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Alpha-gal allergy in a South Asian country

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Abstract

Background Alpha gal syndrome (AGS) is a delayed allergy to red meat, due to IgE to galactose-alpha-1,3-galactose (alpha-gal). Sensitization occurs via tick bites. It has been described in the US, Europe, Australia, Japan and South Korea, but reports from the Indian subcontinent are rare. We report the demographics of alpha-gal allergy for the first time from the Indian subcontinent and possible association with vaccine allergy.

Methods Patients diagnosed with alpha-gal syndrome (AGS) from 2018 to 2024 were selected in this study. AGS was identified by the occurrence of allergic symptoms up to 8 h of ingestion of red meat, with positive serum IgE to alpha-gal > IgE to red meat, and negative IgE to BSA. Allergy to vaccines containing bovine products were also identified in patients with AGS.

Results Fifty-seven patients were identified. Thirty-one (54.3%) were 12 years or younger. There were more females among adults (63.2%) compared to children (50.0%), though statistically not significant. There was no difference between children and adults in relation to clinical features and time of onset of symptoms. However, 5/6 of adults with severe anaphylaxis (grade 5) were females. Six patients with AGS developed allergy, including anaphylaxis, to the measles, mumps, rubella (MMR, $n=3$), rubella ($n=1$), varicella ($n=1$) and anti-rabies ($n=1$) vaccines.

Conclusion AGS is an important cause of food and vaccine allergy in the Indian subcontinent and is commoner in children unlike in other regions. However, the clinical features are similar to adults.

Keywords Alpha-gal allergy, Anaphylaxis, Delayed meat allergy, Vaccine allergy

Background

Food allergy (FA) is "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" [1]. IgE mediated food allergies are the best characterized of food allergies. IgE mediated FA typically manifests within 2 h of exposure. Of the FA, allergy to red meat was historically believed to be rare [2]. Three forms of red meat allergy have been described; (1) primary beef allergy (2) pork cat syndrome and (3) alpha-gal syndrome (AGS) [3]. AGS is a delayed allergy to red meat, due to IgE to an oligosaccharide, galactose-α–1,3-galactose (alpha- gal) [3].

AGS was first described 17 years ago in a paper from the United States. A spate of anaphylactic events occurred in patients with colorectal and head and neck tumors in the southern parts of the United States, who were administered cetuximab, a chimeric mouse-human monoclonal IgG1 antibody against the epidermal growth factor receptor. IgE to alpha- gal present in the monoclonal antibody was implicated [4]. IgE to alpha-gal was also found to be the cause of delayed allergy to red meat (beef, lamb, pork) in the US, and bites from the tick *Amblyomma* was implicated as the trigger [5]. These cases were identified in areas where

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Rocky Mountain spotted fever was prevalent, along with the ticks, *Amblyomma americanum* and *Dermacentor variabilis* [6]. A cross reaction between the salivary proteins of ticks, and red meat was suspected to be responsible for the red meat allergy [5, 6].

Alpha-gal is a carbohydrate expressed in all non-primate mammals, bacteria, parasites and ticks [7]. This moiety is also found in the saliva of ticks. A bite from a tick may sensitize a person, leading to production of serum IgE to alpha-gal. Subsequent exposure to non-primate mammalian meat and chimeric monoclonal antibodies may lead to allergic reactions.

The clinical features of AGS include pruritus, urticaria, angioedema and anaphylaxis; however, symptoms confined to the gastro-intestinal tract may also occur [3]. While most patients are adults, a significant proportion are in the pediatric age group [8, 9], who have predominantly cutaneous and gastrointestinal symptoms [10]. The onset of symptoms is delayed for 3–8 h [11], unlike in typical food allergy, which manifests within 2 h of ingestion. Symptoms may also occur within 2 h of ingestion, as in 16% of patients in one cohort [9].

While food is the most common cause of AGS, drugs and implants containing bovine and porcine components have also been implicated. These include heparin, gelatin, monoclonal antibodies and prosthetic heart valves [11]. A few case reports of allergy to the zoster and measles mumps and rubella (MMR) vaccines due to AGS have also been reported [12–14].

AGS has been reported from all 6 continents [7]. It has been reported in Sri Lanka [15], but is mainly unreported in the Indian subcontinent [7]. Red meat allergy is the 2nd most common cause of food allergy in Sri Lanka, after cow's milk allergy (CMA) [15]. The aim of the present study was to characterize AGS in Sri Lanka, to compare symptoms in children with adults, and to ascertain whether AGS is associated with vaccine allergy.

Methods

Our immunology clinic is the only allergy clinic under the Ministry of Health, Sri Lanka, and caters to the entire country. In this retrospective study, clinic records from 2018 to 2024 were reviewed. Consent of participants was not obtained as medical records can be used without obtaining informed consent if confidentiality and anonymity are preserved according to the National Ethics Committee guideline (Forum for Ethics Review Committees in Sri Lanka, FERCSL Operational Guidance for Committees that Review Ethics 2nd Edition 2018; https://fercsl.lk/wp/wp-content/uploads/2018/12/FERCSL-Guideline-2018.pdf). However, informed written cons ent was obtained from parents of patients with vaccine allergy who were all below 16 years of age, as they were included as case reports in the study. Ethics clearance was obtained from the institutional Ethics Review Committee (ERC No: 22 2024).

Patients included had clinical features suggestive of immediate hypersensitivity, reproducibility between red meat ingestion and symptom(s) occurrence, and confirmation of the relevant food by detection of food allergen-specific IgE. Patients who did not participate in testing, had food allergy leading to asthma or atopic dermatitis, or where the red meat allergen could not be identified, were excluded. The diagnosis of anaphylaxis was based on clinical history and examination findings as noted in the diagnosis card or bed head ticket. Diagnostic criteria for anaphylaxis included one of 2 clinical scenarios: (1) acute onset of skin manifestations associated with respiratory, cardiovascular, or severe gastrointestinal signs or symptoms; or (2) acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known allergen for that patient [16]. The diagnosis of food allergy was based on standard guidelines [17].

Red meat included beef, pork, and mutton. In some cases, exotic mammalian species were also implicated, including venison, wild boar, sambar deer (*Rusa unicolor*) and porcupine.

Confirmation of red meat allergy was based on patient history and the presence of IgE to the implicated food (beef, pork, mutton), demonstrated by specific IgE testing (by Phadia ImmunoCap, using a Phadia 100) or by skin prick testing. Skin prick reagents included commercial extracts of beef and pork (ALK Abello) or fresh beef, pork, and gelatin by prick-to-prick testing. Component resolved diagnostics were performed using Phadia ImmunoCap for bovine serum albumin (nBos d 6 BSA), and alpha-gal (nGal-α–1,3-Gal), and in some patients, bovine gelatin.

AGS was diagnosed when the onset of symptoms occurred up to 8 h after ingestion of red meat, with or without a history of tick bite [11]. Symptoms included cutaneous (urticaria, angioedema), respiratory (cough, wheezing, stridor, dyspnea, hypoxemia), cardiovascular (loss of consciousness, hypotension, syncope or incontinence), and abdominal (severe abdominal pain, recurrent vomiting) manifestations. Patients may not recall tick bites, as they are often painless [11]. Diagnosis was confirmed if IgE to alpha-gal > 0.35 kUA/L, IgE to alpha-gal > IgE to beef/pork/mutton [9], and IgE to bovine serum albumin was negative [3, 15]. Primary red meat allergy was diagnosed where symptoms appeared within 2 h of ingestion, IgE to beef/pork or skin prick testing with commercial extracts were positive, and IgE to alpha-gal was negative.

Statistical analysis

Fisher's exact test was used to compare categorical variables (sex, symptoms, timing, atopy, tick bites), with a p-value of <0.05 considered statistically significant. Geometric means of IgE levels were calculated, and comparison between the 2 groups were made using the Mann-Whitney U test (IgE to alpha-gal and beef). Statistical analysis was performed using SPSS version 20.

Results

Clinical features of AGS

The records of 2,902 patients with acute allergic reactions were reviewed, of whom 57 (1.9%) were diagnosed with AGS (Tables 1 and 2; Fig. 1). All had IgE to alpha-gal > 0.35 kU/L, and 53/54 (98.1%) had IgE to alpha-gal > IgE to beef/pork/mutton. The one patient with IgE to beef > IgE alpha-gal had symptoms after 5 h, and IgE to BSA was < 0.35 kU/L.

In 3/57 (5.2%) patients, IgE to beef/pork was not tested. Of these, two had negative skin prick tests (SPT) for beef, and the third had negative IgE to BSA. All three had IgE to alpha-gal. Two patients reported tick bites, while the third had exposure to ticks but no reported bites.

Only one patient had IgE to BSA > 0.35 kU/L; however, IgE to alpha-gal was greater than to beef, and the patient experienced delayed symptoms. IgE to BSA was not performed in 5/57 (8.7%) patients, all of whom had IgE to alpha-gal. In two of these, SPT to beef was negative. In the other three, IgE to alpha-gal exceeded IgE to beef, and they had delayed reactions to red meat.

Children (≤ 18 years of age) comprised 66% of cases; 31/57 (54.3%) were aged 12 years or younger, and 4/57 (7.0%) were above 50 years of age. Among adults, 63.3% were female, compared to 50% among children, though this difference was not statistically significant.

The red meats most commonly implicated were beef (31/57; 54.3%) and pork 35/57 (61.4%). Mutton was implicated in 11/57 (19.2%) patients. Rare causes included venison (4/57; 7%), lamb, sambar and porcupine meat and beef liver (one patient each). Three patients (3/57; 5.2%) were allergic to cow's milk.

Urticaria alone was reported in 28.1%, anaphylaxis in 66.7%, and gastrointestinal symptoms (vomiting, abdominal pain, diarrhea and dysphagia) in 38.6%, typically along with other organ system involvement). One child had isolated abdominal pain. Both children and adults had a similar incidence of GIT symptoms. There was no significant difference in isolated urticaria, anaphylaxis and severe (grade 5) anaphylaxis between children and adults.

There was no difference between children and adults on the timing of symptoms. Five patients had both immediate and delayed reactions.

A history of tick bites was seen in 18/32 children (56.2%), compared to 5/15 (33.3%) adults. Atopy (allergic rhinitis, asthma and atopic dermatitis and food allergies) was similar in both groups.

Drug allergies

Five patients developed immediate hypersensitivity reactions to drugs. Of the patients with drug allergy, four (two with bronchial asthma) had sensitivity to non-steroidal anti-inflammatory drugs (NSAID); all were 18 years or older. There was no temporal relationship with ingestion of red meat. Two patients had anaphylaxis (confirmed by skin testing) to cefuroxime or ceftriaxone.

Allergy to vaccines

Six patients were allergic to vaccines containing bovine proteins. One patient developed anaphylaxis to the rubella vaccine (patient A) and 3 patients developed anaphylaxis to MMR II (Patient B, C, D). In addition, one patient (number 27 in Table 1) developed urticaria following the varicella vaccine and another patient (number 44 in Table 1) developed urticaria following the anti-rabies vaccine. Two patients (patient 1 and 5 in Table 1) were found to be sensitized to MMR vaccine and were not administered the MMR II as they had seroconverted. Details of patients A-D are given below.

Patient A (number 26 in Table 1), an 11-year-old girl, was referred for assessment of possible food allergy. At the age of 4 years, she developed generalized urticaria, swollen lips, abdominal pain and faintness, 2 ½ to 3 h after eating pork. She had multiple similar episodes subsequently with jelly, beef, yoghurt and curd, but can consume powdered milk, but not cow's milk. On occasion, she develops urticaria after eating ice cream. At the age of 11 years, following the rubella vaccine, she developed itching of the palms, swollen lips, urticaria and nasal congestion within 2–3 min. The pulse rate was 86/min, blood pressure 117/76, respiratory rate was 40/minute and SpO2 98%. She was treated with steroids and anti-histamines. She was given the measles vaccine at 9 months, the live Japanese encephalitis (JE) vaccine at 12 months and the measles and rubella (MR) vaccine at 3 years without incident.

The skin prick test results for cow's milk (4 mm diameter), beef (4 mm) and gelatin (9 mm) were positive. Phadia ImmunoCap results were positive for alpha-gal (90 kU/L), pork (43.5 kU/L), but negative for gelatin (0.29 kU/L) and BSA (< 0.1 kU/L).

While she has dogs with ticks, she did not give a history of tick bites.

Patient B (number 3 in Table 2), a three-year-old girl was referred following anaphylaxis to the 2nd dose of MMR vaccine. She developed wheezing, difficulty in breathing 35 min after vaccination. There was no

Table 1 Clinical features

	Sex	Atopy	Tick bites	Allergy to RM	Interval for CF (hours)	Other allergies	IgE α-gal (kU/L)	IgE RM (kU/L)	IgE BSA (kU/L)	RM SPT	Clinical Features				
											Skin	RT	CVS	GIT	CNS
Age 1–5 years															
1	M	No	UC	Mutton	3.5	MMR(SPT only), CM	16.6			Beef Neg	U				
2	M	No	No	Beef	5	No	56.7	12.3	0.29	-	U				
3	F	Yes	Yes	Pork	0.5	MMR, Ice cream	87.1	37.3	< 0.1	-	U	SOB			
4	F	Yes	No	Pork	1	MMR, CM	45.7	9.09	< 0.1	-	U	SOB Cough			
5	M	No	Yes	Beef	1	MMR (SPT only)	74.1	18.8	< 0.1	-	U	SOB			
6	F	No	No	Pork	0.75	-	1.94	0.76	< 0.1	-	U	SOB			
7	M	No	No	Pork	3	-	32.6	9.58	0.28	-	U, A			AP	
8	M	No	No	Pork Beef	2	-	43.4	29.6	< 0.1	-	U, A	SOB		V	LOC
Age > 5–12 years															
9	M	No	Yes	Pork Beef	2	-	48.5	38.4	0.11	-	U				
10	F	No	Yes	Venison	5	-	36	17.5	< 0.1	-	U		Low BP	AP	
11	F	No	Yes	Beef	4	-	0.95	0.36	< 0.1	-	U	SOB	CP		LOC, Dizzy
12	M	No	Yes	Beef	0.5	CM	18.3	-	-	Beef neg				AP	
13	M	Yes	No	Pork, Beef Mutton	0.5	-	35.7	14.9	< 0.1	-	U			AP	Faint LOC
14	F	No	Yes	Venison	4	-	11.9	-	< 0.1	-	P, U, A	SOB			
15	M	NA	Yes	Pork	5	-	6.91	5.31	-	-	U, A			AP	
16	F	No	No	Beef	1	-	17.4	4.65	< 0.1	-	U, A	Cough W	Low BP		
17	F	Yes	Yes	Beef Mutton	5	-	50.2	18	< 0.1	-	P, U, A	SOB, W Cough	Low BP	V	LOC
18	M	Yes	Yes	Venison	5	-	16.7	13.6	< 0.1	-	U				
19	F	Yes	No	Beef	3	-	7.92	5.63	< 0.1	-	U	SOB W			
20	F	NA	Yes	Pork	NA	MMR	67.3	27.5	< 0.1	Pork 3 mm	U	SOB			
21	M	Yes	Yes	Pork Venison	1.5	-	5.64	2.75	< 0.1	-	U, A	SOB			
22	M	Yes	Yes	Beef	2	-	16.8	12.6	0.16	-	U	SOB	CP	AP	

Table 1 (continued)

	Sex	Atopy	Tick bites	Allergy to RM	Interval for CF (hours)	Other allergies	IgE α-gal (kU/L)	IgE RM (kU/L)	IgE BSA (kU/L)	RM SPT	Clinical Features				
											Skin	RT	CVS	GIT	CNS
23	M	No	Yes	Pork Sambur	5	-	73	59.6	0.94	-	U, A	SOB		V, AP	LOC
24	F	Yes	NA	Pork	8		12.8	9.71	-	-	U, A				
25	F	Yes	NA	Pork Beef	0.25	-	15.6	0.4	< 0.1	-	U, A				
26	F	No	No	Pork Beef	3	Rubella	90	43.5	-	Beef 4 mm	U	SOB			
27	M	NA	UC	Pork Beef	6	VZV	32	22.7	< 0.1	-	U				
28	M	No	No	Pork	5	-	43.5	29.4	< 0.1	-	U	SOB	Low BP, Tachy		
29	F	No	Yes	Beef Mutton	5	-	4.23	3.36	< 0.1	-	U, A				
30	F	No	No	Pork	4	-	3.58	1.88	< 0.1	-	U	SOB			
31	M	No	No	Pork	2.75	-	49.1	4.32	< 0.1	Beef 3 mm	U, A	SOB		V	dizzy
Age > 12–18 years															
32	F	NA	UC	Pork	6	-	73.6	53.1	< 0.1	-	U, A				LOC
33	F	No	No	Pork	0.5	-	54.6	4.84	0.13	-	U	SOB	Low BP, Tachy CP	AP, V	LOC
34	M	No	NA	Pork	8	-	22.5	6.59	< 0.1	-	U	SOB	CP	V	LOC
35	F	No	Yes	Pork Beef	2	-	32.2	22	< 0.1	-	U, A				
36	M	NA	Yes	Beef Mutton	3	-	14.2	7.36	< 0.1	-	U, A				
37	M	No	Yes	Beef	1.5	-	19.7	12.8	< 0.1	-	U			V	LOC
38	F	Yes	No	Pork Mutton	0.3	-	30.3	0.67	< 0.1	-	U				
Age > 18 years															
39	F	No	No	Pork	NK	-	2.94	2.12	< 0.1	-	U	SOB			Dizzy
40	M	Yes	Yes	Mutton	0.5	-	42.3	16.7	42.3		U	Cough		AP, V	
41	F	No	NA	Pork Beef Mutton	4	-	31.4	19.2	0.1	-	U, A	SOB		V	LOC
42	M	Yes	No	Pork Beef	1	-	37.1	16.7	< 0.1	-	U				
43	M	Yes	No	Pork Beef Mutton Porcupine	4	-	5.12	4.05	< 0.1	-	U	SOB		AP, D	LOC

Table 1 (continued)

	Sex	Atopy	Tick bites	Allergy to RM	Interval for CF (hours)	Other allergies	IgE α-gal (kU/L)	IgE RM (kU/L)	IgE BSA (kU/L)	RM SPT	Clinical Features				
											Skin	RT	CVS	GIT	CNS
44	F	No	NA	Pork Beef	2	ARV CM Jelly	13.7	13.6	< 0.1	-	U	SOB W		AP, D	
45	F	No	No	Pork	2	-	4.87	2.33	< 0.1	-	U				LOC
46	F	Yes	Yes	Pork Beef	4	-	14.5	12	< 0.1	-	U				
47	M	No	No	Beef	3	-	1.24	0.37	0.13		U, P	R	CP	AP	Dizzy
48	M	NA	Yes	Lamb	6	-	42.5	16.6	< 0.1	-	U, A, P	SOB, Dysphonia		Dysphagia	
49	F	No	Yes	Beef	5	-	2.54	3.1	< 0.1	-	U				
50	M	No	No	Beef	0.17	-	27	14.4	< 0.1	-	U		CP		
51	F	NA	Yes	Pork Beef	0.17	-	10.7	0.91	< 0.1	-	U, P	SOB R			
52	F	No	No	Beef	5.5	-	9.97	2.39	< 0.1	-	U, A	SOB	Low BP		BV
53	F	Yes	NA	Pork Mutton Beef	0.33	-	51	14	< 0.1	-	U				
54	F	Yes	NA	Pork	5	-	24.2	4.02	< 0.1	-	U		Low BP	V	LOC
55	F	No	No	Pork Beef	5	-	3.05	0.99	< 0.1	-	U			AP, N, V, D	LOC
56	F	Yes	No	Pork	4	-	38.8	3.9	< 0.1	-	U, A, P	SOB	Palpitation		Drowsy
57	M	No	No	Pork Beef	2	-	35	22.7	< 0.1	-	U				

A angioedema, *AP* abdominal pain, *ARV* anti rabies vaccine, *BP* blood pressure, *BSA* bovine serum albumin, *BV* blurring of vision, *CF* clinical features, *CM* cows' milk, *CNS* central nervous system, *CP* chest pain, *CVS* Cardio vascular system, *D* diarrhea, *F* female, *GIT* gastro intestinal tract, *LOC* loss of consciousness, *M* male, *MMR* measles mumps rubella vaccine, *N* nausea, *NA* not available, *P* pruritus, *R* rhonchi, *RM* red meat, *RT* respiratory tract, *SOB* shortness of breath, *SPT* skin prick test, Tachy Tachycardia, *U* urticaria, *UC* uncertain, *V* vomiting, *VZV* varicella zoster vaccine, *W* wheezing

Table 2 Demographic, clinical, and Immunologic characteristics of patients with AGS

	All	Children ≤ 18 years	Adults	Comparison (*p* value children vs. adults)
Number (percentage)	57 (100)	38 (66.7)	19(33.3)	
Age in years median (range)	12 (2.25–61)	8 (2.25–18)	28 (20–61)	
Male sex (%)	26(45.6)	19 (50)	7(36.8)	0.41 †
Symptoms				
Hives alone (%)	16(28.1)	11(28.9)	5 (26.3)	>0.99 †
Anaphylaxis (%)	39 (68.4)	26 (68.4)	13 (68.4)	>0.99 †
+ GIT (%)	21(36.8)	13 (34.2)	8 (42.1)	>0.58†
GIT alone (%)	1 (1.8)	1 (2.6)	0 (0)	
Abdominal pain (%)	13 (22.8)	8 (21.1)	5 (26.3)	>0.74 †
Respiratory (%)	29 (50.8)	19 (50)	10 (52.6)	>0.99 †
Grade 5 anaphylaxis (%)	17 (29.8)	11 (28.9)	6 (31.6)	>0.99 †
Timing				
0-≤1 hour (%)	14 (24.5)	10 (26.3)	4 (22.2)	>0.76 †
>1-≤2 hours (%)	10 (18.2)	6 (16.2)	4 (22.2)	0.71†
≤ 2 hours (%)	24 (43.6)	16 (43.2)	8 (44.4)	>0.99 †
>2 hours (%)	31 (56.4)	21 (56.8)	10 (55.6)	>0.99 †
Uncertain (%)	2 (3.5)	1(2.6)	1 (5.3)	
Atopy/Out of 50 (%)	18/50 (36)	11/33 (33.3)	7/17 (41.2)	>0.76 †
Tick bite/Out of (%)	23/47 (48.9)	18/32 (56.2)	5/15 (33.3)	0.21 †
IgE to Alpha-gal > 0.35 IU/mL (%)	57 (100)	38 (100)	19 (100)	
IgE to alpha-gal IU/mL GM (range)	18.36 (0.95–87.1)	22.3 (0.95–87.1)	12.99(1.24–38.8)	0.064 ††
IgE to beef/pork/mutton* > 0.35 IU/mL/Out of (%)	54/54 (100)	35/35(100)	19/19 (100)	
IgE to beef/pork/mutton IU/mL GM (range)	7.16 (0.36–53.1)	8.73(0.36–53.1)	4.98(0.37–22.7)	0.12 ††
IgE to BSA > 0.35 IU/mL **/Out of (%)	1/52 (1.9)	1/33 (3.0)	0/19 (0)	
IgE to alpha-gal>IgE to beef/pork #/Out of (%)	53/54 (98.1)	35/35 (100)	18/19 (94.7)	

* Of the 3/57 patients where IgE to beef/pork was not done, in two, skin prick testing (SPT) for beef was done and were negative. In the third, IgE to BSA was negative. In all three IgE to alpha-gal was positive. Two gave a history of tick bites. The other was exposed to ticks, but did not give a history of bites

**One patient had a positive IgE to BSA, but IgE to red meat < alpha-gal, and there was delayed allergy to red meat. IgE to BSA was not done in 5 patients. In all 5, IgE to alpha-gal was positive. In two patients, skin prick testing to beef was negative. In the other three, IgE to alpha-gal > IgE to beef and they had delayed reactions to red meat

In one patient IgE to red meat > alpha gal, IgE to BSA < 0.1, interval to reaction was 2 ½ hours

† Fisher's exact test

†† Mann-Whitney *U* test

urticaria. She was dyspneic, and rhonchi were present. SpO2 was 95% on room air. Adrenaline was administered, along with nebulization. Three months previously, she had developed urticaria, 3 1/2 hours after eating pork. She had eaten red meat (venison) without incident one year previously. She had been bitten by a tick a few months prior to the reaction to pork. Four weeks after the reaction following the MMR vaccine, she had developed urticaria and wheezing 35 min after eating chocolate ice cream, for which she had been administered adrenaline and nebulized. Her serum IgE to alpha-gal (87.1 kU/L), mutton (37.3 kU/L), cow's milk (13.0 kU/L) were positive, but IgE to gelatin (0.14 kU/L), BSA (< 0.1 kU/L) were negative.

Patient C (number 4 in Table 2), a three-year-old girl was referred following anaphylaxis to the 2nd dose of MMR vaccine at 3 years of age. Within 5 min of administration, she developed a papule at the injection site, followed by a cough and shortness of breath. She was given adrenaline and rushed from a peripheral to a general hospital, where she developed urticaria. This settled with oral chlorpheniramine and cetirizine. She gives a history of cough and difficulty in breathing 30 min after eating pork at the age of 1 ½ years. She also developed urticaria 6 h after drinking cow's milk, and avoids red meat and cow's milk. IgE to alpha-gal was 45.7 kU/L, cow's milk 1.98 kU/L, pork 9.09 kU/L, BSA < 0.1 kU/L. She does not give a history of tick bites.

Patient D (number 20 in Table 2), an 8-year-old female was referred for assessment of allergy. She was bitten by ticks at 3–4 years of age, and developed papules at the site. At the age of 3 years, she developed cough and urticaria (one papule) over the chest, 30 min after the second dose of MMR. She also develops urticaria within one hour of eating beef as well as yoghurt, but can eat jelly, curd and ice cream. Her IgE to alpha-gal (67.3 kU/L), beef (27.5 kU/L) was positive, but negative for BSA (<

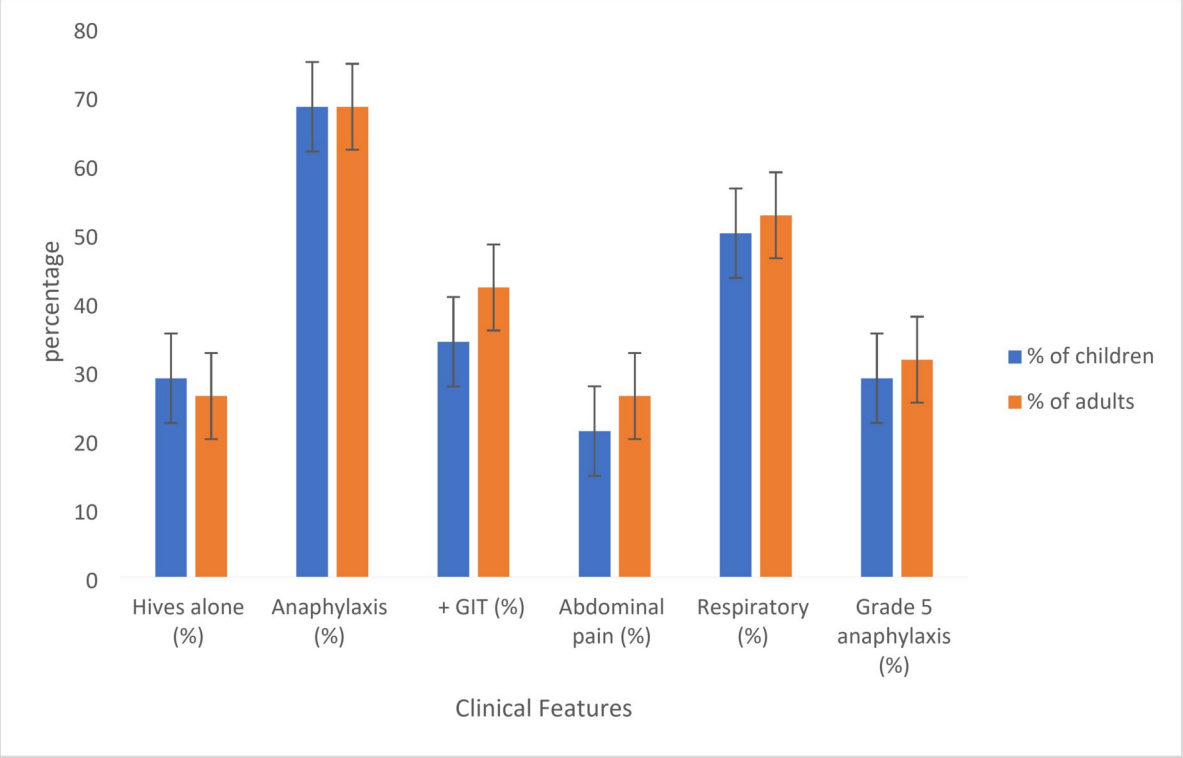

Fig. 1 Percentage distribution of clinical features

0.1 kU/L). Skin prick tests for pork (3 mm) and gelatin (3 mm) were positive.

Discussion

There is a paucity of data on AGS from South Asia [7], which includes the Indian subcontinent and 25% of the world's population. Only two papers highlight the presence of AGS from the subcontinent, and both are from Sri Lanka [15, 18]. One paper by our group mentions AGS as a cause of food allergy without giving demographic or clinical details [15], whereas the second discusses AGS as a possible cause of idiopathic anaphylaxis [18]. In that paper [18], only 12 (35%) of patients with IgE to alpha-gal had consumed red meat before the reaction. The present paper includes 57 patients with AGS, with a comparison of clinical features in children and adults in Sri Lanka, and is therefore the only paper from the subcontinent giving detailed demographic and clinical data on AGS.

Sixty six percent were children and the median age was 12 years. This is unusual; in most studies, adults predominate [11]. Similarly, in another study of 261 patients, 88% were adults [9]. However, 70% of subjects were below 18 years in a South African study [19]. Sex distribution was equal in children, which is unlike studies in the US, where there was a male preponderance [8, 9]. However, there was a female preponderance in adults, similar to the study in the US [9].

Most patients with AGS have a delayed onset of symptoms 3–8 h after ingestion of red meat [11]. A delay of at least 2 h (median 150 min) was reported in 84% of patients in another study from the US [9]. 43% of our patients had an early onset (≤ 2 h), similar in both children and adults. An early onset (≤ 2 h) has been reported previously; in the US study [9], 16% of patients, both children and adults, had an early onset. However, in the study in South Africa, a study predominantly of younger patients with challenge proven AGS (with a mean age of 12 years), an onset of symptoms had a mean of 108 min (range 45–375 min) [19]. While the reason for the early onset in children is not known, an actual difference in timing between children and adults, the type of food used for the food challenge or factors unique to the population tested were postulated as responsible [19]. A few patients in our cohort had both immediate and late onset al.lergy after ingestion of red meat. The reason for this is uncertain.

Co- factors, such as non-steroidal anti-inflammatory drugs, alcohol and exertion lower the threshold for AGS [20]. However, no such correlation was identified in our cohort.

The clinical features included urticaria (98.2%), gastrointestinal (GIT) (38.6%), respiratory (50.8%) and anaphylaxis (66.7%). This contrasts with a study from the US [9] where GIT symptoms were more common (64%) but rates of urticaria (90%) and anaphylaxis (60%) are similar.

The nature of symptoms was similar in children and adults, including isolated skin manifestations, gastro intestinal (GIT) symptoms along with other symptoms, anaphylaxis and severe anaphylaxis. There was no significant difference in symptoms between the 2 groups in the US as well [9]. Only one patient, a child, had isolated abdominal symptoms in our cohort, along with an adult who had similar features with cow's milk and gelatin, but had urticaria as well with red meat. Patients with isolated GIT symptoms have been observed in a few studies. Isolated abdominal pain was reported in 21% of oral food challenge (OFC) confirmed cases, mainly in women, among black South Africans [19], and isolated GIT symptoms in 11% of cases in an US study [21]. Isolated abdominal pain may be underdiagnosed in this condition [22] and it is probable that AGS with isolated abdominal pain is under reported in Sri Lanka as well.

Twenty nine percent of our patients with anaphylaxis had severe anaphylaxis (Grade 5) [23]; all had severe symptoms pertaining to the cardiovascular system. Most lost consciousness, while some had hypotension. 5/6 adults with severe anaphylaxis were females; this gender preponderance was not seen in children. The reason is unclear. However, the sample size is small.

Atopy (mainly allergic rhinitis or bronchial asthma) was identified equally in children and adults in our population. A study from Europe showed that most patients with AGS were middle aged, and more than half were atopic. Atopy was associated with pulmonary manifestations of anaphylaxis in that cohort [24]. No such relationship was shown in our patients.

A history of tick bites was more often reported in children (56.2%) compared to adults (33.3%) but it was not significant. Tick bites may be painless, and therefore an absence of such a history may be common [11].

AGS has been reported in substantial numbers in the US, linked with the Lone Star tick (*Amblyomma americanum*), in Australia, where *Ixodes holocyclus* is implicated, and in Europe where *I ricinus* is responsible [7]. Reports of AGS from Asia are rare, except in Japan and South Korea [7]. The ticks responsible for AGS in Sri Lankan patients is unknown; however, *A. testudinarium*, implicated in AGS in Japan [7], has been identified in both the wet and dry zones of Sri Lanka [25]. Patients with AGS were from both zones. *Amblyomma* and *Ixodes* species have also been identified in Sri Lanka [25].

Vaccine allergy

Allergy to red meat has been implicated in vaccine allergy [16, 26]. The implicated vaccines include the rubella, measles, measles mumps and rubella (MMR), varicella and anti-rabies (Vero cell) vaccines [27]. The MMR, measles, rubella and varicella vaccines marketed in Sri Lanka contain bovine gelatin and bovine serum albumin (BSA); the Vero cell rabies vaccine contains polygeline, derived from gelatin. Allergy to gelatin is responsible for vaccine allergy in the US and other countries [26]. In Sri Lanka, while allergy to red meat is implicated in vaccine allergy, the allergen responsible was found to be BSA [27].

Only four patients with AGS having vaccine allergy have thus far been identified; to the MMR, varicella and zoster vaccines in the US [12, 14, 28]. The present paper identifies 6 patients with AGS who developed allergy to vaccines. These included allergy to the MMR ($n = 3$), rubella ($n = 1$), varicella ($n = 1$) and anti-rabies vaccine ($n = 1$). All six patients had allergy to red meat, with a delayed onset in three patients; all had IgE to alpha-gal > IgE to red meat, and no IgE to BSA. Studies have indicated that the MMR, varicella and zoster vaccines available in the US can bind and deplete IgE to alpha-gal [12, 14]. The vaccines used in the US contain the bovine products, gelatin and fetal calf serum. Gelatin contains alpha-gal epitopes [29]. The two studies [12, 14] implicate the alpha-gal epitopes found in gelatin, and not in fetal calf serum, as responsible for binding and depleting alpha-gal specific IgE. The amount of gelatin in the vaccine may be important, as IgE to alpha-gal did not bind to the yellow fever vaccine, which had half the content of gelatin compared to the MMR and zoster vaccines [12]. Alpha-gal epitopes found in gelatin is the probable allergen responsible for vaccine allergy in our patients. Two of our vaccine allergic patients were tested for IgE to gelatin. Both had levels < 0.35 kU/L. The two patients in the US with vaccine allergy also had low serum concentrations of IgE to gelatin [12, 14]. Alpha-gal allergic individuals may have negative IgE to gelatin [30], and therefore, AGS may confound clinical testing for gelatin allergy [12]. However, it is likely that AGS is a rare cause of vaccine allergy [28]. Therefore, it is advisable to elicit a history of immediate and as well as delayed (2–8 h) red meat allergy before administration of vaccines containing bovine products.

Difficulties in the diagnosis of AGS

Due to the delay in onset of symptoms, unlike with other food allergies, both patients and caregivers may miss the diagnosis [11]. The symptoms may vary from mild reactions to severe anaphylaxis, and not all exposures lead to symptoms making diagnosis difficult. In addition, the invitro test is expensive, and commercial skin test reagents have limited sensitivity [11].

Limitations

There are several shortcomings in our study. Due to financial constraints, IgE to all red meats (beef, pork and mutton) could not be done; indeed, in a few instances, IgE to mutton, and not the implicated red meat was evaluated. However, there is cross reactivity between the three red meats. Secondly, whilst intracutaneous tests

were carried out to detect sensitization, the more sensitive intradermal tests were not done. Thirdly, sample size ($n = 57$) was relatively small, especially the adult population ($n = 19$). A larger sample may have given more statistically significant results. Fourthly, inhibition studies were not done in patients with vaccine allergy which may have confirmed the results. Finally, we did not perform skin testing with the culprit vaccines.

Conclusion

This study reveals that AGS is a significant cause of allergy in the Indian subcontinent and is commoner in children unlike in other regions. There were more females among adult patients, compared to children although not statistically significant. There was no difference in clinical features between children and adults. However, severe anaphylaxis was more common in adult females. AGS may rarely be responsible for vaccine allergy.

Abbreviations

AGS	Alpha-gal syndrome
aTd	Adult tetanus diphtheria
BSA	Bovine serum albumin
CMA	Cows' milk allergy
FA	Food allergy
GIT	Gastrointestinal tract
MMR	Measles, mumps, rubella vaccine
MR	Measles, rubella vaccine
NSAID	Non-steroidal anti-inflammatory drugs
OFC	Oral food challenge

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None.

Authors' contributions

DD - Conceptualization, formal analysis, methodology, writing. Chandima K- Methodology, reviewed manuscript. Chathurika K - Methodology, reviewed manuscript. NF- Methodology, reviewed manuscript. JI- Methodology, reviewed manuscript. RdS - Conceptualization, formal analysis, methodology, writing.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Granted by the Ethic Review Committee of the Medical Research Institute, Sri Lanka. ERC 22/2024. The research was in compliance with the Declaration of Helsinki.

Consent to participate was not obtained as it was waived by the Ethics Review Committee of the Medical Research Institute, Sri Lanka (Project number ERC/22/2024).

Consent for publication

Case reports of 4 patients with vaccine allergy were included. Informed, written consent for publication was obtained from the parents of these 4 patients.

Competing interests

The authors declare no competing interests.

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