

Clinical Communications

Long-term dynamics of omega-5 gliadin-specific IgE levels in patients with adult-onset wheat allergy

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Clinical Implications

- Omega-5 gliadin-specific IgE levels in the majority (>85%) of patients with adult-onset omega-5 gliadin allergy did not decrease over time during several years of observation, implying a poor prognosis for this disease.

TO THE EDITOR:

Wheat is a recognized cause of adult-onset food allergy, but the etiology, presentation, and possibly disease prognosis of adult-onset wheat allergy (WA) is heterogeneous. In Japan, there has been a recent epidemic of WA caused by skin and/or rhinoconjunctival sensitization to hydrolyzed wheat protein (HWP) contained in facial soap.¹ In this case, decreased gluten-specific IgE levels and attenuation of WA symptoms over time, after discontinuing use of the soap, have been documented in most patients.²

A common clinical phenotype of adult-onset WA worldwide is wheat-dependent exercise-induced anaphylaxis, characterized typically by anaphylaxis after exercise following wheat ingestion

and accompanied by elevated levels of specific IgE-antibody to omega-5 gliadin (O5G). More recently, Kennard et al³ have suggested “omega-5 gliadin allergy” as a more precise nomenclature for this disease entity, considering that some patients experience WA symptoms even with other cofactors such as alcohol, nonsteroidal anti-inflammatory drugs, or in some cases without identifiable cofactors at all.⁴ However, the long-term prognosis of patients with this disease entity has not been well documented so far and it is not known whether IgE levels also decrease over time, as with HWP-induced WA.⁵ Because the dynamics of IgE levels over time may have some predictive value for allergy outcome,⁶ we hypothesized that prognosis for these patients could be predicted by sequential monitoring of O5G-specific IgE.

To this end, to study the dynamics of changes in O5G-specific IgE levels, we performed a retrospective medical chart-based review of 111 consecutive adult (≥ 16 years) outpatients with adult-onset O5G allergy, in more than 95% of which exercise was a cofactor (commonly known as wheat-dependent exercise-induced anaphylaxis) (see Table E1 in this article’s Online Repository at www.jaci-inpractice.org), seen at 6 hospitals in Japan between November 2010 and October 2014. All recorded data on IgE levels at each outpatient visit up to November 2016 were analyzed. IgE specific for O5G was usually quantified at the time of routine outpatient monitoring. O5G allergy was defined as meeting the following 2 criteria: first, allergic symptoms to wheat identified by (a) 2 or more reliable positive histories of immediate allergic symptoms following ingestion of wheat products, or (b) positive results on oral provocation tests with wheat; and second, predominant sensitization to O5G, recognized as O5G-specific IgE levels not only positive (≥ 0.35 kU_A/L) but also higher than the gluten-specific IgE levels (as assessed by the ImmunoCAP method; Phadia AB, Uppsala, Sweden) in the same patient. This limitation is essential to exclude WA associated with certain other clinical entities, because some patients with childhood-onset WA, as well

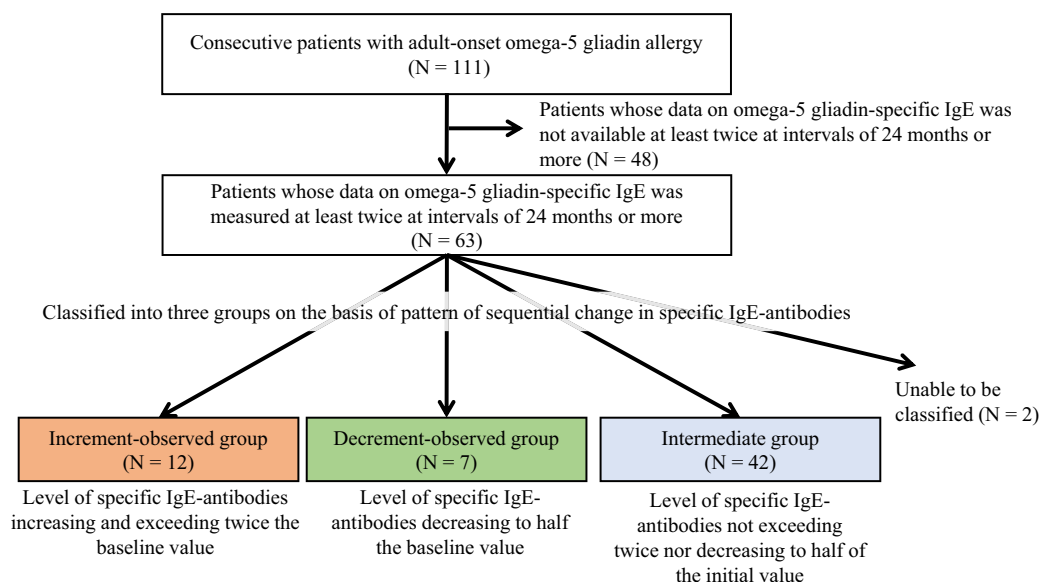


FIGURE 1. Flow chart for patient selection.

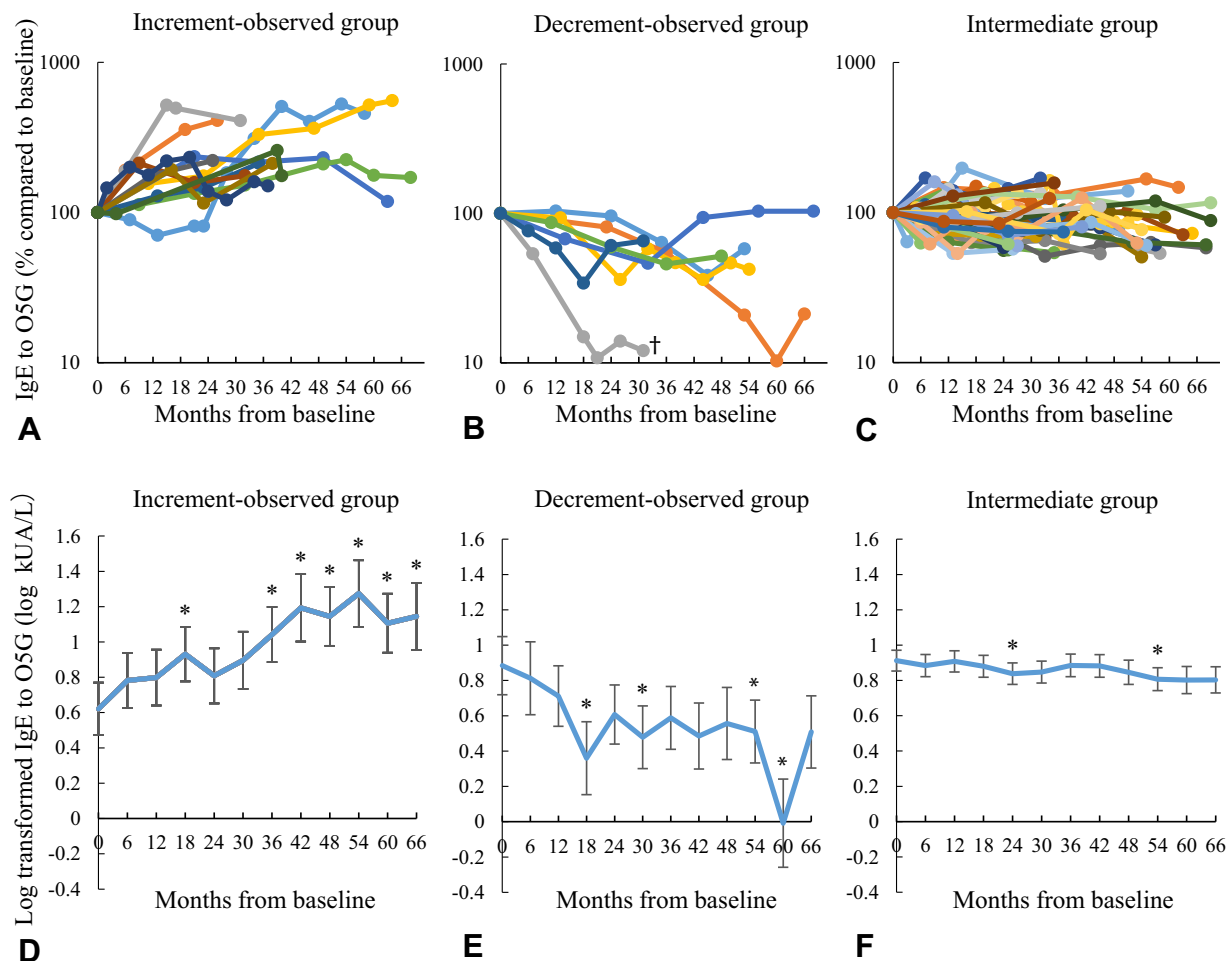


FIGURE 2. Changes in levels of IgE specific for O5G from baseline during the observation period in the 3 groups. Percentage change (A-C) and change in the log-transformed specific IgE levels analyzed with a generalized linear mixed model for repeated-measures analysis (D-F). * $P < .05$ compared with baseline. †Patient classified as sign-off because of remission for outpatient follow-up status.

as WA induced by the use of HWP-containing facial soap, also possess O5G-specific IgE, but the levels are lower than antibodies to gluten.² The present study was approved by the local ethics committees of all participating institutions.

On reviewing the medical record charts, we extracted data on frequencies and details of WA symptoms, WA cofactors, and serum levels of total IgE and IgE specific for wheat, gluten, or O5G at the earliest opportunity after November 2010 (baseline). Because the major aim of this study was to monitor changes in O5G-specific IgE levels, we limited the analysis to patients with relevant data available at least twice at intervals of 24 months or more, estimated to be a sufficient time interval for the evaluation of sequential changes in IgE levels (Figure 1). Patients were stratified into 3 groups on the basis of the pattern of dynamic changes in O5G-IgE levels as follows: (1) “increment-observed group,” defined as specific IgE increasing over time and exceeding twice the baseline value; (2) “decrement-observed group,” defined as specific IgE decreasing to at least half the baseline value; and (3) “intermediate group,” where specific IgE did not exceed twice the baseline value or decrease to half the baseline value over time. Only 2 patients were not classifiable in this way because their IgE levels exceeded twice the baseline value

but also decreased to less than half the baseline value during the observation period (see Figure E2 in this article’s Online Repository at www.jaci-inpractice.org). The status of each outpatient at their last follow-up visit during the observation period was determined by the attending physician as indicated in the medical record, as follows: (1) sign-off due to remission, (2) dropped out, and (3) still being followed up. Data were analyzed using SPSS Version 24.0 (IBM, New York, NY).

The study included 111 consecutive outpatients with adult-onset O5G allergy. We were able to analyze 63 of these patients in detail; the other 48 could not be included because data on O5G-specific IgE were not measured at least twice with an interval of at least 24 months between assessments. The baseline characteristics of the analyzed patients were not significantly different from the baseline characteristics of those not analyzed except for outpatient follow-up status, observation period, and frequency of patients whose WA was confirmed by oral food challenge (Table E1). The number of patients in the increment-observed, decrement-observed, and intermediate groups was 12 (19%), 7 (11.1%), and 42 (66.7%), respectively (Figure 2, A-C; see Figure E1, A-C, in this article’s Online Repository at www.jaci-inpractice.org). For longitudinal data analysis of log-

transformed O5G-specific IgE levels, a linear mixed-effect model with random slope and visit as fixed effects, adjusted by Satterthwaite's approximation, was constructed (Figure 2, D-F). A gradual and significant increase in O5G-IgE level was present in the increment-observed group (Figure 2, D). In contrast, a gradual and significant decrease was observed in the decrement-observed group (Figure 2, E). The level was unchanged in the intermediate group, except for a slight but significant reduction at 24 and 54 months (Figure 2, F). It is important to note that only 1 patient in the decrement-observed group fell into the "sign-off due to remission" outpatient group. O5G-specific IgE levels at baseline and patient characteristics were not significantly different between patients in the 3 groups classified according to the pattern of dynamic changes in O5G-IgE (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

To our knowledge, this is the first study to show that O5G-specific IgE levels in the majority (>85%) of patients with O5G allergy did not decrease over time during several years of observation. The dynamics of specific IgE documented in this study imply a poor prognosis for this disease, and are quite different from what is seen for WA induced by HWP-containing facial soap, where specific IgE levels typically trend down. The reason for this difference cannot be determined in the present study. A possible explanation may be related to the difference in the route of sensitization: sensitization in HWP allergy is known to occur through skin or conjunctiva,⁷ whereas this has not been shown to be the case in O5G allergy where sensitization may occur through different routes including the oral route.⁸ It is generally believed that the prognosis of adult-onset orally sensitized food allergy is poor, although clinical studies supporting this idea have been lacking.

Some limitations of our study are related to its retrospective nature. We were unable to perform oral provocation tests, and did not have any detailed information on wheat consumption status. Nor do we know whether and when the patients experienced WA symptoms during the observational period. This hampers the determination of associations between dynamics of IgE levels and disease prognosis.

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Conflict of interests: Y. Chinuki, Y. Fukutomi, M. Hide, and E. Morita report grants from the Japan Agency for Medical Research and Development, during the conduct of the study. Y. Chinuki reports personal fees from Kaken, Kyowa Hakko Kirin Co., Ltd, Kyorin Pharmaceutical Co., Ltd, Novartis Pharma K.K., MSD K.K., TAIHO Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Santen Pharmaceutical Co., Ltd, and Torii Pharmaceutical Co., Ltd, outside the submitted work. Y. Fukutomi reports personal fees from Thermo Fisher Diagnostics K.K., Torii Pharmaceutical Co., Ltd, Kyorin Pharmaceutical Co., Ltd, Novartis Pharma K.K., MSD K.K., and TAIHO Pharmaceutical Co., Ltd, outside the submitted work. E. Nakatani reports personal fees from Celgene K.K., outside the submitted work. A. Fukunaga reports personal fees from Kaken, Kyorin Pharmaceutical Co., Ltd, Sanofi K.K., TAIHO Pharmaceutical Co., Ltd, Shire Plc, Sumitomo Dainippon Pharma Co., Ltd, Torii Pharmaceutical Co., Ltd, Maruho Co., Ltd, and CSL Bering K.K.; grants and personal fees from Novartis Pharma K.K., and Mitsubishi Tanabe Pharma Corporation, outside the submitted work. M. Hide reports personal fees from Kaken, Kyorin Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Sysmex Corporation, and Teikoku Seiyaku Co., Ltd; grants and personal fees from Kyowa Hakko Kirin Co., Ltd, Novartis Pharma K.K., MSD K.K., TAIHO Pharmaceutical Co. Ltd, SHIONOGI & Co., Ltd, Torii Pharmaceutical Co., Ltd, and Sanofi K.K., outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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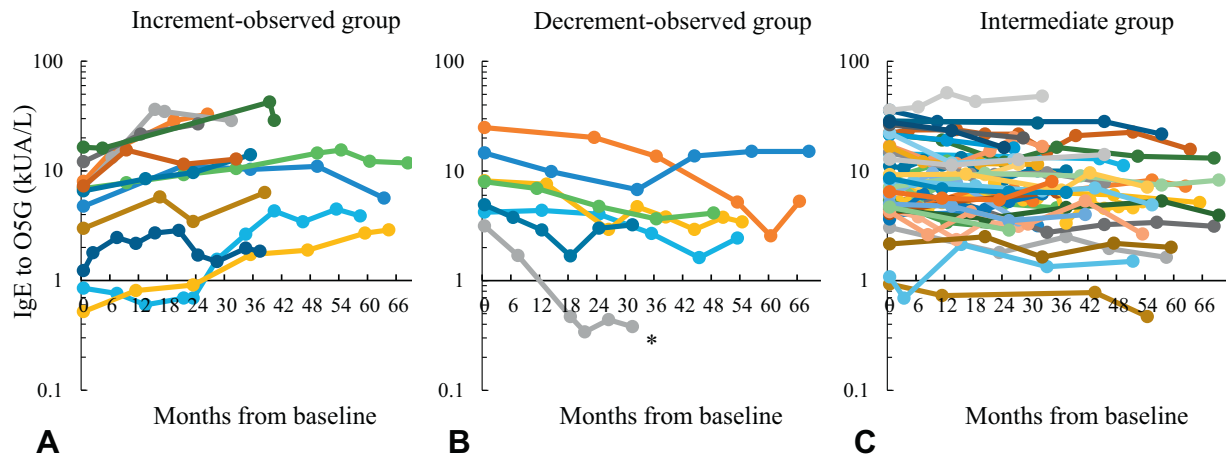


FIGURE E1. Sequential change in IgE specific for O5G during the observation period in the (A) increment-observed group, (B) decrement-observed group (B), and (C) intermediate group. The y-axis is set as a log 10 scale. *Patient classified as sign-off because of remission for outpatient follow-up status.

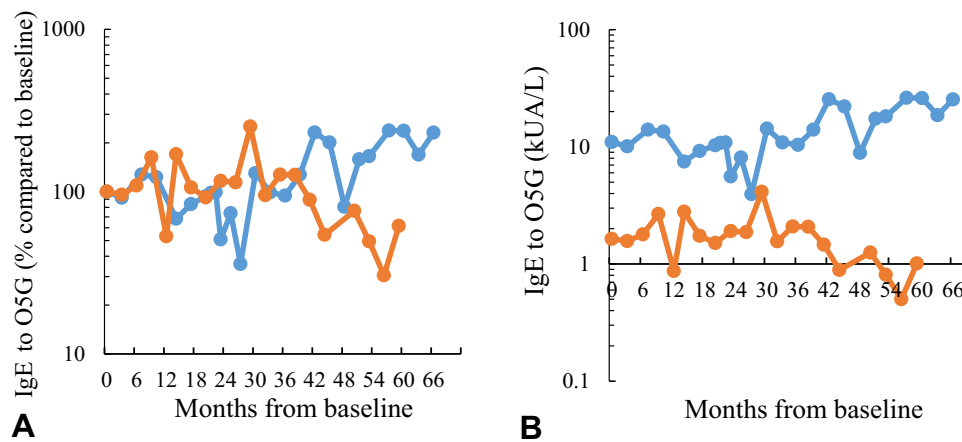


FIGURE E2. Changes in levels of IgE specific for O5G during the observation period for 2 patients who were not classifiable into either group. Percentage change from baseline (A) and sequential change (B). The y-axis is a log 10 scale.

TABLE E1. Patients' characteristics*

Characteristic	Analyzed patients (n = 63)	Not-analyzed patients (n = 48)	P value
Age at the first visit (y), mean $\pm$ SD	47 $\pm$ 15	47 $\pm$ 15	.94
Sex: male, n (%)	40 (64)	35 (73)	.31
Observation period (mo), median (range)	55 (24-69)	0 (0-23)	<.001
Frequency of anaphylaxis by wheat, n (%)			
0	7 (11)	9 (19)	.70
1	29 (46)	19 (40)	
2	10 (16)	8 (17)	
>2	17 (27)	12 (25)	
Symptoms of WA, n (%)			
Skin	63 (100)	48 (100)	1.00
Respiratory tract	22 (35)	15 (31)	.84
Gastrointestinal	14 (22)	8 (17)	.63
Cardiovascular system involvement	50 (79)	33 (69)	.27
Cofactor for WA, n (%)			
Exercise	60 (95)	47 (98)	.63
NSAIDs	6 (10)	6 (13)	.76
WA confirmed by OFC, n (%)	19 (30.2)	4 (8.3)	<.01
Total IgE (kU/L) [†] , median (range)	292.7 (29.1-2777)	339 (35.7-1570)	.51
Specific IgE (ImmunoCAP) (kU _A /L), median (range)			
Wheat [‡]	0.44 (0.34-11.6)	0.68 (0.34-6.4)	.98
Gluten [§]	2.05 (0.34-25.9)	1.20 (0.34-12.3)	.30
O5G	7.09 (0.52-35.9)	6.64 (1.33-52.5)	.46
Outpatient follow-up status, n (%)			
Sign-off due to remission	1 (2)	0 (0)	<.001
Drop-out	7 (11)	36 (75)	
Under follow-up	55 (87)	12 (25)	

NSAID, Nonsteroidal anti-inflammatory drug; OFC, oral food challenge.

To evaluate the statistical differences between the groups, χ^2 test or Fisher exact test was used for categorical variables, and Mann-Whitney *U* test was used for continuous variables. *P* values less than .05 were considered statistically significant. Shapiro-Wilk test was used to evaluate normality.

*Patients in this study were from 6 Japanese hospitals: National Hospital Organization Sagamihara National Hospital, Shimane University Hospital, Fujita Health University Hospital, Kobe University Hospital, Hyogo Prefectural Kakogawa Medical Center, and Hiroshima University Hospital.

[†]Data are available for 57 analyzed patients and 42 not-analyzed patients.

[‡]Data are available for 59 analyzed patients and 45 not-analyzed patients.

[§]Data are available for 62 analyzed patients and 46 not-analyzed patients.

TABLE E2. Patients' characteristics among 3 groups classified by the pattern of dynamic changes in O5G-specific IgE*

Characteristic	Increment-observed group (n = 12)	Intermediate group (n = 42)	Decrement-observed group (n = 7)	P value
Age at the first visit (y), mean $\pm$ SD	47 $\pm$ 14	48 $\pm$ 16	40 $\pm$ 15	.44
Sex: male, n (%)	9 (75)	26 (14)	3 (43)	.39
Observation period (mo), median (range)	38 (25-68)	37 (24-69)	48 (31-68)	.78
Frequency of anaphylaxis by wheat, n (%)				
0	1 (8)	4 (10)	2 (29)	.29
1	6 (50)	20 (48)	1 (14)	
2	2 (17)	8 (19)	0 (0)	
>2	3 (25)	10 (24)	4 (57)	
Symptoms of WA, n (%)				
Skin	12 (100)	42 (100)	7 (100)	1.00
Respiratory tract	3 (25)	15 (36)	2 (29)	.91
Gastrointestinal	2 (17)	11 (26)	1 (14)	.72
Cardiovascular system involvement	11 (92)	31 (74)	5 (71)	.51
Cofactor for WA, n (%)				
Exercise	12 (100)	40 (95)	7 (100)	1.00
NSAIDs	2 (17)	3 (7)	1 (14)	.41
Total IgE (kU/L) [†] , median (range)	272.0 (31.8-610)	308.5 (40.6-2777)	132.5 (29.1-1510)	.17
Specific IgE (ImmunoCAP) (kU _A /L), median (range)				
Wheat [‡]	0.42 (0.34-4.96)	0.46 (0.34-11.6)	0.39 (0.34-4.84)	.85
Gluten [§]	1.35 (0.34-3.01)	2.38 (0.34-25.9)	2.76 (0.86-7.70)	.16
O5G	6.74 (0.52-16.4)	7.61 (0.93-16.2)	7.98 (3.15-24.9)	.25
Outpatient follow-up status, n (%)				
Sign-off due to remission	0 (0)	0 (0)	1 (14)	.21
Drop-out	1 (8)	5 (2)	1 (14)	
Under follow-up	11 (92)	37 (88)	5 (71)	

NSAID, Nonsteroidal anti-inflammatory drug.

To evaluate the statistical differences between the groups, χ^2 test or Fisher exact test was used for categorical variables, and Mann-Whitney *U* test was used for continuous variables. *P* values less than .05 were considered statistically significant. Shapiro-Wilk test was used to evaluate normality.

*Patients in this study were from 6 Japanese hospitals: National Hospital Organization Sagamihara National Hospital, Shimane University Hospital, Fujita Health University Hospital, Kobe University Hospital, Hyogo Prefectural Kakogawa Medical Center, and Hiroshima University Hospital.

[†]Data are available for 11 patients in the increment-observed group, 38 patients in the intermediate group, and 6 patients in the decrement-observed group.

[‡]Data are available for 12 patients in the increment-observed group, 39 patients in the intermediate group, and 6 patients in the decrement-observed group.

[§]Data are available for 12 patients in the increment-observed group, 41 patients in the intermediate group, and 7 patients in the decrement-observed group.