes zoster vaccines, although it is believed that anaphylactic reactions to vaccines are rare: approximately one per one million vaccines administered¹⁶.

Anaphylactic reactions have been reported following intake of gummy candies made with gelatin derived from pork¹⁷ and following the application of an antifungal ovule which contained alpha-gal in the capsule¹⁸. Three cases of allergic reactions have also been reported following a heart valve replacement with a biological bovine or porcine valve¹⁹, although all three patients tolerated the valve replacement.

Conclusions

In our population, alpha-gal syndrome is more frequent among men and those who live in a rural area. A skin test with gelaspan appears to be more useful than tests with commercial extracts.

The correct diagnosis of late anaphylaxis to mammal meat is hindered by the late onset of clinical manifestations, patients' capacity to tolerate the food on some occasions, and patients' inability to correctly identify the trigger. All of this makes it necessary to take a very careful medical history when faced with a patient who presents with symptoms which could be severe and whose allergological diagnosis is relatively simple.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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