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Exploring food-specific IgG responses in pediatric allergic disorders: A retrospective cross-sectional study

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Abstract
Background: The role of immunoglobulin G (IgG) responses to food as potential triggering factors in allergic disorders continues to be debatable, and is not endorsed by most allergy societies.
Objective: To explore the prevalence of specific IgG immune responses to common foods in pediatric allergic disorders and any potential relationship between them.
Methods: A retrospective study was conducted on children and adolescents diagnosed with allergic disorders at the Ekthar Clinic in Jeddah City. Food-specific IgG (FS-IgG) antibody test results were collected from their medical records.
Results: Seventy-five children with a mean age of 8.5 years (SD = 5.3) were included. The overall allergic diagnosis determined atopic dermatitis as the most common (57.3%, 43 participants), followed by food allergy and allergic rhinitis (each 40%, 30 participants), and bronchial asthma (29.3%, 22 participants). Food-specific IgG levels were elevated in all participants. The foods with the highest levels of FS-IgG were dairy products (88%: cow's milk [86.6%], sour milk [81.3%], sheep's milk [74.7%], cheese [72%], and goat's milk [70.7%]), followed by gluten-containing products (81.3%: wheat [70.7%], gluten [69.3%], and spelt [66.6%]), and eggs (66.6%). Significant correlations ($P < 0.05$) were found between atopic dermatitis and several foods; chronic urticaria and chicken and lamb; asthma and ocean perch; allergic rhinitis and rennet cheese; and allergic conjunctivitis and potato, pollock, and lamb.
Conclusion: Among pediatric allergic disorders, dairy, gluten, and eggs were the most detected foods in FS-IgG tests, with some notable correlations with other foods. FS-IgG testing may help identify potential triggers in refractory allergic disorders.

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Introduction

Allergic disorders have increased significantly worldwide in recent decades, with prevalence rates ranging from 10–30% of the population[1] and rates reaching up to 40% in children.[2] The profound impact of these diseases on patients' physical, psychological, and social well-being is a cause for concern.

Allergic disorders have various mechanisms, including atopic dermatitis, bronchial asthma, allergic rhinitis, allergic conjunctivitis, and food allergies.[2] Immunoglobulin E (IgE) antibodies are a common mediator. However, patients with allergic disorders and clinicians know that other mechanisms can also trigger reactions, necessitating further research and understanding.[3]

Adverse responses to food due to immune mechanisms are typically categorized into two types: (a) those mediated by IgE antibodies, which are characteristic of food allergy; (b) those mediated by IgG antibodies, which are involved in food intolerance.[4] Clinical observations have suggested that food-specific IgG (FS-IgG) antibodies may be linked with some delayed adverse food reactions.[5]

Globally, the prevalence of IgE-mediated food allergies is around 3–10% among children.[3] However, most food reactions reported by the general population are probably due to food intolerance, even though the exact prevalence of non-IgE food allergy remains uncertain. Conditions such as food protein-induced enterocolitis syndrome and food protein-induced allergic proctocolitis are estimated to affect less than 1% of children.[6]

Lately, the prevalence of allergic diseases has been rising among patients with non-IgE-mediated food allergies.[7] Furthermore, food consumption may exacerbate certain allergic diseases due to IgE-mediated or non-IgE-mediated mechanisms.[8] The primary symptoms of non-IgE-mediated food allergy typically manifest in the gastrointestinal system but could involve the skin and lungs.[5]

In a review, food can exacerbate asthma attacks and lead to severe asthma, and eliminating certain foods may improve asthma control.[9] A significant improvement in peak expiratory flow rate was found in asthmatic children who avoided milk and eggs.[10] Also, food may exacerbate atopic dermatitis in children based on challenge tests,[11] and diet elimination may decrease its severity.[12] Moreover, food elimination in refractory allergic rhinitis may be an effective adjuvant treatment.[13]

However, the effectiveness of exclusion diets for managing children with allergic disorders remains controversial and contested due to limited research and conflicting findings.[14] Furthermore, healthy people produce and maintain FS-IgG antibodies against some food antigens. Disturbances in antigen or antibody levels may lead to immune complexes that cause disease.[15]

Notably, most updated management guidelines of international allergy societies for diagnosing allergic disorders recommend against performing food IgE testing in any allergic disorders without a history consistent with potential IgE-mediated food allergy. Additionally, they do not recommend the search for any FS-IgG as a possible triggering factor in allergic disorders, due to the lack of solid evidence of such a trigger.[3,16–19]

Despite the controversy, according to a recent review, IgG-mediated food hypersensitivity has been associated with a wide range of specific and nonspecific symptomatology, which has been implicated in many allergy disorders.[20] Hence, this study aims to explore any IgG immune responses to common foods in children with allergic disorders in Saudi Arabia.

Methodology

Study design and population

A retrospective cross-sectional study assessed the utility of testing for FS-IgG in children diagnosed with allergic disorders. This study aims to determine FS-IgG prevalence in children and explore potential associations between IgG-reactive foods and allergic disorders.

The study involved a review of electronic medical records between 2021 and 2023 (January 2021 to April 2023). Seventy-five male and female patients aged between 1 and 18 years who attended the Ekthar allergy clinic in Jeddah with allergic disorders such as atopic dermatitis, bronchial asthma, allergic rhinitis, allergic conjunctivitis, urticaria, and angioedema were included in the study. Pediatric cases with chronic diseases such as congenital heart disease, chronic kidney disease, and systemic diseases or immunosuppressive disorders were excluded from the study because they could potentially confound the results related to FS-IgG testing in allergic disorders.

The data collection sheet included each patient's age, gender, chief complaint, and primary and secondary diagnoses. The chief complaint determined the primary diagnosis, whereas the secondary diagnosis involved identifying any additional allergic disorders noted in the child's medical history. Furthermore, the FS-IgG identified through the ImuPro test was recorded for each participant, including the food items and corresponding antibody levels.

Ethical approvals

The study adhered to ethical standards and received the required approvals from the Ekthar Clinic administration department. Throughout the research, patient confidentiality and data protection were strictly maintained, and verbal consent was obtained from all participants.

Food-specific serum IgG assays

ImuPro (R) is an enzyme-linked immunosorbent assay (ELISA) for FS-IgG used to measure concentrations in 90 different foods. The results were read using a Dynex ELISA reader (Dynex Technologies, Inc., Chantilly, VA, USA) at 450 nm. The IgG concentration of each food antigen was expressed as units per milliliter. Then, the results were categorized into normal, high, and very high levels.

Descriptive statistics

The data were analyzed using Statistical Package for the Social Sciences (SPSS) software (IBM Corp. Released 2012.

IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Qualitative variables were expressed using percentages, while mean and standard deviations were used for quantitative variables. The prevalence was determined by calculating the proportion of participants with elevated FS-IgG levels. Associations between IgG-reactive foods and allergic disorders were assessed using the Kruskal–Wallis test to analyze non-normally distributed data. This study aimed to assess the differences in the mean ranks IgG levels among different groups.

Results

The study included 75 participants, with a nearly equal distribution between males (50.7%) and females (49.3%). The mean age of the participants was 8.5 years, with a standard deviation (SD) of 5.3 years. When categorized by age, the predominant study groups were preschool children (1–5 years) and adolescents (13–18 years) (34.7% each); see Table 1.

Leading primary allergic diagnoses were atopic dermatitis (42.6%), bronchial asthma (18.7%), and food allergy (18.7%).

Table 1 The demographic and clinical characteristics of the participants.

		Frequency	Percent
Gender	Male	38	50.7
	Female	37	49.3
Age	Range	1–18	
	Mean ± SD	8.5 ± 5.3	
Age categorization	Preschool children	26	34.7
	School-aged children	23	30.6
	Adolescents	26	34.7
Primary diagnosis	Atopic dermatitis	32	42.7
	Bronchial asthma	14	18.7
	Food allergy	14	18.7
	Urticaria	7	9.3
	Angioedema	4	5.3
	Allergic conjunctivitis	2	2.7
	Allergic rhinitis	2	2.7

SD: Standard deviation.

All demographics and clinical characteristics of the participants are listed in Table 1.

Among the overall (primary and secondary) allergic diagnoses surveyed, atopic dermatitis was the most common diagnosis (57.3%), followed by food allergy and allergic rhinitis (40.0% each), and bronchial asthma (29.3%); see Table 2.

Table 3 represents data on the top 20 foods associated with abnormally elevated (high and very high) levels of FS-IgG and their means. Dairy products were in the lead (88%: cow's milk [86.6%], sour milk [81.3%], sheep's milk [74.7%], cheese [72%], and goat's milk [70.7%]), followed by gluten-containing products (81.3%: wheat [70.7%], gluten [69.3%], and spelt [66.6%]), eggs (66.6%), and oats (58.7%).

The statistical analysis of mean FS-IgG ranks revealed several significant correlations and associations ($P < 0.05$). A significant association was observed between patients with atopic dermatitis and various foods, such as aubergine, broccoli, chili cayenne, courgette, cucumber, leek, olive, onion, sweet pepper, buckwheat, rice, lamb's lettuce, mustard, oregano, paprika, pepper, thyme, grape, kiwi, lemon, nectarine, linseed, pumpkin, walnut, peppermint, and yeast.

Moreover, a high mean rank of FS-IgG for ocean perch was exclusively associated with patients with asthma. By contrast, a high mean rank of FS-IgG for the meadow mushroom was distinctly correlated with non-asthmatic children. In patients with allergic rhinitis, a significant correlation was found exclusively with a high mean rank of FS-IgG for rennet cheese. Patients with allergic conjunctivitis exhibited significant correlations with elevated mean ranks of FS-IgG for potato, Pollock fish, and lamb meat. Furthermore, a high mean rank of FS-IgG for chicken and lamb was significantly associated with chronic urticaria. None of the tested foods showed any correlation with angioedema.

Intriguingly, maize, rice, guar flour, Pollock, salmon, beef, lamb, black pepper, banana, and pineapple were significantly correlated with four or more allergic disorders. Conversely, the meadow mushroom was significantly correlated with fewer allergic disorders.

Discussion

IgG antibodies are crucial in defending the body, yet they significantly mediate inflammation when in complexes.[21]

Table 2 The history of overall primary and secondary allergic diagnoses in descending order.

Overall allergic disorders	Present		Absent	
	Frequency	Percent	Frequency	Percent
Atopic dermatitis	43	57.3	32	42.7
Allergic rhinitis	30	40.0	45	60.0
Food allergy	30	40.0	45	60.0
Bronchial asthma	22	29.3	53	70.7
Angioedema	9	12.0	66	88.0
Urticaria	9	12	66	88.0
Allergic conjunctivitis	6	8.0	69	92.0

Table 3 The top 20 foods according to the highest abnormal food-specific IgG test levels.

Food	Normal		High levels of FS-IgG		Very high levels of FS-IgG		Abnormal FS-IgG levels (high and very high)		Mean ± SD
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Cow's milk	10	13.3	13	17.3	52	69.3	65	86.6	63.0 ± 51.7
Sour milk	14	18.7	16	21.3	45	60	61	81.3	46.0 ± 44.4
Sheep milk	19	25.3	21	28	35	46.7	56	74.7	40.2 ± 45.5
Rennet cheese	21	28	20	26.7	34	45.3	54	72	41.4 ± 49.6
Goat milk	22	29.3	23	30.7	30	40	53	70.7	35.1 ± 41.3
Wheat	22	29.3	12	16	41	54.7	53	70.7	36.9 ± 39.8
Gluten	23	30.7	24	32	28	37.3	52	69.3	25.9 ± 29.7
Spelt	25	33.3	16	21.3	34	45.3	50	66.6	32.8 ± 38.6
Egg	25	33.4	23	30.6	27	36	50	66.6	32.6 ± 43.3
Oat	31	41.3	20	26.7	24	32	44	58.7	29.1 ± 43.7
Rye	33	44	21	28	21	28	42	56	19.7 ± 27.0
Pistachio	34	45.3	21	28	20	26.7	41	54.7	24.2 ± 35.2
Barley	36	48	27	36	12	16	39	52	16.4 ± 32.1
Cashew	40	53.3	19	25.3	16	21.3	35	46.6	20.9 ± 32.1
Kiwi	40	53.3	19	25.3	16	21.3	35	46.6	16.3 ± 23.9
Soya	40	53.3	25	33.3	10	13.3	35	46.6	11.9 ± 14.7
Hazelnut	41	54.7	10	13.3	24	32	34	45.3	23.0 ± 34.2
Orange	41	54.7	17	22.7	17	22.7	34	45.4	15.7 ± 21.9
Red cabbage	44	58.7	18	24	13	17.3	31	41.3	13.7 ± 20.5
Sesame	44	58.7	19	25.3	12	16	31	41.3	26.1 ± 39.7

Their role in allergic disorders remains to be clarified. When the immune system produces improper immune responses from FS-IgG antibodies, these antibodies may form complexes with food antigens and be capable of initiating an inflammatory response.[22] It could thus be hypothesized that persistent inflammation, induced by food, might be the potential underlying cause of refractory treatment observed in some allergic disorders.

According to the literature review, this is the first study to explore the relationship between FS-IgG antibodies and children with allergic disorders in Saudi Arabia. Surprisingly, all participating children had high levels of FS-IgG for the foods tested, which is more prevalent than in other reported studies. The most commonly detected foods were dairy, those containing gluten, and eggs, and this finding is close to other previously published studies.

The study reveals consistent patterns and some similarities in the distribution of high FS-IgG in children with allergic disorders across different countries. A study from Poland found that over half of the children with food allergies had high FS-IgG levels for milk, eggs, and wheat flour.[23] A study from China found high FS-IgG levels, mainly for eggs, wheat, and milk, in children with atopic dermatitis and chronic urticaria.[24] A large-scale Chinese study with food intolerance showed that nearly all children had high FS-IgG levels, notably for eggs, milk, and soybeans.[25] In Saudi Arabia, a retrospective study revealed that among children and adult patients with allergic disorders, high FS-IgG foods were cola nuts, yeast, wheat, beans, peas, corn, and eggs.[26] In another Saudi study, the top five foods associated with high FS-IgG in children were, in descending order, cow's milk, oats, sour milk, rennet cheese, and ricotta cheese.[27]

These findings highlight a significant association between FS-IgG in children with allergic disorders. Atopic dermatitis correlated significantly with the high mean ranks of FS-IgG antibodies for several foods (vegetables, fruits, spices, and others). Furthermore, urticaria was significantly associated with chicken and lamb, but no food correlated with angioedema. Interestingly, ocean perch uniquely correlated with asthmatic patients, and the meadow mushroom correlated with non-asthmatic children. Moreover, only cheese correlated significantly with allergic rhinitis, while potato, pollock fish, and lamb correlated with allergic conjunctivitis.

In comparison, a study from Taiwan found that high FS-IgG for egg whites, milk, peanuts, and almonds had significant correlations with allergic rhinitis in children.[28] A Chinese study of children with atopic dermatitis revealed a significant association between the high FS-IgG levels for eggs, milk, tomatoes, and soybeans compared with that in children without atopic dermatitis.[29] Another study from China found a notable association between high FS-IgG levels for milk and asthma, allergic rhinitis, and allergic conjunctivitis.[30]

The present study detected statistical significance between foods associated with FS-IgG and multiple allergic disorders. However, the meadow mushroom was linked to a single rather than multiple allergic disorders. A recent publication from China revealed an association between high FS-IgG levels for wheat and soybeans and multiple allergic disorders. Still, the meadow mushroom was not associated with allergic disorders.[30] This pattern suggests that certain foods may have a systemic effect on children with allergic disorders, affecting multiple organ systems. It highlights

the need for a broad approach to dietary management in patients with allergic disorders.

Currently, elimination diets based on FS-IgG for diagnosing and managing allergic disorders are limited and controversial. On the one hand, a study of children with allergic disorders in China revealed a remarkable improvement following elimination diets based on FS-IgG testing.[30] Another study from Japan on children with atopic dermatitis showed that the level of FS-IgG decreases after food avoidance.[31] On the other hand, two studies of children with atopic dermatitis showed no improvement after avoiding foods based on FS-IgG tests.[32,33]

Conflicting findings from clinical studies suggest a complex interplay between dietary factors and allergic disorders; further investigation is warranted to uncover the possible explanation of these associations. These observations align with emerging theories that non-IgE-mediated responses, particularly those involving IgG, may significantly contribute to the inflammation observed in allergic disorders. Understanding these mechanisms could lead to more targeted therapeutic approaches to manage allergic symptoms associated with specific food sensitivities.

This study had some limitations. Firstly, retrospective studies are inherently limited by the data originally recorded; thus, the accuracy and completeness of the medical records dictate the quality of the data available for analysis. Secondly, it included a small and convenient sample of participants from a single allergy immunology clinic. Thirdly, the absence of a control group of nonallergic children makes it challenging to attribute the observed IgG responses solely to allergies definitively. Lastly, further follow-up to monitor improvement in the children's conditions is necessary to establish a definitive causal relationship between FS-IgG testing and allergic disorders. These limitations stress the need for larger prospective studies with control groups in future to explain the role of FS-IgG antibody testing in pediatric allergic disorders.

In conclusion, this study contributes to the growing body of literature suggesting that IgG-mediated food sensitivities are more relevant in the context of allergic diseases in children than previously understood. To the authors' knowledge, this is the first report of FS-IgG testing among pediatric patients with allergic disorders in Saudi Arabia. It showed that dairy, gluten, and eggs were the most detected foods and that some allergic disorders had significant correlations with certain foods. The potential for food identification based on IgG tests in uncontrolled allergic disorders as a valuable adjuvant investigational tool is intriguing. Therefore, it is necessary to conduct longitudinal controlled trials to evaluate the benefit of dietary elimination based on FS-IgG test results and its long-term outcomes on allergic symptoms. This may help to solidify the role of FS-IgG testing in clinical practice to guide the elimination of potential triggering foods that can be considered in the management of allergic patients with persistent symptoms.

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