Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.59.009317

Emergent Allergens in Gastroenterology and Allergy

María Teresa Audícana Berasategui[1]* and Ana Martínez-Arcediano[2]

[1]*Departamento de Alergia e Inmunología, Hospital Universitario Araba, Edificio Consultas Externas, Calle Francisco de Viana sn, Spain*

[2]*Departamento de Alergia, Hospital Universitario Basurto, Spain*

***Corresponding author:** Ana Martínez-Arcediano, Departamento de Alergia, Hospital Universitario Basurto; Avenida Montevideo18, Pabellón Arrupe, Consultas Externas Alergia, Bilbao, 48013, Bizkaia, Spain

ARTICLE INFO

Received: November 06, 2024

Published: November 19, 2024

Citation: María Teresa Audícana Berasategui and Ana Martínez-Arcediano. Emergent Allergens in Gastroenterology and Allergy. Biomed J Sci & Tech Res 59(3)-2024. BJSTR. MS.ID.009317.

ABSTRACT

Adverse reactions to food that induce gastrointestinal (GI) symptoms are common in children. The appearance of a food allergy is more common in the pediatric population and young adults and GI symptoms are frequent. However, during the last two decades we have witnessed the debut of some allergic reactions to food in adulthood and even in elderly people and in these cases the allergens involved are the fish parasite Anisakis simplex and the oligosaccharide galactose-alpha-1,3- galactose (alpha-gal), present in mammal meats and dairy products [1-5]. These reactions are mediated by the type I hypersensitivity mechanism that occurs in the presence of specific immunoglobulin E (sIgE) and involves mast cells, eosinophils, among other immune cells.

Knowledge of these allergens that affect the digestive system and can induce severe systemic reactions, is essential to treat correctly these patients and prevent subsequent more severe reactions. Life- threatening food allergic reactions require dissemination to healthcare workers involved in the care of people at risk of anaphylaxis.

Keywords: Anisakis; Allergy; Allergen; Galactose-Alpha-1; 3- Galactose; Alpha-Gal; Meat Allergy; Tick Bite

Abbreviations: SIGE: Specific Immunoglobulin E; Alpha-Gal: Galactose-Alpha-1,3- Galactose; GI: Gastrointestinal; NSAIDs: Non-Steroidal Anti- Inflammatory Drugs; BAT: Basophil Activation Test; AGS: Alpha Gal Syndrome

Introduction

Digestive symptoms are usually present in food allergies within the context of anaphylaxis and are more common in children than in adults. Food is the most common trigger of anaphylaxis in children, adolescents, and young adults [2]. Insect bites and drugs are relatively common triggers in middle-aged and elderly adults.

Anisakis simplex (AS) and alphagal have been shown to be hidden allergens in recent years in our region of Northern Spain [1,5]. However, they are allergens present on the 5 continents in different measure and have in common that they usually appear in adulthood, generate digestive pathology and can be modified by enhancing factors. In atopic people and specifically in people allergic to peanuts, it has been shown that there is a reservoir of IgE-producing cells at the level of the upper gastrointestinal tract [6]. The authors identified a large number of IgE-expressing B cell clones in the stomach, duodenum, and peripheral blood compared to people who did not have food allergies and propose that IgE-producing B cells are probably activated in gastrointestinal tract.

First Cases of Proven Allergy to Anisakis and Alpha-Gal, Two Movie Stories

The first cases of human infection by a species of the Anisakidae family were recorded more than 60 years ago in relation to the consumption of raw or smoked fish [7-12]. However, in the last 20 years, Anisakis has become a highly studied parasite due to its ability to induce an allergic response. Although the most commonly described pathologies are digestive in relation to the consumption of raw or undercooked fish, multiple cases of urticaria/angioedema and anaphylaxis have been reported after the first cases described in Japan and Spain respectively by Kasuya and Audicana [1,13]. The first case of anaphylaxis demonstrated by skin testing and sIgE against Anisakis was reported in 1995 in a 52-year-old woman who was a heavy fish consumer and had eaten a small portion of hake while cooking it [1]. This case opened the spectrum of some anaphylaxis, previously classified as idiopathic and that could be attributed to this parasite based on its allergy study [14]. Human beings are not a natural host of this parasite and in this sense, several studies have shown that Anisakis

generates a complex combined response of the direct action of the larvae that invade the digestive tissue and the T and B cell immunological reaction of the host [14]. Specifically, this response includes precisely the generation of total polyclonal IgE and sIgE against the parasite. These levels of IgE antibodies can be measured at the time of infestation and their values decline as time passes. In this recent article, we can see a review of the immune-mediated reaction induced by this parasite over the last two decades [15].

Many of the allergy studies to this parasite demonstrate that the measures recommended in the general population to prevent parasitization (adequate cooking and freezing) may not be effective in this scenario. In fact, some Anisakis allergens are very resistant to heat and freezing and therefore, despite these measures, it cannot be ensured that the death of the larvae guarantees protection against allergic episodes [16]. Therefore, suspecting an allergy to this parasite requires knowledge of the subject and asking the patient about food consumption prior to the episode. The first patients allergic to alpha-gal due to mammalian meats were described by Commins et al. in the United States in 2009 and were associated with severe hypersensitivity reactions induced to the first infusion of cetuximab in adult patients [3,17]. Surprisingly, all patients had had a recent medical history compatible with red meat allergy and all came from a geographic area where the lonely star tick causes multiple bites. Finally, it was found that the link between red meat and cetuximab was a carbohydrate named galactose-α-1, 3-galactose (alpha-gal), also present in ticks. Alpha-gal, is an oligosaccharide commonly expressed on non-primate mammalian proteins and glycolipids, such as mammalian meats (beef, pork, lamb...), gelatin and dairy products [3,4,17]. It is also contained in different drugs like the monoclonal antibody Cetuximab, and widely present in nature (protozoan parasites, viruses and bacteria among others) being one of the major responsible for causing rejections in xeno-transplants [17-19].

All immune-competent humans have IgG antibodies specific for the carbohydrate alpha-gal (closely related to B blood group), and the tittle of Ig G seems to be also related with allergic reactions too [18,20]. Natural exposure to alpha-gal due to tick bites and probably also due to hymenopteran bites among other arthropods, induces the production of sIgE antibodies against alpha-gal in some people [21]. The diagnosis has improved in recent years. A decade ago, neither skin tests nor determination of sIgE against alpha-gal were available and skin tests with mammalian meats or milk due to alpha-gal, have low sensitivity. In order to confirm allergy to alpha-gal, we performed Basophil Activation Tests (BATs) with Cetuximab with high percent of positivity in meat allergic subjects. Subsequently, once the determination of sIgE by Phadia was available, the diagnosis could be confirmed [4]. It is a novel finding in Allergy that a carbohydrate is capable of generating an allergic response through insect bites and that it behaves as a potent panallergen present in both foods and drugs.

Clinical Features in Anisakis Simplex Allergy

Patients usually do not suspect fish as the cause of their digestive or allergic reaction because they are adults, non-atopic and have previously tolerated fish for decades and often even between episodes [22]. Sometimes the onset of the condition is hives or non- specific digestive symptoms, but in other cases it is severe anaphylaxis [23]. Since the description of the first cases, digestive symptoms have always been relevant in the case of allergy to Anisakis. This fact is not surprising considering the latest findings by Iweala and Burks mentioned above that may complement previous findings on the pathogenesis of digestive infestation and sensitization to Anisakis [6]. In a study/review on cases of anaphylaxis recorded in 16 years, GI symptoms were present in 70% of all patients, only behind the cutaneous features (94%). Among the digestive symptoms, vomiting was the most frequently reported. The ratio of females to males was 2.5:1 and the median age was 59 years (range 18 - 88 years) [23]. This age group usually consumes drugs that can act as cofactors (non-steroidal anti-inflammatory drugs (NSAIDs) and hypotensive agents, among others) and are also characterized by including more fish in their diet. The first signs of this allergic reaction are not always immediate, although they usually appear between 30 and 120 minutes after eating infected fish, sometimes it can take up to six hours [1,15]. The GI toxicity of NSAIDs is well known by the medical community, but the effect of these drugs as promoters of allergic reactions to foods is known by allergist as well [5,24].

Cofactors may explain why ingestion of food sometimes causes an anaphylactic reaction and sometimes does not. Among the cofactors most frequently related to reactions to foods are exercise and NSAIDs. Regarding the enhancing factors, since the first cases described, NSAIDs were described on several occasions as being involved in the recording of drugs consumed together with fish. Pharmacological cofactors (NSAIDs, ACE inhibitors and beta-blockers) were implicated in 47% of the patients studied and in some of them, NSAIDs were the suspected cause of anaphylaxis instead of Anisakis [23].

Clinical Features in Alpha Gal Allergy

The first cases diagnosed by Commins et al. had several unusual features in food allergy. They were delayed in 22/24 patients, range in time delay from 3 to 6 hours, and frequently accompanied of nausea, diarrhea, or indigestion before a reaction, although, the most commonly reported symptom was itching (15/24 patients); subsequently, isolated GI symptoms such as diarrhea, abdominal cramping, gastroesophageal reflux and emesis have been described in a large cohort of patients by the same author [3,21]. In our initial series described 10 years ago, predominantly, the patients were middle-aged men, although subsequently, we have also described Alpha Gal Syndrome (AGS) in kids and young adults [25]. They lived or worked in the countryside and all of them had all been bitten by ticks and 3 reported that they seemed to be particularly prone to tick bites. Compounding

factors were involved in 8 of the 10 patients (exercise in 3 cases and intake of NSAIDs in 5). With regard to dairy products, two patients developed allergy 2 hours after yogurt ingestion during the study. Clinical symptoms were quite similar to previously reported cases of Anisakis allergy with similar time lag (2-6 hours) after the ingestion of the responsible food. Digestive symptoms (stomach pain, diarrhea and emesis) were also present in patients diagnosed with alpha-gal allergy, although less frequently than Anisakis allergy (3/10) (4). A decade later, in an unpublished series of 47 patients from Vitoria-Gasteiz (Basque Country) allergic to alpha-gal, 14 (30%) had abdominal symptoms [26]. The diagnosis has improved in recent years. A decade ago, alpha-gal sIgE (>0,1kUA/L) was not commercially available in Spain and skin tests with mammalian meats or milk due to alpha-gal, have low sensitivity.

For that reason, we performed Basophil Activation Tests (BATs) with Cetuximab with high percent of positivity in responding subjects at the concentration of 0,025mg/mL (39%-94%). Subsequently, Phadia- Thermo Fisher generously provided an Ig E specific alpha gal CAP to confirm the diagnosis [4]. Therefore, alpha-gal allergy diagnosis is occasionally quite difficult because patients are usually non atopic adults, used to eat meat without symptoms previously, compounding factors may be involved and reactions are usually delayed [1,3,4,5,21] except in the case of Cetuximab, explained by intravenous injection and plenty exposure. The presence of galactose-α-1,3-galactose on both Fab segments of the cetuximab antibody allows for the efficient cross-linking of IgE on mast cells. In addition, mammalian skin tests are quite unreliable and it is necessary to request alpha gal sIgE. As in the case of Anisakis, the condition may begin when cutaneous symptoms start or anaphylaxis occurs. In several series of patients have been described who improved with a free mammalian meat diet [3,4,21,27]. Looking at future, it is recommended to avoid not only mammalian meats, but also dairy products in some people, as well as drugs like cetuximab, infliximab, natalizumab, probably ramicirumab, personal products that contain glycerin, lanolin, myristic acid or excipients/stabilizing compounds such as carrageneean or stearic acid [5,21] even rubber may be avoided in some cases [21]. Other products derived from mammals (gelatin-based hemostatic agents, gelatin-containing vaccines, snake antivenom equine and non- primate thyroid extracts. Additionally, heparin and bioprosthetic heart valves are of particular interest during cardiac surgery because contain also alpha-gal. Therefore, complete avoidance is not easy. In very sensitized patients or with important symptomatology, other treatment options can be long action antihistamines and oral cromolyn solution, useful in those patients with lingering gastrointestinal symptoms. In addition, metformin in a small series of patients has also improved patients [21].

Discussion

Reciprocal multidisciplinary knowledge is important and this review aims to emphasize the relevance of little-known allergens in adults that have gained importance in recent years. An allergy to both must be suspected by taking a history directed at the consumption of fish or meat in the 6-8 hours' prior, taking NSAIDs, tick bites or other arthropods (in the case of alpha-gal) and recent allergy manifestations (hives and /or angioedema) associated with digestive symptoms or other anaphylactic symptoms.

To summarize 3 topics to remember:

1. Allergy to Anisakis simplex and alphagal explains unexpected reactions that occur with the ingestion of fish and meat/dairy products in adults or the elderly.
2. Drug allergy (NSAIDs) is suspected in some cases and cofactors are present in more than half of the cases.
3. The suspected diagnosis can prevent new and more serious episodes and in the case of alpha-gal it is also recommended to avoid some medications.

Allergy and Gastroenterology have common links and these new allergens reinforce them even more.

References

1. Audicana MT, Fernández de Corres L, Muñoz D, Fernández E, Navarro JA, et al. (1995) Recurrent anaphylaxis due to Anisakis simplex parasitizing sea-fish. J Allergy Clin Immunol 96: 558-560.
2. Beyer K, Eckermann O, Hompes S, Grabenhenrich L, Worm M, et al. (2012) Anaphylaxis in an emergency setting - elicitors, therapy and incidence of severe allergic reactions. Allergy 67(11): 1451-1456.
3. Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, et al. (2009) Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol 123(2): 426-433.
4. Martínez Arcediano A, Audicana Berasategui MT, Longo Areso N, Ibáñez EF, Balza de Vallejo OV, et al (2014) Allergy to galactose-alpha-1,3- galactose: Clinical features and the diagnostic value of cetuximab. J Investig Allergol Clin Immunol 24(6): 450-452.
5. Martínez-Arcediano A, Camino E, Beristain M, Velasco M, LongoN, et al. (2024) Is Alpha-Gal an Emerging Allergen in Drug Allergy?. Current Treatment Options in Allergy, p. 1-9.
6. Iweala OI, Choudhary SK, Addison CT, Batty CJ, Kapita CM, et al. (2020) Glycolipid-mediated basophil activation in alpha-gal allergy. J Allergy Clin Immunol 146(2): 450-452.
7. Asato R, Wakuda M, Sueyoshi T (1991) A case of human infection with Anisakis physeteris larvae in Okinawa, Japan. Jpn J Parasitol 40: 181-183.
8. Kagei A, Sano M, Takahashi Y, Tamura Y, Sakamoto M, et al. (1978) A case of acute abdominal syndrome caused by Anisakis type-II larva. Jpn J Parasitol 27: 427-431.
9. Ishikura H, Kikuchi K, Nagasawa K, Ooiwa T, Takamiya H, et al. (1993) Anisakidae and anisakidosis. In: T Sun (Edt.)., Progress in clinical parasitology. New York: Springer-Verlag 3: 43-102.
10. Van Thiel PH, Kuipers FC, Roskam TH (1960) A nematode parasitic to herring, causing acute abdominal syndromes in man. Trop Geogr Med 12: 97-113.

11. Im K, Shin H, Kim B, Moon S (1995) Gastric anisakiasis cases in Cheju- do, Korea. Korean J Parasitol 33: 179-186.
12. Sakanari JA, Mckerrow JH (1989) Anisakiasis. Clin Microbiol Rev 2: 278-284.
13. S Kasuya, H Hamano, S Izumi (1990) Mackerel-induced urticaria and Anisakis. Lancet 335(8690): 665.
14. Añibarro B, F J Seoane, M V Múgica (2007) Involvement of hidden allergens on food allergic reactions. J Investig Allergol Clin Immunol 17(3):168-172.
15. Audicana MT, Kennedy MW (2008) *Anisakis simplex*: from obscure infectious worm to inducer of immune hypersentitivity. Clin Microbiol Rev 21(2): 360-379.
16. Audicana MT (2022) *Anisakis,* Something Is Moving inside the Fish. Pathogens 11(3): 326.
17. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, et al. (2008) Cetuximab-induced anaphylaxis and IgE specific for galactose-α-1,3- galactose. N Engl J Med 358(11): 1109-1117.
18. Cabezas-Cruz A, Hodžić A, Román-Carrasco P, Mateos- Hernández L, Duscher GG, et al. (2019) Environmental and Molecular Drivers of the α-Gal Syndrome. Front Immunol 31(10): 1210.
19. Cowan PJ, Aminian A, Barlow H, Brown AA, Chen CG, et al. (2000) Renal xenografts from triple-transgenic pigs are not hyperacutely rejected but cause coagulopathy in non-immunosuppressed baboons. Transplantation 27;69(12): 2504-2515.
20. Joral A, Azketa N, Sanchez P, Vélez-Del-Burgo A, Aranzabal- Soto MA, et al. (2022) The Quantification of IgG Specific to α-Gal Could Be Used as a Risk Marker for Suffering Mammalian Meat Allergy. Foods 4;11(3): 466.
21. Commins SP (2020) Diagnosis & management of alpha-gal syndrome: lessons from 2,500 patients. Expert Rev Clin Immunol 16(7): 667-677.
22. Audicana M, M García M, Del Pozo MD, Moneo I, Díez J, et al. (2000) Clinical manifestations of allergy to *Anisakis simplex*. Allergy 55: 28-33.
23. Audicana MT, Girao I, Longo N (2017) *Anisakis simplex*, a New Hero in the Anaphylaxis Scene. SM Emerg Med Crit Care 1(2): 1008.
24. Cardona V, Luengo O, Garriga T, Labrador-Horrillo M, Sala-Cunill A, et al. (2012) Co-factor-enhanced food allergy. Allergy 67(10): 1316-1318.
25. Martínez Arcediano A, Audicana Berasategui MT, Longo Areso N, Fernandez Ibañez E, Balza de Vallejo OV, et al. (2021) The relevance of compounding factors and the risk of anaphylaxis in 63 patients allergic to alpha gal. Allergy: European Journal of Allergy and Immunology 110: 546-547.
26. (2019) Oral Communication at the International Symposium. Avances y Perspectivas en Alergia Cutánea e Inmunología. SERIE DE CASOS ALÉRGICOS A GALACTOSA-ALPHA-1,3 GALACTOSA EN ÁLAVA. Ana Martínez Arcediano1, Maria Teresa Audícana Berasategui1, Maria Natividad Longo Areso1, Maria Olga Villarreal Balza De Vallejo1, Aroa Campandegui Lecuona2, Marta Velasco Azagra1, Eduardo Fernandez Ibañez.1Hospital Universitario Araba (HUA), Vitoria- Gasteiz, España; 2 Universidad del Pais Vasco (UPV-EHU), Vitoria- Gasteiz, España, pp. 23-26.
27. Macdougall JD, Thomas KO, Iweala OI (2022) The Meat of the Matter: Understanding and Managing Alpha-Gal Syndrome. Immunotargets Ther 15(11): 37-54.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.59.009317

Ana Martínez-Arcediano. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php