

# Sensitization to alpha-gal as a cause of idiopathic anaphylaxis

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## Abstract

**Background:** The cause for anaphylaxis cannot be identified after extensive evaluation in a large proportion of patients, who are classified as having ‘idiopathic anaphylaxis’ (IA). As food consumption patterns, genetic background, and environmental factors can lead to differences in allergen sensitization patterns in different regions, we sought to identify the aetiology of IA in cohort of Sri Lankan patients. **Methods:** Of the patients referred to our clinic following anaphylaxis, 65 were recruited as a cause could not be identified. The events that led to the episode of anaphylaxis, the triggers, the severity of symptoms and treatment received were recorded and skin prick test, ISAC ImmunoCAP test and serum tryptase was carried out. **Results:** Of the 65 patients, 42/65 (64.6%) were females and 49/65 (75.38%) were adults. 46/65 (70.8%) had grade II anaphylaxis and 34/65 (52.3%) were found to have specific IgE to alpha-gal, with symptoms occurring 0.5 to 6 hours since ingestion of food. Of those who had specific IgE to alpha-gal, 12 (35.3%) had consumed red meat and 10 (29.4%) milk products (3 had consumed fermented buffalo milk), before the episode of anaphylaxis. Difficulty in breathing, swelling of lips and syncope was significantly higher in those who were not sensitized to alpha-gal, while diarrhoea and abdominal pain were more common in those sensitized to alpha-gal, although this was not significant. **Conclusion:** A large proportion of patients presenting with IA were found to be sensitized to alpha-gal, which was the likely cause of their anaphylaxis.

## Introduction

The incidence of anaphylaxis has continued to rise globally based on hospitalised data from Europe, United states, Australia, Brazil and some Asian countries such as South Korea and Taiwan [1, 2]. However, the actual incidence is likely to be several folds higher due to mis-diagnosis, mis-classification, due to under reporting [1] and also because allergies and anaphylaxis being neglected in many developing countries, due to other disease priorities [3]. Food allergy was shown to be the predominant cause of anaphylaxis, followed by drugs and venom, in many countries [1, 2, 4]. However, in a large proportion of cases, even after extensive evaluation, a trigger cannot be identified, and such cases are classified as ‘idiopathic anaphylaxis’[5].

Approximately 10% of children and 30 to 60% of adults presenting with anaphylaxis are classified as having idiopathic anaphylaxis (IA), as a trigger cannot be identified [5]. Mast cell disorders such as mastocytosis, mast cell activation syndrome and hereditary  $\alpha$ -tryptasaemia, are some of the conditions that can cause IA, and screening for these diseases have been suggested in the diagnostic work-up [6]. Allergy to Galactose- $\alpha$ -1,3-galactose ( $\alpha$ -gal), has shown to be important cause of anaphylaxis in those in whom a cause cannot be identified [7]. Alpha-gal allergy typically occurs 3 to 6 hours after ingestion of red meat and has shown to occur due to IgE antibodies specific to the carbohydrate epitope found on mammalian meat [8]. Since the identification of  $\alpha$ -gal allergy as an important cause of delayed anaphylaxis, screening for the presence of allergy to  $\alpha$ -gal has been included in the diagnostic workup in a patient, in whom a possible cause of anaphylaxis cannot be identified [7]. Other important causes where IA was shown to be food dependent exercise induced anaphylaxis (FDEIA), due to presence of IgE to omega-5-gliadin [5]. FDIEA, has indeed

shown to be an important cause especially in patients who present at specialised allergy clinics. In one study, 12.2% of patients were identified as having FDIEA [9].

Although the incidence of anaphylaxis is not reported in many lower middle-income countries (LMICs), the incidence of asthma and asthma related mortality has shown to be rising [10]. Diseases related to allergies are neglected in many LMICs with adrenalin not used in many instances, in the management of anaphylaxis and long-term management of patients with anaphylaxis being sub-optimum due to the non-availability of adrenalin autoinjectors [3, 11]. Although there is no data on the incidence of anaphylaxis and other allergic diseases in Sri Lanka, there is a high prevalence of asthma and allergen sensitization reported among Sri Lankan children [11, 12]. Furthermore, many patients with anaphylaxis present to specialised allergy clinics in Sri Lanka where food allergy, FDIEA and allergy to vaccines have been identified as the predominant causes of anaphylaxis [9, 13, 14]. As food consumption patterns, genetic background, and environmental factors can lead to differences in allergen sensitization patterns in different geographical regions, we sought to identify the possible triggers of IA in Sri Lankan patients presenting to specialised allergy clinics in Sri Lanka.

## Materials and methods

### Patients

This study was approved by the All patients who were referred to our clinic with a history of anaphylaxis for further management were recruited to the study following informed written consent. The clinical features during anaphylaxis, and the treatment received was available with the patients' clinical records and the diagnosis cards issued by the hospitals. The patients were evaluated for the possible aetiological factors, and contributing co-factors for the development of anaphylaxis and then relevant skin prick tests were carried out to identify the allergen. Those in whom we could not identify a possible allergen by skin prick tests were classified as having idiopathic anaphylaxis (IA). Accordingly, from January to December 2021, 65 patients were considered to have IA. In all patients the events that led to the episode of anaphylaxis, the foods that were consumed, the severity of symptoms and treatment received were recorded.

Severity of anaphylaxis was classified according to the criteria defined by Brown et al 2004 [15]. Accordingly, those who developed loss of consciousness, confusion, collapse, cyanosis or with oxygen saturation of <92% or incontinence were classified as having had severe anaphylaxis (grade 3).

Ethical approval was obtained from the Ethics Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka.

### Skin prick tests (SPT) for suspected allergens

A qualified health professional performed this test after ensuring that facilities for resuscitation were available if the need arose. Oral antihistamines and topical skin corticosteroids were stopped for the required duration prior to testing. Skin prick testing with the commercial allergens (Immunotek, Spain) or prick-to-prick testing were carried out according to the guidelines set by the European Academy of Allergy and Clinical Immunology by Muraro et al., 2014 [16]. A positive and a negative control were included in all instances. The size of the wheal was recorded at 15 minutes and a test was considered positive if the wheal size is >3mm of the negative control.

### ISAC ImmunoCAP

The Immuno-solid phase allergen chip (ISAC) ImmunoCAP testing was carried out according to the manufacturers instructions. This enables testing for specific IgE against 112 allergen components in a multiplex assay (supplementary data). Results were measured with a biochip scanner (Capital bio Lux scanner) and evaluated using specialized software (MIA Array software) as per manufacturers instructions. The results were reported in ISAC Standardized Units (ISU-E) and interpretation was done according to international guidelines [17] as shown below.

<0.3 ISU-E: Undetectable

0.3 to 0.9 ISU-E: Low

1 to 14.9 ISU-E: Moderate/High

>15 ISU-E: Very High

### ImmunoCAP tryptase

The ImmunoCAP tryptase was measured in serum samples according to the manufacturer's instructions using Thermo-Fisher Phadia 100. The results were generated using a calibration curve and the threshold for a positive result was considered to be values  $> 11\mu\text{g/l}$ .

### Statistical analysis

Statistical analysis was performed using graph pad prism version 9 and non-parametric statistical tests were used. The differences in clinical features between those who had sensitization to alpha-gal compared to others during the episode of anaphylaxis was expressed as the odds ratio (OR), which was obtained from standard contingency table analysis by Haldane's modification of Woolf's method. The Fisher's exact test was used to determine the p value.

### Results

#### Allergen sensitization patterns in those who had idiopathic anaphylaxis (IA)

65 patients were classified as having IA, as we could not identify a cause from the history or by carrying out skin prick tests. Of them 42 (64.6%) were females and 49/65 (75.38%) were adults. 8/65 (12.3%) patients had grade 1 anaphylaxis, 46 (70.8%) had grade 2 anaphylaxis and 11 (16.9%) patients had grade 3 anaphylaxis. The allergen sensitization pattern of these 65 patients measured by ISAC Immunocap is shown in Table 1. 34 (52.3%) patients were found to have specific IgE to alpha-gal, while 11 (16.9%) were sensitized to cow's milk. All 11 patients who were sensitized to cow's milk were also sensitized to alpha-gal. The other main allergens that these patients were sensitized to were house dust mite in 20 (30.8%) patients, and grass pollen in 16 (24.6%). 7/65 (10.8%) of patients were found to be sensitized to tropomyosin and 5/7 (71.43%) of them were also sensitized to house dust mite. Although seven were sensitized to tropomyosin, only 4/7 (57.14%) of them had developed symptoms following ingestion of shrimp. 3/7 (42.86%) of those who had specific IgE to tropomyosin also had IgE to shrimp and only one of them reported a reaction following ingestion of shrimp.

#### Differences in clinical features in patients who had sensitization to alpha-gal compared to others

Of the 34 patients who were found to have specific IgE to alpha-gal, 16 (47.1%) did not have any detectable IgE to any of the other allergens included in the ISAC ImmunoCAP. Of the 34 patients 14 (41.2%) were male 22 (64.7%) were adults. The clinical features in those with IA, sensitized to alpha-gal compared to patients sensitized to other allergens are shown in Table 2. The alpha gal patients reported an average of 2 episodes of anaphylaxis and the other patients reported an average of 3 episodes at the time of presentation. Urticaria and itching were the commonest symptoms in both groups. Difficulty in breathing, swelling of the lips and syncope was significantly higher in those who were not sensitized to alpha-gal (Table 2). In contrast, diarrhoea and abdominal pain were commoner in those who were sensitized to alpha-gal, compared to others although this was not significant.

Of those who had specific IgE to alpha-gal, 12 (35.3%) had consumed red meat before the episode of anaphylaxis, 14 (41.2%) milk products, 2/34 (5.9%) products containing gelatine (sweets and gelatine containing capsules), while ten 10 (29.4%) did not recall consuming red meat or any milk products prior to the episode. Of the 14 who had consumed milk products, 3 (8.8%) had consumed fermented buffalo milk. 16/34 (47.1%) who were sensitized to alpha-gal had never consumed red meat and had not consumed red meat prior to the reaction.

Of these 34 patients, 14 (41.2%) had low levels (0.3 – 0.9 ISU-E) of specific IgE to alpha-gal, 14 (41.2%) had moderate/high levels (1 – 14.9 ISU-E) and 6 (17.6%) had very high levels ( $>15$  ISU-E). The specific IgE levels

did not correlate with the severity of anaphylaxis (Spearman's  $r = 0.14$ ,  $p = 0.42$ ). While most individuals had anaphylaxis between 30 minutes to 6 hours since consumption of food, the time since consumption of food and development of anaphylaxis varied from immediate to up to 12 hours. 7/34 (20.6%) patients developed anaphylaxis immediately ( $<30$ mins), 12 (35.3%) from 30 minutes to two hours after ingestion, 10 (29.4%) between 2 to 6 hours after ingestion of food and 5 (14.7%) after six hours after ingestion of food.

22/34 (64.7%) patients had other allergic diseases such as allergic rhinitis (14, 41.2%), asthma (10, 29.4%) and atopic dermatitis (3, 8.8%). While the majority of patients had only food-associated allergies, six patients reported an episode(s) of drug allergy, three patients reported an insect & insect venom associated allergy and one patient reported a vaccine-associated allergy resulting in anaphylaxis.

### Serum tryptase levels in patients with unexplained anaphylaxis

Serum tryptase levels were done on the patients in whom specific IgE to any food could not be identified by SPT and were negative for all the allergens included in ISAC immunocap, due to limited funding. Accordingly, serum tryptase was done in 11/65 (16.9%) patients, who all had levels within the normal range ( $<11\mu\text{g/l}$ ).

### Discussion

In this study we have shown that sensitization to alpha-gal was the predominant cause (52.3%) of IA in patients presenting to our clinic. 12 (35.3%) had consumed red meat prior to developing anaphylaxis and therefore, alpha-gal allergy is likely to be the most likely trigger in these patients. 16/34 patients who were sensitized had never consumed any red meat, as red meat consumption is not frequent among many ethnic groups in Sri Lanka. Therefore, although they did have specific IgE to alpha-gal possibly following a tick bite, it is not clear if the presence of alpha-gal specific antibodies played a role in causing anaphylaxis, in these patients. Interestingly, 14/34 patients who were found to be sensitized to alpha-gal had consumed milk products and not red meat prior to the reaction. 3 of these patients had consumed fermented buffalo milk and not cow's milk. It has been shown that many individuals who are sensitized to alpha-gal react to different types of dairy products, with 70 to 90% of individuals with alpha-gal allergy reacting to milk products in different studies [18, 19]. It was shown that although patients with alpha-gal allergy did not react to the main allergens in cow's milk, they reacted to bovine- $\gamma$ -globulin, lactoferrin and lactoperoxidase [19]. Therefore, it is possible that in the 14 patients with alpha-gal allergy who developed anaphylaxis following ingestion of milk, was due to sensitization to these components in milk.

Two patients developed anaphylaxis following consumption of gelatine containing products and were also found to have specific antibodies to alpha-gal. Alpha-gal has been reported in gelatine containing products previously [8], and therefore, the presence of alpha-gal in these products could have triggered anaphylaxis in these two patients. In fact, individuals who do not have any specific IgE to gelatine but have specific IgE to alpha-gal have shown to develop anaphylaxis following administration of vaccine, which has been shown to be due to the alpha-gal component in gelatine [20-22]. Therefore, it is recommended that gelatine containing vaccines should be administered with caution or should be avoided if possible in those with alpha-gal allergy [21].

The other causes of anaphylaxis in our cohort could be wheat dependent exercise induced anaphylaxis, and hidden ingredients or contaminants in food such as shrimp and cashew. Three of our patients had specific IgE to omega-5-gliadin and we previously reported that wheat dependent exercise induced anaphylaxis was a frequent cause in patients referred to allergy clinics in Sri Lanka, possibly because of the difficulty in diagnosis [9, 13]. Seven of our patients also had specific IgE to tropomyosin, although only 4 of them reported symptoms following ingestion of shrimps. Although the presence of specific IgE to tropomyosin is considered to be a good predictor of allergy to shrimp, tropomyosin in house dust mite, has shown to strongly cross react with shrimp tropomyosin [23, 24]. While generation of such cross reactive IgE in those who have allergy to house dust mite, are shown to sometimes cause reactions to shrimp, this is not the case in all instances [24].

A large proportion (64.7%) of patients had other allergic diseases such as allergic rhinitis (41.2%), asthma (29.4%) and atopic dermatitis (3, 8.8%), suggesting that these individuals had many IgE mediated diseases. Many (32.3%) had specific IgE to house dust mite, 24.6% to grass pollen and 13.5% to tree pollens, with some being sensitized to multiple allergens. Therefore, in addition to the allergens tested by skin prick tests and ISAC ImmunoCap, they could be sensitized to other unidentified allergens, which triggered their anaphylaxis. Although it is recommended that serum tryptase to be done in all individuals presenting with IA, due to limitations in funding, we only did this test in those, in whom a trigger could not be identified. All such individuals, had serum tryptase within the normal range, suggesting that they are unlikely to have a mast cell disorder.

In summary, a large proportion of patients presenting with IA were found to be sensitized to alpha-gal, which was the likely cause of their anaphylaxis. Importantly, 14/34 individuals developed anaphylaxis following ingestion of milk products and 2/34 after ingestion of gelatine. As these products are also shown to contain alpha-gal, it would be important to test for the presence of alpha-gal allergy in those who present with IA, due to the presence of alpha-gal in these products.

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**Table 1. Allergen sensitization pattern among patients who presented with idiopathic anaphylaxis.**

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Allergen

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**Alpha-gal**

**House dust mite** *B.tropicalis*: Mite group 5 (Blo t 5) *D. farinae* Cysteine protease (Der f 1) NPC2 family (Der f 2) *D. Pt*

**Grass pollen** Bermuda grass: Grass group 1 (Cyn d 1) Timothy grass: Berberine bridge enzyme (Phl p 4) Grass group 5 (

**Tree pollen** Plane tree: Putative invertase inhibitor (Pla a 1) Japanese Cedar: Pectate lyase (Cry j 1) Cypress: Pectate ly

**Cow's milk** Transferrin (Bos d lactoferrin) Alpha-lactalbumin (Bos d 4) Beta-lactoglobulin (Bos d 5) Casein (Bos d 8) Cro

**Cross-reactive Carbohydrate Determinants (MUXF3)**

**Tropomyosin** Anisakis (Ani s 3) Cockroach (Bla g 7) D. Pteronyssinus (Der p 10) Shrimp (Pen m 1)

**Animal:** Cat - Fel d 1 (Uteroglobin)

**Shrimp** Arginine kinase (Pen m 2) Sarcoplasmic calcium binding protein (Pen m 4)

## Allergen

**Wheat** – *Triticum aestivum* Omega-5 gliadin (Tri a 19.0101) Lipid transfer protein (nsLTP) Tri a 14  
Aspergillus fumigatus Mitogillin family (Asp f 1) Peroxisomal protein (Asp f 3)  
**Soybean** Storage protein, Beta-conglycinin (Gly m 5) Storage protein, Glycinin (Gly m 6)  
**Storage mite:** *L. destructor* - NPC2 family (Lep d 2)  
**Cashew-nut:** Storage protein, 11S globulin (Ana o 2)  
**Weed pollen – Saltwort:** Pectin methylesterase (Sal k 1)

**Table 2. Clinical features of those with unexplained anaphylaxis sensitized to alpha gal compared with patients who had no alpha-gal specific IgE**

Symptom	Patients with alpha-gal sensitization N (%)	Patients sensitized to other allergens N (%)	P value	Odds Ratio (95% CI)
Anaphylaxis grade 1 2 3	8 (23.5%) 19 (55.9%) 7 (20.6%)	0 (0%) 27 (87.1%) 4 (2.9%)	0.005 0.007 0.51	Infinity (2.23 to [?]) 0.18 (0.06 to 0.62) 1.750 (0.45 to 5.8)
Urticaria	32 (94.1%)	31 (100%)	0.49	0 (0 to 2.35)
Abdominal pain	15 (44.1%)	9 (29.0%)	0.30	1.9 (0.67 to 5.47)
Itching	32 (94.1%)	31 (100%)	0.49	0 (0 to 2.35)
Vomiting	3 (8.8%)	3 (9.7%)	>0.99	0.9 (0.2 to 4.13)
Diarrhoea	6 (17.7%)	3 (9.7%)	0.48	2.0 (0.53 to 7.79)
Swelling of lips	19 (55.9%)	26 (83.9%)	<b>0.02</b>	0.24 (0.08 to 0.74)
Difficulty in breathing	24 (70.6%)	31 (100%)	<b>0.001</b>	0 (0 to 0.3)
Syncope	14 (41.2%)	25 (80.7%)	<b>0.002</b>	0.17 (0.51 to 0.54)
Redness in eyes	5 (14.7%)	0	0.05	Infinity (1.4 to [?])
Loss of consciousness	8 (23.5%)	4 (12.9%)	0.35	2.08 (0.59 to 6.7)
Sneezing	3 (8.8%)	0	0.24	Infinity (0.81 to [?])
Wheezing	21 (61.8%)	23 (74.2%)	0.3	0.56 (0.2 to 1.5)