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Article type : Research Letter

20/11/25

Specific IgE Antibody Levels during and after Food-induced Anaphylaxis

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/CEA.13796](https://doi.org/10.1111/CEA.13796)

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Funding: AllerGen NCE – Conflict of Interests: None

Acknowledgements: only authors listed above contributed to the manuscript

Word count: 1509 – 4 tables and 1 figure

To the Editor:

Food-induced allergic reactions are diagnosed through corroboration of a suggestive clinical history with appropriate confirmatory tests. The major confirmatory tests include skin prick tests and serum specific immunoglobulin E (sIgE) levels. When the diagnosis is inconclusive, oral food challenges are performed (1).

In clinical practice it is believed that skin prick tests and serum sIgE levels should not be measured during anaphylaxis, the most severe manifestation of food-induced allergy (2). It is advised to wait at least one month after the reaction before proceeding with these confirmatory tests to avoid false negative results (2). Nonetheless, there are little data on the temporal trends of sIgE levels during and after food-induced anaphylaxis. Further, there are no data on the change in sIgE levels for a culprit allergen in comparison to other sIgE levels for known tolerated foods during the same time points.

We aim to assess the differences in food sIgE levels during, and after anaphylaxis for culprit allergens and unrelated tolerated foods.

Children presenting to the Emergency Department of the Montreal Children's Hospital with food-induced anaphylaxis were recruited for the Cross-Canada Anaphylaxis Registry (C-CARE) between 2012 and 2019. Patients were identified and informed consent was obtained by a member of the research team for collection of data and blood. Anaphylaxis was defined when at least two organ systems were involved in the allergic reaction, or if hypotension occurred (3). Severity was defined according to a grading system established in a position paper on management of childhood anaphylaxis (4).

A standardized data entry form was used to document symptoms, triggers and management of anaphylaxis as previously described (5). Two to four hours after symptoms occurred, tryptase and sIgE levels of the reported culprit food allergen as well as of an unrelated tolerated food were assessed. The unrelated food was known to be tolerated by the patient and was not ingested around the time of anaphylaxis. It can include any of the foods listed in Table 1 as food triggers.

Tryptase and sIgE levels of the culprit food allergen and an unrelated tolerated food were also assessed a second time after the reaction. The goal was to include as many time points as possible between the reaction and the post-reaction measurements. The earliest post-reaction measurements could only be obtained 1-week after the onset of symptoms. Only cases in which the culprit food allergen was clearly reported and subsequently established based on allergist assessment through corroboration of history, positive skin tests, or food challenge were included. SIgE levels were measured using PhadiaImmunoCAP. SIgE and tryptase levels during and after reaction were logged and compared with the parametric paired t-test. Multivariable linear regression models adjusted for age and sex were used to evaluate factors associated with changes in sIgE levels of the suspected culprit allergen including time interval between measurements during and after anaphylaxis, tryptase levels difference during and after anaphylaxis, reaction severity, and atopy. All statistical analyses were done using R version 4.0.0 (R core Team [2013]; R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the ethics committee of the Montreal Children's Hospital- McGill University Research Ethics Board. C-CARE Study (Cross Canada Anaphylaxis Registry). Reb study # is GEN 10-203.

Among 53 pediatric patients between 4 months and 17 years old, the median age was 1.9 years [Interquartile Range (IQR: 1.0-4.9)] and 43.9% were males (Table 1). sIgE levels of the reported culprit allergen increased on average 1.67 (95% CI [1.32, 2.14]) fold after anaphylaxis (Table 2, Figure 1). Among the 36 patients who had sIgE levels of unrelated tolerated foods measured, the difference during reaction and post-reaction was not substantial (0.90 (95% CI [0.72, 1.11])) (Table 2). Tryptase levels during and after anaphylaxis were measured in 49 of the 53 children. All had higher levels during the reaction, which subsequently decreased. Thirty-two children (65.3%) had a difference of at least $2 \text{ ug/L} + 1.2 \times [\text{postreaction tryptase level}]$ consistent with the expected change during anaphylaxis (5).

The median time interval between measurements during and after reaction was 4 weeks (IQR= 3.0-8.0) and the range was 1 to 260 weeks (Table 1).

A subset of five patients had culprit sIgE levels measured before and during the reaction (Table 3). This data was added to assess if sIgE levels to culprit foods decreased during reaction and increased back to baseline levels afterwards versus whether the levels were low at baseline and increased following anaphylaxis. The mean sIgE levels during reaction correspond to 0.85 (95% CI [0.63, 1.13]) of pre-reaction levels. The median time interval between measurements before and during reaction was 4 weeks (IQR= 4.0-5.0) and the range was 2 to 260 weeks (Table 3). Since we cannot predict which patients will have an anaphylactic reaction and to what specific allergen, it is challenging to get data prior to reaction. Hence, our pre-reaction sIgE levels sample was limited.

Children with atopic disease were more likely to have a higher difference in sIgE levels for the reported culprit allergen (beta-coefficient 17, 95% CI [5.2, 30]) (Table 4). In other words, in those with history of atopy, sIgE levels increased on average by 17 kUa/L after reaction. The time interval between measurements during and after anaphylaxis does not appear to significantly influence the difference in sIgE levels for the reported culprit allergen (beta-coefficient -0.05, 95% CI [-0.017, 0.07]) (Table 4).

Our study reveals for the first time that sIgE levels to culprit foods increase after an anaphylactic reaction while sIgE levels to unrelated tolerated foods do not change substantially. This concept suggests that changes in sIgE levels may contribute to identification of the true culprit food when history is unclear. Nonetheless, at this point it is not clear if the average 1.67-fold increase in allergen sIgE levels is clinically significant or if smaller changes will occur with allergic reactions that are not anaphylactic. Further, it is reported that IgE levels decrease over time and hence the absolute differences in IgE levels might change over time in the same patient (6). In future studies, it would be interesting to stratify data by culprit food as this might allow the discovery of allergen-specific average values that might be more clinically significant and allow better reproducibility of the results. In addition to sIgE levels for unrelated tolerated foods, it would be useful to measure levels for known allergens that recruited patients were not exposed to during the documented reaction.

It is reported that during anaphylaxis basophils migrate in response to IgE-mediated stimulation likely through the secretion of monocyte chemoattractant protein-1 from mast cells (7). The lower levels of sIgE during anaphylaxis may serve as a protective mechanism as it would further reduce the risk of basophile degranulation in the circulation and the development of more systemic symptoms (7). It is also possible that sIgE levels to culprit foods drop during anaphylaxis due to consumption of

culprit IgE during the reaction (8). However, only 5 of 53 children had sIgE levels for culprit foods measured before the reaction. More data is needed to study these hypotheses.

Children with underlying atopic disease, had higher sIgE levels after anaphylaxis. The higher likelihood of Th2 response in children with atopy possibly accounts for the higher differences in sIgE levels (9).

We conducted a prospective study on the temporal trends of sIgE after food-induced anaphylaxis. As mentioned previously, clinical practice recommends a delay in testing due to the expectation of false-negative results occurring up to four weeks after an allergic reaction (2). This premise was challenged in a study on venom allergy that showed that skin test and serum- venom-specific IgE performed within one week after a systemic reaction can yield positive results in more than three-quarters of patients following insect sting anaphylaxis (10). However, this study did not assess food-induced anaphylaxis. Our study is the first to provide insight into the temporal trends of sIgE for food-induced anaphylaxis. We did not compare changes in sIgE in food induced anaphylaxis versus drug or venom induced anaphylaxis. However, we expect similar trends given that recent studies by our group and others reveal that tryptase levels consistent with anaphylaxis occur in the majority of cases induced by food in children (5).

We could not ascertain if the number of weeks between measurements during and after reaction influences changes in culprit sIgE levels since our results are not statistically significant.

Consequently, we could not determine the optimal time interval to detect elevation of sIgE.

This can be attributed to our small sample size that reflect the difficulty of getting patients to return for repeat testing. Our study has additional potential limitations. All recruited patients were children recruited at one center. Furthermore, measurements of total IgE levels would be a good addition to better assess if there were any significant changes in IgE levels not accounted for by the increase in sIgE levels of culprit foods.

In conclusion, our study shows that following anaphylaxis, sIgE levels to culprit food allergens increase, while sIgE levels to unrelated tolerated foods do not change substantially. These findings suggest a potential innovative use of time-dependent changes in sIgE levels as a method to identify the culprit food when history is unclear. Further studies with a larger sample size and additional time points before and after anaphylaxis are needed to better assess the temporal trends of sIgE levels and characterize its role in diagnosing the cause of anaphylaxis.

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Table 1. Patient Characteristics among Children presenting to the Emergency Department with Anaphylaxis

N = 53	
Range of Age in Years at Reaction	(0.3, 17.3)
Median Age in Years at Reaction (IQR)	1.9 (1.0-4.9)
Number of Males (% male)	29 (43.9%)
Range of Time Interval in Weeks between Measurements during and after Reaction	(1.0-260.0)
Median Time Interval in Weeks between Measurements during and after Reaction (IQR)	4 (3.0-8.0)
Food Trigger	
Tree nut	15 (28.3%)
Egg	12 (22.6%)
Milk	7 (13.2%)

Peanut	7 (13.2%)
Sesame	5 (9.4%)
Soy	2 (3.8%)
Fish	1 (1.9%)
Shellfish	1 (1.9%)
Wheat	1 (1.9%)
Kiwi	1 (1.9%)
Lentils	1 (1.9%)
N = 46	
Reaction Severity (5)	
Mild	12 (26.1%)
Moderate	29 (63.0%)
Severe	5 (10.9%)
N = 50	
Comorbidities	
Atopic Comorbidity	38 (76.0%)
No Atopic Comorbidity	12 (24.0%)
N = 49	
Known Drug Allergy	1 (2.0%)
Admission	
Not Admitted	47 (96.0%)
Intensive Care Unit	1 (2.0%)
Hospital Ward	1 (2.0%)
N = 51	
Outpatient Treatment (outside the Hospital)	
Intramuscular Epinephrine	20 (39.2%)

Antihistamines	23 (45.1%)
Anti-H2	0 (0.0%)
Beta-Agonist	1 (2.0%)
Corticosteroid	0 (0.0%)
Other	4 (7.8%)
No Treatment	16 (31.4%)
Inpatient Treatment	
Intramuscular Epinephrine	31 (60.8%)
Intravenous Epinephrine	1 (2.0%)
Antihistamines	13 (25.5%)
Anti-H2	0 (0.0%)
Beta-Agonist	3 (5.9%)
Corticosteroid	3 (5.9%)
IV Fluids	1 (2.0%)
Other	6 (11.7%)
No Treatment	8 (15.7%)

Table 2. SIgE and Tryptase levels among Children presenting to the Emergency Department during and after Anaphylaxis

Variables	Number of Patients	Average during Reaction	Average after Reaction	Average Difference during and after Reaction	IQR	Range	Average Multiplicative Difference during and after Reaction [95% CI]^a
SIgE levels for Suspected Culprit Allergen (kUa/L)	53	17.4	24.9	7.48	(-0.08, 8.47)	(-1.5, 93.13)	1.67 [1.32, 2.14]
SIgE levels for Unrelated Tolerated Food (kUa/L)	36	15.0	15.7	0.70	(-0.11, 0.16)	(-8.4, 15.8)	0.90 [0.72, 1.11]
Tryptase levels (ug/L)	49	11.1	4.25	6.87	(1.5, 8.2)	(0, 31.2)	0.45 [0.38, 0.52]

a: parametric paired t-test

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Table 3. sIgE Levels for Suspected Culprit Allergen before and during Anaphylaxis in Five patients

Range of Time Interval in Weeks between Measurements before and during Reaction	(2.0-260.0)
Median Time Interval in Weeks between Measurements before and during Reaction (IQR)	4 (4.0-5.0)
Average sIgE levels before Reaction (kUa/L)	45.3
Average sIgE levels during Reaction (kUa/L)	44.0
Average Difference sIgE levels before and during reaction (kUa/L)	-1.30
Average Multiplicative Difference sIgE before and during reaction [95% CI]^a	0.85 [0.63, 1.13]

a: parametric paired t-test

Table 4. Effect of Time and Atopic Comorbidities on SIgE levels Difference during and after Anaphylaxis while adjusting for Age and Sex

Variable(s)	Beta-coefficient (95% CI) ^a
Time Interval in Weeks between Measurements during and after Reaction	-0.05 [-0.17, 0.07]
Age	0.93 [-0.023, 1.9]
Male	-0.78 [-10, 8.5]
Comorbidities	
• Atopic Comorbidity	17 [5.2, 30]
• No Atopic Comorbidity (reference)	
Age	0.02 [-9.2, 9.2]
Male	-0.55 [-15, 14]

a: multivariable linear regression model

Accepted Article

