

Original Article

Clinical and Serological Characterization of the α -Gal Syndrome—Importance of Atopy for Symptom Severity in a European Cohort

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What is already known about this topic? Individuals have been diagnosed with the galactose- α 1,3-galactose (α -Gal) syndrome all over the world, based on delayed allergic reactions after mammalian meat consumption and antibodies directed against the carbohydrate α -Gal.

What does this article add to our knowledge? This in-depth characterization of red meat–allergic patients from Europe reveals a uniform, middle-aged group, with anaphylaxis in nearly half of the patients. Atopy increased the risk of anaphylaxis with pulmonary manifestations.

How does this study impact current management guidelines? The detailed patient characterization will increase the awareness of the different clinical phenotypes of the α -Gal syndrome, and will thereby contribute to improved diagnosis and management of patients with allergic reactions after mammalian meat consumption.

BACKGROUND: The galactose- α 1,3-galactose (α -Gal) syndrome (AGS) is a novel form of food allergy. Patients experience delayed severe allergic reactions after mammalian meat consumption due to IgE antibodies directed against the carbohydrate α -Gal present in mammalian meat. The onset of the disease is associated with tick bites.

OBJECTIVE: To characterize a cohort of patients with AGS from Sweden on a clinical and serological level, and identify risk factors for disease severity.

METHODS: A total of 128 patients with symptoms after mammalian meat intake and IgE to α -Gal were included.

Medical examination and diagnosis were made by an allergologist and questionnaires were filled in regarding onset of symptoms, tick exposure, and airborne allergies. Serum IgE reactivity against multiple food and airborne allergens, as well as protein extract from the tick *Ixodes ricinus*, was measured using ImmunoCAP.

RESULTS: The majority of patients were middle aged, with equal gender distribution. Nearly all reported symptoms more than 2 hours after meat consumption. Urticaria (90%) and gastrointestinal symptoms (74%) were most common. Almost half of the patients suffered from anaphylaxis, and α -Gal IgE levels were significantly higher among these patients compared with those without anaphylaxis. Nearly all patients had been tick bitten and 75% had IgE against *I. ricinus*. More than half of the patients with AGS were atopic, and atopy increased the risk of anaphylaxis with pulmonary manifestations. Only 2 patients belonged to blood group B/AB.

CONCLUSION: AGS is an upcoming food allergy where patients report severe symptoms and tick bites. Atopy was found to affect the manifestation of the disease in Swedish patients. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Galactose- α 1,3-galactose; α -Gal syndrome; Airborne allergy; Atopy; Anaphylaxis; Food allergy; Red meat allergy

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Over the past few years, a new type of food allergy, the galactose- α 1,3-galactose (α -Gal) syndrome (AGS), has been recognized, wherein mostly middle-aged patients experience delayed severe allergic reactions after consumption of mammalian meat and mammalian products. The reactions are caused by IgE antibodies against the carbohydrate epitope α -Gal, which is not

Abbreviations used

 α -Gal- Galactose- α -1,3-galactoseAGS- α -Gal syndrome

CI- Confidence interval

GI- Gastrointestinal

OR- Odds ratio

ROC- Receiver operating characteristic

only present on glycolipids and glycoproteins from mammalian sources but also in some pharmaceuticals (cetuximab, antivenom, gelatin-containing vaccines).¹ The IgE reactivity against nonprotein epitopes, the delayed nature of the reaction, the onset in middle age, previous tolerance to mammalian meat, and a strong association with tick bites are features exclusive to AGS.²⁻⁵ Recently, α -Gal-carrying proteins have been identified in saliva from various tick species, including the European tick *Ixodes ricinus*, pointing to the fact that AGS is the first allergic disease where sensitization is induced by allergen exposure via ticks.^{6,7}

Today, AGS has been described worldwide.⁸⁻¹⁰ Most studies have reported on AGS among adults, but the syndrome has also been identified among pediatric patients.^{9,11} As AGS is being increasingly recognized, there is a need to better understand its clinical and immunological features. So far, most publications on AGS report individual cases or studies on relatively small study groups.¹²⁻¹⁷ Recently, Platts-Mills et al¹⁰ reported AGS in a large population of patients with self-reported allergy to mammalian meat. That study was based on serum assays and detailed questionnaires among subjects from the United States. Here we analyzed the clinical and humoral characteristics of a European cohort of 128 patients who underwent a clinical examination by an allergologist due to symptoms of delayed allergic reactions after red meat consumption. Risk factors for disease severity were further explored.

METHODS

Patient cohort

Patients with symptoms of delayed allergic reactions after mammalian meat consumption attended the adult Allergy Unit at Södersjukhuset in Stockholm and were examined and diagnosed by the same allergologist with many years of experience in food allergy. Blood samples were drawn for the analysis of IgE antibodies to α -Gal. Diagnosis of mammalian meat allergy was defined as symptoms after mammalian meat consumption and IgE to α -Gal (≥ 0.1 kU_A/L). In total, 128 patients with AGS were enrolled in the study. All patients answered a detailed questionnaire regarding onset of and type of symptoms, tick exposure, and airway symptoms due to pollens or furry animals and asthma. An early reaction was classified as onset of symptoms ≤ 2 hours after red meat consumption and a delayed reaction as onset of symptoms after > 2 hours.¹⁸ Anaphylaxis is defined as a severe, usually rapid onset and potentially life-threatening systemic hypersensitivity reaction from several organ systems, which always includes respiratory and/or cardiovascular manifestations. Symptoms from the skin, mucous membranes, gastrointestinal (GI) tract, and the central nervous system are usually seen.¹⁹ Anaphylaxis was subdivided in cases with 1 or more cardiovascular symptoms (hypotension, syncope) and cases with 1 or more pulmonary symptoms (dyspnea, wheeze-bronchospasm, stridor, hypoxemia). Furthermore, IgE antibodies to a panel of different food and inhalant allergens were measured. Atopy was defined as IgE

TABLE I. Cohort characteristics

Parameter	
Sex (m:f)	64:64
Age, median years (min-max)	51 (19-76)
α -Gal IgE, median kU _A /L (min-max)	15.3 (0.26-144)
Total IgE, median kU/L (min-max)	121.5 (8.6-2200)
Percentage α -Gal IgE of total IgE*, median (min-max)	14 (0.00-66)
A/O blood group (%)	98.4

 α -Gal, Galactose- α -1,3-galactose.*Quantitatively the same units where the "A" in kU_A/L indicates that the IgE levels are allergen specific.

antibodies to 1 or more of the inhalant allergens birch, timothy, and cat (rFel d 1). The major cat allergen Fel d 1 was used as proxy for cat because cat dander extract contains α -Gal. Patients were diagnosed with airborne allergy if they were atopic and had airway symptoms after exposure to birch, timothy, or cat. The patients were blood typed according to routine methods (Blood Center, Karolinska University Hospital). Thirty-nine of the included patients were part of a previous report.²⁰ The study was approved by the local ethics committee (Ethical permit No 2011/1604-31/2, 2018/2483-32), performed in accordance with the declaration of Helsinki, and all patients gave their written informed consent.

ImmunoCAP IgE determination

Serum samples were tested by ImmunoCAP (Thermo Fisher AB, Uppsala, Sweden) for total IgE level and allergen-specific IgE antibody reactivity to α -Gal (bovine thyroglobulin, α 215), beef, moose, pork, chicken, milk, dog, cat, the major cat allergen rFel d 1, birch, and timothy. IgE antibodies against tick proteins (*I. ricinus*) were measured by coupling 5 μ g biotinylated whole-body *I. ricinus* tick protein extract to Streptavidin ImmunoCAP as described by Hamsten et al.²⁰ All IgE determinations were analyzed according to the manufacturer's instructions. The cutoff for total IgE was ≥ 2 kU/L and for allergen-specific IgE, ≥ 0.1 kU_A/L.

Statistical analysis

Statistical analysis was performed with GraphPad Prism, version 6 (GraphPad software, La Jolla, Calif). Quantitative measurements of IgE antibodies were compared using Mann-Whitney *U* tests or Kruskal-Wallis tests followed by Dunn's post test when comparing multiple groups. Frequencies were compared using Fisher's exact test. Spearman's rank correlation was used to calculate the strength and direction of an association between 2 variables. Receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic value of IgE levels. A *P* value of less than .05 was considered significant. Binary logistic regression was performed using Stata 15.0 (StataCorp LLC, College Station, Texas). The Venn diagram was made using the DrawVenn tool (<http://bioinformatics.psb.ugent.be/webtools/Venn/>).

RESULTS

Demographic and main immunological and clinical manifestations of the cohort

The demographic data of the patients are shown in Table I. Nearly all patients lived in the greater Stockholm area, whereas 2 patients lived further south. The group consisted of 64 males and 64 females. Most patients were middle aged, with a median age of 51 years (range, 19-76 years). At the time of enrollment,

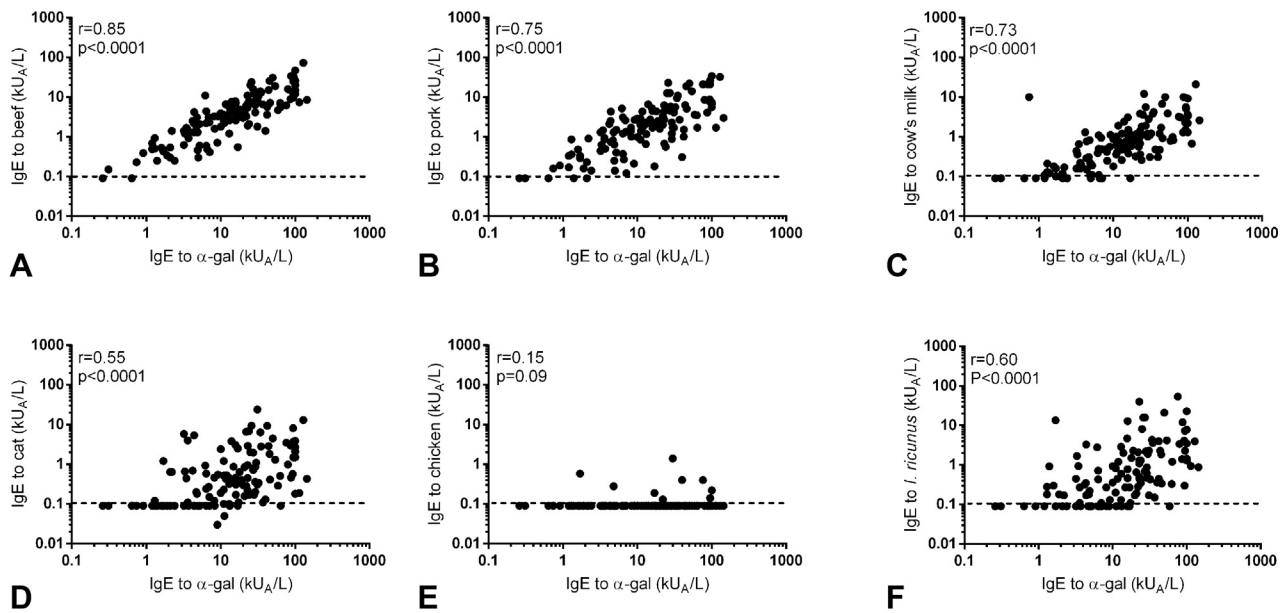


FIGURE 1. Correlations between IgE levels to α -Gal and (A) beef, (B) pork, (C) cow's milk, (D) cat, (E) the non-galactose- α -1,3-galactose-containing chicken, and (F) the European tick *Ixodes ricinus*.

72.8% of the patients were more than 40 years of age, and 28.1% were older than 60 years. All reported allergic symptoms (cardiovascular or respiratory symptoms due to anaphylaxis, urticaria, angioedema, and GI discomfort, or a combination of these symptoms) after mammalian meat consumption and had IgE antibodies to α -Gal (median of 15.3 kU_A/L; range, 0.26-144 kU_A/L). Their median total IgE level was 121.5 kU/L (range, 8.6-2200 kU/L). In 63.3% of the patients, the percentage of α -Gal antibodies exceeded 10% of their total IgE, and in 12.5% of the patients, α -Gal-IgE accounted for more than 30% of their total IgE. Nearly all (98.4%) patients belonged to the A/O blood groups. The IgE levels to α -Gal of the 2 blood group B/AB donors were 5.0 and 17.0 kU_A/L.

Serological characterization in relation to AGS

Almost all patients were IgE positive for beef and pork (98.4% and 96.1%, respectively), and the majority were also positive for the other α -Gal-containing allergen sources (moose 86.7%, milk 91.4%, cat 75%, dog 83.6%) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In contrast, only 7% of the patients were IgE positive against the non- α -Gal-containing allergen source chicken. The α -Gal IgE levels exceeded the IgE levels against beef and pork in all patients, but also against dog in 99.2%, and against cat in 96.9% of the patients. Strong correlations between IgE antibodies to α -Gal and beef ($r = 0.85$, $P < .0001$; Figure 1, A), pork ($r = 0.75$, $P < .0001$; Figure 1, B), and cow's milk ($r = 0.73$, $P < .0001$; Figure 1, C) were observed, whereas moderate but significant correlation was noted between α -Gal IgE and cat ($r = 0.55$, $P < .0001$; Figure 1, D) antibodies.

Characterization of symptom onset and manifestation of AGS

Regardless of gender, the majority of patients (82.6%) reported symptoms more than 2 hours after mammalian meat

consumption (Figure 2, A). The α -Gal IgE levels did not differ between patients experiencing an early (2 hours or less) versus a delayed reaction (more than 2 hours) (Figure 2, B). The most common symptom was urticaria (89.8%; Figure 3, A), which was reported significantly more by patients with a delayed reaction ($P < .0001$; Figure 2, C). GI symptoms also occurred frequently (74.2%; Figure 3, A). Patients suffering from GI symptoms were significantly younger than those without these symptoms ($P < .0001$; Figure 4, A). A small group of patients ($n = 8$) reported only GI symptoms, but their α -Gal IgE levels and total IgE levels were similar to the other patients (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Furthermore, angioedema occurred in 60.2% of the patients, and the frequency was significantly higher in women ($P = .03$; Figure 4, B). As many as 47% of the patients suffered from anaphylaxis. In nearly 56%, this diagnosis was based on the presence of cardiovascular manifestations, and in 30%, on respiratory symptoms. A smaller group of anaphylactic patients (14%) suffered from both cardiovascular and pulmonary manifestations. All anaphylactic patients suffered from urticaria as well, and many reported other symptoms at the same time. The most common combination was anaphylaxis (cardiovascular and/or respiratory symptoms), angioedema, urticaria, and GI symptoms (Figure 3, B). Patients experiencing anaphylaxis had significantly higher IgE levels to α -Gal and beef compared with patients without an anaphylactic reaction (Figure 4, C and D; $P = .03$ and $.04$, respectively). ROC curve analysis showed that both α -Gal and beef IgE levels could predict anaphylaxis in patients with AGS (Table E2, available in this article's Online Repository at www.jaci-inpractice.org, $P = .03$ and $.04$, respectively), although the ability to discriminate between patients with and without anaphylaxis was low (area under the curve was 0.61 and 0.60, respectively). The percentage of α -Gal-IgE or beef-IgE of total

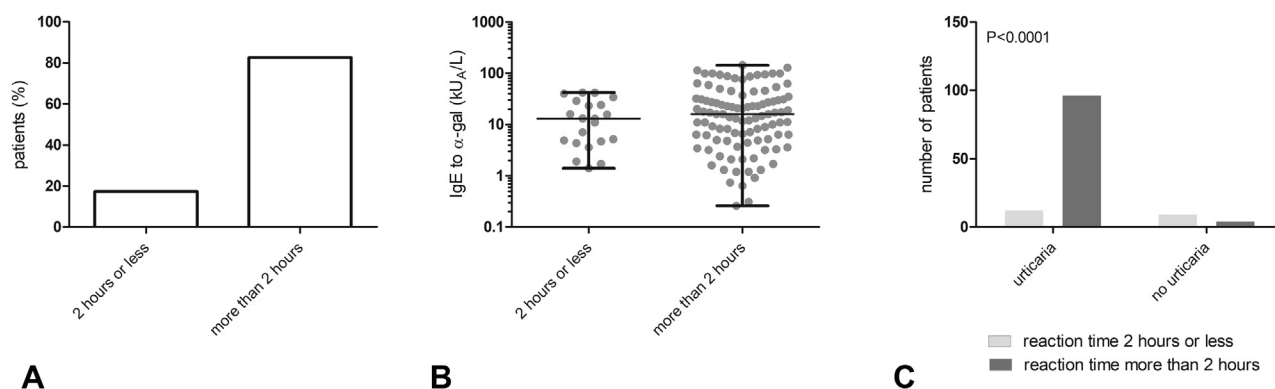


FIGURE 2. **A**, Early onset (2 hours or less) versus delayed onset (more than 2 hours) symptoms. **B**, Galactose- α -1,3-galactose IgE levels were compared using a Mann-Whitney *U* test. **C**, Frequency of urticaria in patients with early and delayed symptom onset was compared using Fisher's exact test.

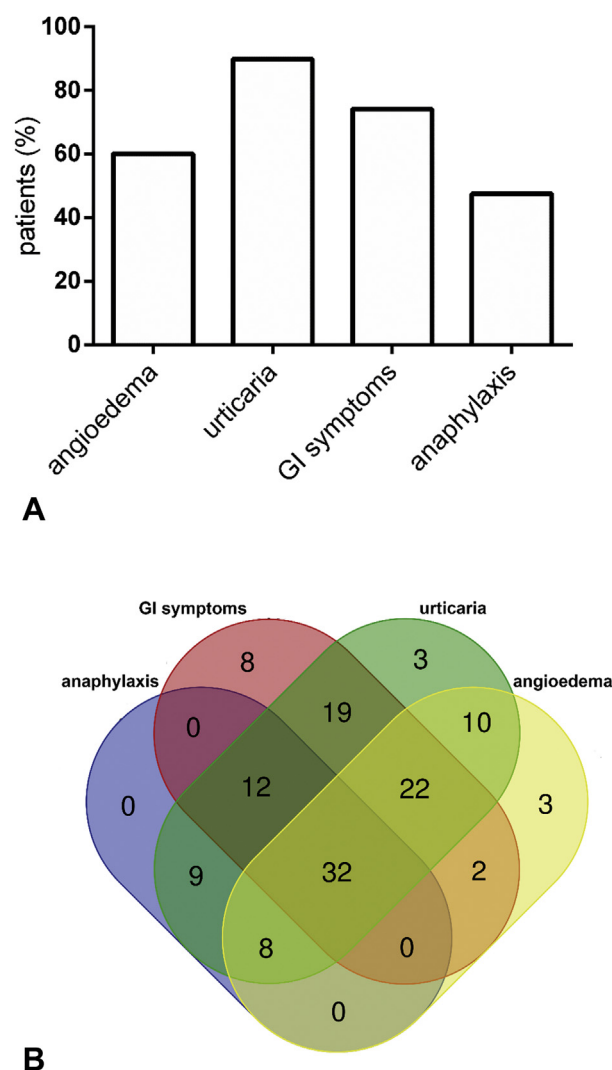


FIGURE 3. Overview of reported symptoms. **A**, Frequency of symptoms. **B**, Venn diagram of symptoms. *GI*, Gastrointestinal.

IgE did not predict anaphylaxis in patients with AGS. Also, none of the other symptoms reported were associated with higher IgE levels to α -Gal or beef, total IgE levels or α -Gal/total IgE percentage.

Tick bites and disease onset

All but one patient reported tick bites, which they obtained when they were outdoors. Seventy-nine percent of the included patients remembered the season they experienced their first AGS symptoms. In almost half of the patients, disease onset was in autumn (45.5%), and for 37.6%, in summer (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). When we further explored the impact of tick bites with respect to sensitization to *I. ricinus*, we noted that 75% had IgE reactivity against *I. ricinus*. The median of these positive cases was 0.88 kU_A/L (range, 0.11-54.0 kU_A/L). When comparing the IgE levels with α -Gal and *I. ricinus*, we noted that the *I. ricinus*-specific IgE levels were consistently lower than those to α -Gal. Furthermore, a moderate correlation between the 2 was observed ($r = 0.60$, $P < .0001$; Figure 1, *F*).

Atopy, airborne allergy, and asthma

We also addressed the question whether patients with AGS more often have an atopic phenotype, defined as IgE reactivity against 1 or more of the 3 most common inhalant allergens in Sweden (birch, timothy, and cat), compared with the general Swedish population. Fifty-four percent of the patients were found to be atopic. This figure is significantly higher than reported for the general Swedish population (33.5%) ($P < .0001$),²¹ even with a cutoff of 0.35 kU_A/L. More than one-third of the patients were sensitized to birch (38%) and timothy grass (37%), and 25% to rFel d 1 (Table II). Polysensitization was common. Thirty-eight percent were sensitized to 2 of the inhalant allergens and 31% to all 3 allergens.

Nearly half of the cohort (44%) was diagnosed with airborne allergy. In a multivariable logistic regression model, we noted that being sensitized to birch gave the highest risk of having airborne allergy (odds ratio [OR], 15.37; 95% confidence interval [CI], 4.80-49.11; $P < .0001$) (Table II). Furthermore, 24.2% of the patients had a doctor's diagnosis for asthma, which is also significantly higher compared with the Swedish

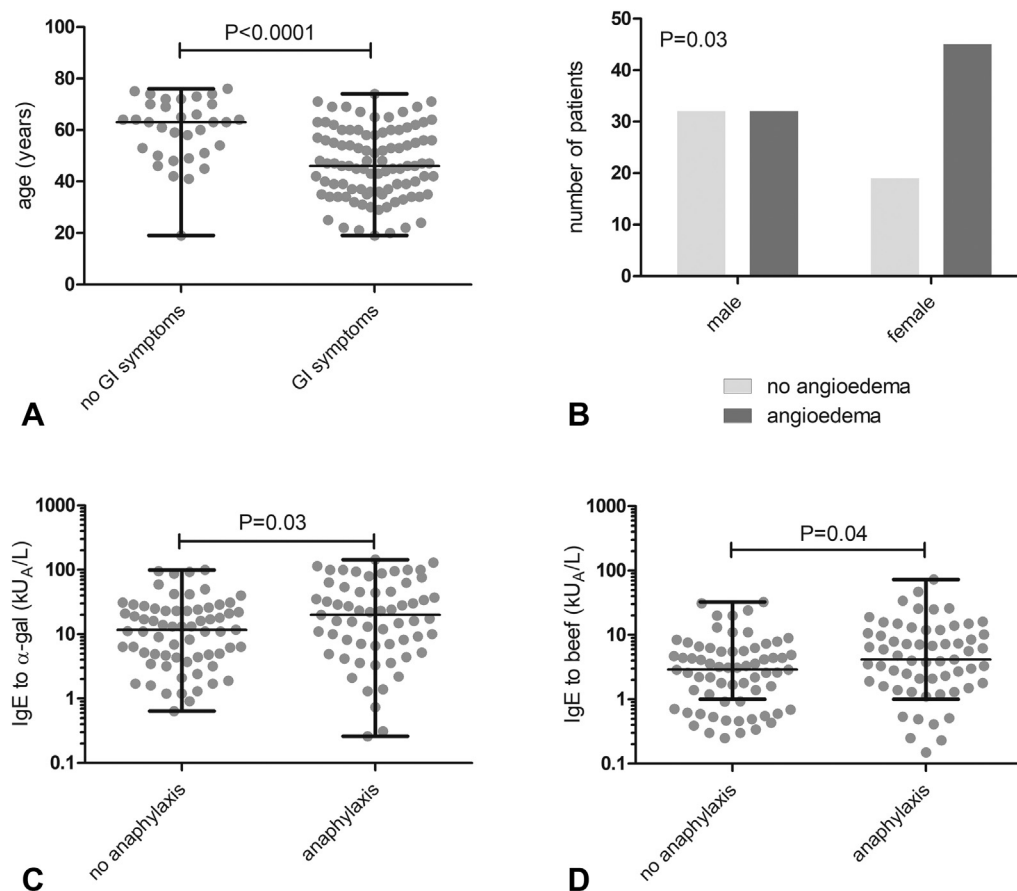


FIGURE 4. Characteristics associated with α -Gal syndrome symptoms. **A**, Age of patients with and without GI symptoms. **B**, Frequency of angioedema in male and female patients. IgE levels to **(C)** α -Gal and **(D)** beef in patients with and without an anaphylactic reaction. Frequencies were compared using a Fisher's exact test, whereas age and IgE antibody levels were compared using Mann-Whitney U tests. α -Gal, Galactose- α -1,3-galactose; GI, gastrointestinal.

TABLE II. Sensitization profile of inhalant allergens in patients with AGS

Factor	Characteristics		Association with airborne allergy	
	Sensitized patients (%)	IgE, median (min-max)	OR (95% CI)	P value
rFel d 1 sensitization	25	0.74 (0.10-100)	11.5 (2.98-44.4)	<.001
Timothy sensitization	37	1.5 (0.10-56)	7.14 (2.23-22.85)	.001
Birch sensitization	38	1.9 (0.11-36)	15.4 (4.80-49.1)	<.001

AGS, Galactose- α -1,3-galactose syndrome; CI, Confidence interval; OR, odds ratio.

population (14.9%) ($P < .01$).²² The majority (77.4%) of these asthmatic patients suffered from allergic asthma.

Atopy in relation to α -Gal IgE levels and AGS symptoms

The IgE levels to α -Gal (Figure 5, A, $P < .04$) and the other α -Gal-containing allergen sources (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org) were significantly higher among patients with atopy. When we elucidated risks for individual symptoms in a multivariable logistic regression model, we noted that atopy seemed to be a significant risk factor for anaphylaxis (OR, 2.06; 95% CI, 1.00-4.25; $P = .05$) (Figure 5, B). When distinguishing between

different anaphylactic symptoms, atopy had no effect on anaphylaxis with cardiovascular manifestation, but increased the risk of anaphylaxis with respiratory symptoms (OR, 3.17; 95% CI, 1.18-8.50; $P = .02$) (Figure 5, C).

DISCUSSION

Here we provide the first clinical and serological characterization of a large cohort of mammalian red meat-allergic patients from Northern Europe, in which the patients were well characterized and thoroughly investigated by the same physician with many years of experience with AGS. We noted an equal gender distribution of the disease. Patients were middle aged. However, there are pediatric AGS patients in the greater

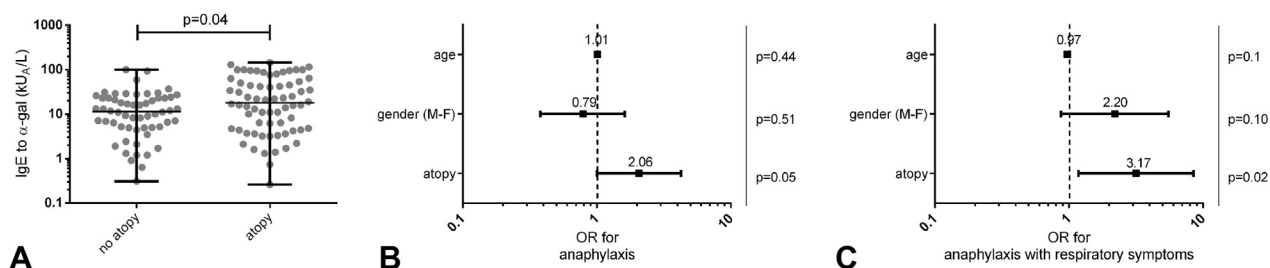


FIGURE 5. Effects of atopy among patients with AGS. **A**, α -Gal IgE levels in atopic and nonatopic patients with AGS were compared using Mann-Whitney *U* tests. ORs for **(B)** anaphylaxis and **(C)** anaphylaxis with breathing difficulties, in relation to age, gender, and atopy. α -Gal, Galactose- α -1,3-galactose; AGS, α -Gal syndrome; OR, odds ratio.

Stockholm area, but the number seems to be low compared with the reported adult cases. Furthermore, nearly half of the patients had experienced anaphylaxis, and they had significantly higher IgE levels to α -Gal compared with nonanaphylactic patients. Atopy was found to be significantly more frequent in patients with AGS compared with the general Swedish population. In addition, atopy increased the risk of anaphylaxis with respiratory symptoms. We also observed that patients belonging to blood group B were less than 2%, which is in line with our previous data showing that self-tolerance to the B-antigen results in a reduced risk of sensitization to α -Gal and development of AGS.²³ The percentage was lower in Sweden compared with the United States, where 8% of the patients with AGS belonged to blood group B.¹⁰

We performed a broad analysis of IgE reactivity against α -Gal-containing allergen sources. Beef-specific IgE, which was present in all but one patient, showed the highest level and the strongest correlation with α -Gal IgE levels. However, the α -Gal IgE levels exceeded those of beef IgE, which reflects that α -Gal is the primary epitope in beef for these patients. The majority of the patients also showed IgE reactivity to other known α -Gal sources, including pork, cow's milk, cat, and dog, with higher frequencies compared with the general Swedish population,^{24,25} indicating that the IgE reactivity is mainly due to the presence of the α -Gal epitope. We were indeed able to show that the high IgE reactivity to cat allergen extract (75%) above all seemed to be directed against α -Gal as only 25% of the patients were IgE positive for the main cat allergen, rFel d 1. Thus, evaluation of the IgE response on a molecular level in patients with AGS will help to unravel genuine sensitization and scrutinize the contribution of α -Gal in α -Gal-containing protein extracts.

The symptoms that patients experienced after mammalian meat intake, such as urticaria, angioedema, GI symptoms, and anaphylaxis, resemble the symptoms described in mammalian meat allergy in other parts of the world.^{20,26,27} We noted that almost half of the patients with AGS suffered from anaphylaxis, reflecting the severe status of the disease. Recently, Platts-Mills et al¹⁰ reported an even higher figure of 60% in their large cohort of US patients with AGS. Furthermore, Pattanaik et al²⁸ described that the most common identified etiology of adult anaphylaxis in Tennessee, USA, was α -Gal. Carter et al²⁹ pointed out that due to the delay in reaction, anaphylaxis in patients with AGS could be overlooked as idiopathic anaphylaxis. Therefore, the actual number of patients with AGS with anaphylaxis might be higher also in Sweden.

We observed that the reported anaphylactic reactions in most cases were associated with cardiovascular manifestations. This is in contrast to most food allergies, in which respiratory symptoms are more common during anaphylactic reactions.³⁰ In venom allergy, on the other hand, patients are also prone to suffer from cardiovascular reactions during anaphylaxis.^{31,32} One striking similarity between AGS and venom allergy is the route of sensitization. Both patients with AGS and venom-allergic patients are clearly sensitized through the skin by tick bites and hymenoptera stings, respectively. However, if and why sensitization via the skin is related to anaphylactic reactions involving the cardiovascular system observed in patients with AGS and venom-allergic patients needs further investigation.

A major part of the patients suffered from GI symptoms. All but one of the patients with AGS below the age of 40 had GI symptoms, showing that this symptom is most pronounced in the youngest 25% of the patients in our cohort. A small group of patients only had GI symptoms. As GI symptoms are related to a range of different disorders, such as inflammatory bowel disease and irritable bowel disease, a correct diagnosis can often be difficult to make. These data show that AGS should be considered as a cause for GI symptoms in younger individuals when it is observed in combination with only urticaria³³ or with no other allergy-related symptoms.

Several studies have shown that IgE to α -Gal is the best biomarker to identify red meat-allergic patients,^{9,34} but its association with the different AGS clinical phenotypes has not been investigated. We observed that the α -Gal IgE levels were higher in patients with anaphylaxis. However, the ROC analysis indicated that, although significant, the α -Gal IgE levels do neither efficiently discriminate between anaphylactic and non-anaphylactic patients, nor between patients with or without other symptoms. Thus, the α -Gal IgE level seems not to reflect disease severity.

We could also underline the importance of tick bites for AGS as all but one patient reported that they had been tick bitten. This was confirmed by the presence of IgE against *I. ricinus* in the majority of cases and the significant correlation between *I. ricinus* and α -Gal IgE levels. The presence of α -Gal-containing proteins in saliva of *I. ricinus* and other AGS-related tick species was recently confirmed,^{6,7} underlining that ticks may induce sensitization by exposing their host to α -Gal. We also observed that in most patients, the AGS symptoms started in summer or autumn, a few months after the period of the year when people are outdoors and may be exposed to ticks. This is in line with the

report by Hashizume et al,³⁵ who recently demonstrated that repeated tick bites were associated with increased α -Gal IgE levels. However, not all of our patients had IgE reactivity against *I. ricinus*, which corresponds to our previous findings among blood healthy donors from a highly endemic tick area where only one-third of the α -Gal IgE-positive donors had IgE against *I. ricinus*.³⁶ We noted furthermore that the absence of these IgE antibodies was related to lower α -Gal IgE and total IgE levels.

Atopy was more common in our AGS population compared with the general Swedish population.²¹ Moreover, the IgE levels to α -Gal were higher in atopic compared with nonatopic patients. Although atopy has been linked to food allergy in general,³⁷ a lower percentage of atopic patients was observed in a cohort of AGS from the United States and no differences in α -Gal IgE levels between atopic and nonatopic patients were seen.¹⁰ One reason for the discrepancy could be the definition of atopy. We used a cutoff of 0.10 kU_A/L, the commonly used cutoff in the clinical setting in Sweden, whereas the study from the United States had a higher cutoff (≥ 0.7 kU_A/L). Furthermore, the allergens included in the definition differed depending on exposure (birch/timothy/cat in Sweden, dust mites/ragweed/timothy in the United States).

Interestingly, atopy was found to increase the risk of having anaphylaxis with respiratory symptoms in patients with AGS. However, no association was found with asthma, which is probably due to the lower number of patients having asthma compared with being atopic. This is in line with a larger study on anaphylactic patients in Central Europe that also showed that the presence of atopic diseases was associated with respiratory symptoms during anaphylaxis.³¹ Sensitization to airborne allergens establishes an environment in the lung that promotes airway inflammation. This has previously, for example, been shown in mouse models where nasal sensitization induced infiltration of immune cells, and led to inflammation in the lungs on challenge with an unrelated allergen.³⁸⁻⁴⁰

In conclusion, here we provide the first detailed description of AGS in a large, European cohort of patients with AGS. Patients with AGS were found to form a relatively uniform group of middle aged males and females, mainly suffering from urticaria and GI symptoms as well as anaphylaxis. More than half of the patients were found to be atopic and atopy increased the risk of experiencing anaphylactic symptoms in the respiratory system. As AGS is a relatively new and upcoming disease, knowledge of the patients' detailed clinical and immunological characteristics is warranted to increase the awareness and management of the syndrome.

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ONLINE REPOSITORY

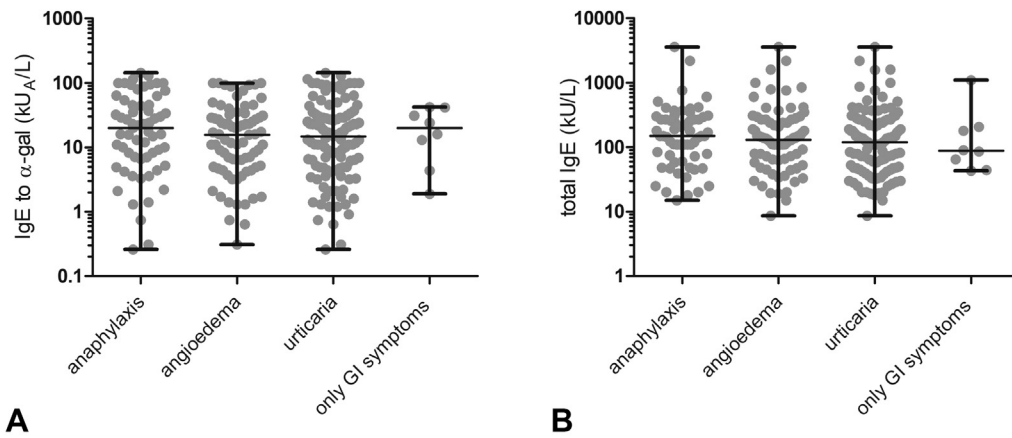


FIGURE E1. (A) α -Gal-specific IgE and (B) total IgE levels in patients with only GI symptoms versus patients with other common symptoms. α -Gal, Galactose- α -1,3-galactose; GI, gastrointestinal.

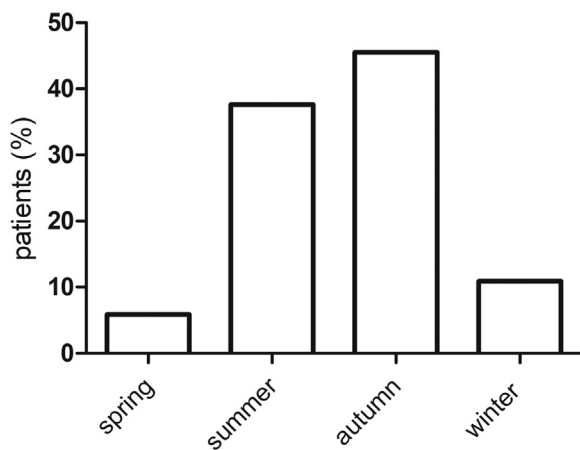


FIGURE E2. Seasonal fluctuations in disease onset.

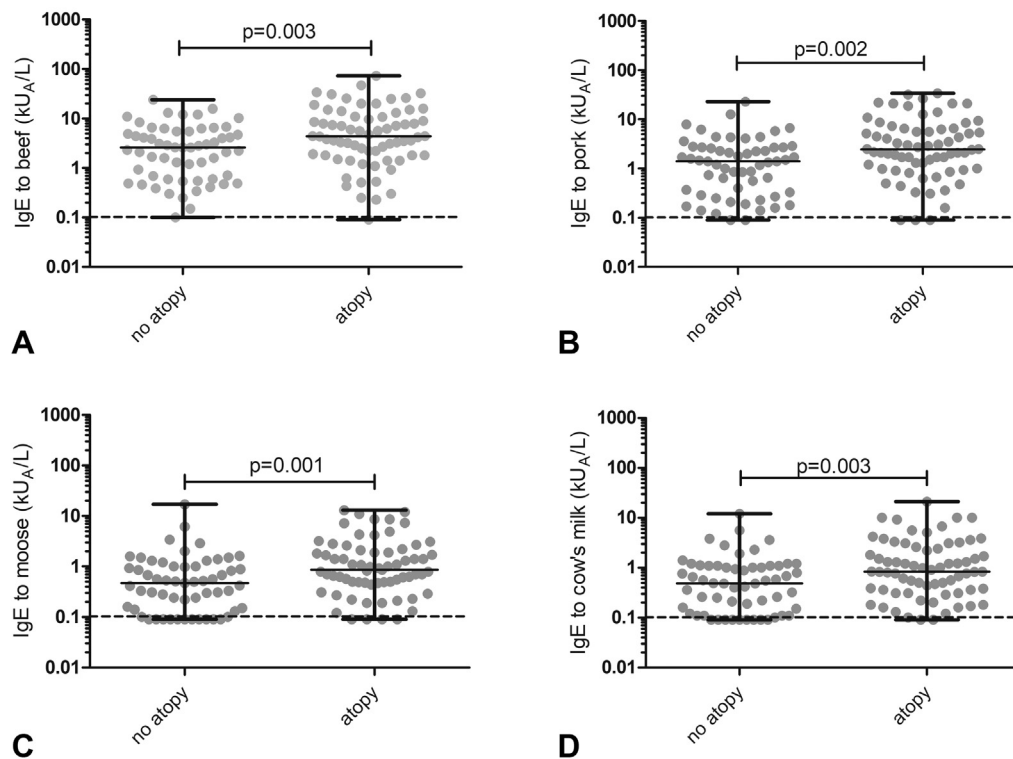


FIGURE E3. IgE levels against (A) beef, (B) pork, (C) moose, and (D) cow's milk in patients with AGS with or without atopy. AGS, Galactose- α -1,3-galactose syndrome.

TABLE E1. Serological characterization in relation to AGS

Extract	Sensitized patients (%)	IgE, median kU _A /L (min-max)
Beef	98.4	3.55 (0.15-73.0)
Pork	96.1	2.1 (0.12-34.0)
Moose	86.7	0.82 (0.1-17.00)
Milk	91.4	0.82 (0.1-21.0)
Cat	75.0	0.58 (0.1-100.0)
Dog	83.6	0.64 (0.1-19.0)
Chicken	7.0	0.28 (0.13-1.4)

AGS, Galactose- α -1,3-galactose syndrome.

TABLE E2. ROC curve analysis to estimate the predictive value of IgE against α -Gal and beef, for the presence of a symptom in patients with AGS

Symptom	IgE	AUC	95% CI	P value
Anaphylaxis	α -Gal	0.6134	0.5149-0.7119	.03
	Beef	0.6075	0.5090-0.7061	.04
GI	α -Gal	0.5992	0.4821-0.7164	.09
	Beef	0.5622	0.4442-0.6802	.29
Urticaria	α -Gal	0.5084	0.3622-0.6545	.92
	Beef	0.6515	0.5337-0.7693	.07
Angioedema	α -Gal	0.5119	0.4057-0.6182	.82
	Beef	0.5134	0.4115-0.6153	.80

α -Gal, Galactose- α -1,3-galactose; AGS, α -Gal syndrome; AUC, area under the curve; CI, confidence interval; GI, gastrointestinal; ROC, receiver operating characteristic.

Bold values are significant at $P < .05$.