

A Multicenter Evaluation of Diagnosis and Management of Omega-5 Gliadin Allergy (Also Known as Wheat-Dependent Exercise-Induced Anaphylaxis) in 132 Adults



Lucinda Kennard, MD^a, Iason Thomas, MD^b, Krzysztof Rutkowski, MD^b, Vian Azzu, MD, PhD^c, Patrick F.K. Yong, MD, PhD^d, Bogusia Kasternow, MD^d, Hannah Hunter, BSc^b, Naeema M.O. Cabdi, MD^e, Alla Nakonechna, MD, PhD^{e,f}, and Annette Wagner, MD^a *Cambridge, London, Guilford, and Liverpool, United Kingdom*

What is already known about this topic? Omega-5 gliadin allergy (also known as wheat-dependent exercise-induced anaphylaxis) is a rare wheat allergy that often presents with severe anaphylaxis in the context of exercise or other cofactors such as nonsteroidal anti-inflammatory drugs and alcohol.

What does this article add to our knowledge? The diagnosis is often delayed (>1 year) and a minority of patients (11%) have no identifiable cofactor. A gluten-free diet and the avoidance of wheat before exercise led to reductions in future omega-5 gliadin allergic reactions of 67% and 69%, respectively.

How does this study impact current management guidelines? Omega-5 gliadin specific IgE should be tested in all patients with unexplained anaphylaxis. Antihistamines and an epinephrine autoinjector must always be prescribed because one-third of patients still have allergic reactions despite optimal dietary advice.

BACKGROUND: Omega-5 gliadin allergy (also known as wheat-dependent exercise-induced anaphylaxis) is a rare allergy to wheat that often presents with intermittent severe anaphylaxis in the context of a cofactor, such as exercise.

OBJECTIVE: To undertake a detailed clinical characterization of the largest cohort of patients with omega-5 gliadin allergy to date.

METHODS: We retrospectively analyzed the demographic characteristics, presentation, investigation, and management of 132 patients presenting with omega-5 gliadin allergy in 4 UK centers.

RESULTS: There were significant delays in diagnosis of 1 to 5 years (40% of patients) and more than 5 years (29% of patients). The commonest cofactors were exercise (80%), alcohol (25%), and nonsteroidal anti-inflammatory drugs (9%). A minority of patients (11%) had no identifiable cofactor. The level of specific IgE to omega-5 gliadin does not predict the severity of allergic reactions. Patients who adhered to a gluten-free diet and those who avoided wheat in combination with exercise achieved the largest reductions in subsequent allergic reactions of 67% and 69%, respectively.

CONCLUSION: Omega-5 gliadin allergy is a rare wheat allergy that presents with severe anaphylaxis. The diagnosis is frequently delayed, and therefore we recommend that all adult patients presenting with anaphylaxis of unclear cause should have omega-5 gliadin specific IgE tested. A gluten-free diet or avoidance of wheat-based meals in combination with exercise (if the cofactor is exercise) helps to significantly decrease the risk of future allergic reactions. However, antihistamines and an epinephrine autoinjector must always be prescribed because one-third of patients continue to have allergic reactions despite dietary advice. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1892-7)

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^aDepartment of Allergy, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

^bDepartment of Allergy, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

^cDepartment of Medicine (Gastroenterology and Hepatology Subdivision), University of Cambridge, Cambridge, United Kingdom

^dDepartment of Allergy and Clinical Immunology, Royal Surrey County Hospital, Guildford, United Kingdom

^eDepartment of Allergy, Broadgreen Hospital, Liverpool, United Kingdom

^fLiverpool Hope University, Liverpool, United Kingdom

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Corresponding author: Lucinda Kennard, MD, Department of Allergy, Cambridge University Hospitals NHS Foundation Trust, Hills Rd, Cambridge CB2 0QQ, UK. E-mail: LK@doctors.org.uk.

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INTRODUCTION

Food-dependent exercise-induced anaphylaxis (FDEIA) is a rare subtype of food allergy. It was first reported in 1979 as a

Abbreviations used

FDEIA- Food-dependent exercise-induced anaphylaxis

NSAID- Nonsteroidal anti-inflammatory drug

SPT- Skin prick test

WDEIA- Wheat-dependent exercise-induced anaphylaxis

shellfish allergy,¹ but now wheat is recognized as the commonest cause of FDEIA.² Wheat allergy prevalence in adults has been reported to be 0.21% in a Japanese study.³ Typically, severe anaphylaxis occurs after wheat consumption with exercise as a cofactor (as the name of the disorder highlights) or with other cofactors such as alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), infection, stress, and female sex hormones/menstruation.⁴ It has been shown that cofactors lower the threshold for allergic reactions to wheat in these patients by increasing the amount of allergen absorbed from the gut^{5,6} or potentially by increasing the immunogenicity of omega-5 gliadin.^{5,7} Most patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) have specific IgE antibodies to omega-5 gliadin,^{2,8} with a sensitivity of 91% and a specificity of 92%.⁹ Other wheat subunits such as glutenins and alpha-/beta-/gamma-gliadin have been identified as rare causes of WDEIA; however, tests for these are not routinely available in clinical practice.^{2,8} There is currently no international standardized management for patients with WDEIA, with a previous study showing that only 39% of patients were prescribed an epinephrine autoinjector.⁹

We present a detailed characterization of the largest multicenter cohort of patients with omega-5 gliadin allergy (also known as WDEIA), focusing on presentation, diagnostic methodology, and management/outcomes with the aim of improving and standardizing care for this rare, but serious, immunological disorder.

We shall refer to this allergy as omega-5 gliadin allergy throughout this article because this is more precise nomenclature than the old term WDEIA.

METHODS

We performed a retrospective study on patients older than 18 years presenting to adult allergy clinics with a clinical history compatible with allergic reactions after wheat consumption and with omega-5 gliadin specific IgE level of more than 0.35 kU/L, reviewed by an allergist with exclusion of other causes of allergic reactions. Four UK centers (Guy's London, Cambridge, Liverpool, and Guildford) submitted data for 132 adult patients in a standardized spreadsheet for analysis. Ethical clearance for this retrospective anonymized study was not required according to UK law. All data collected were obtained purely for clinical reasons and no patient-identifiable information was available to clinicians who were not part of the clinical care team. The spreadsheet included information on the patient's age; sex; delay in diagnosis; symptoms; type of wheat causing the reactions; whether dietary modification occurred; whether the patient had dietitian input; frequency of reactions after dietary change; medical history; length of follow-up; specific IgE to omega-5 gliadin, wheat, gluten, rye, barley, and oat (when performed); skin prick testing (SPT) results for wheat, wheat isolate (when performed), and other allergens; and baseline and acute total tryptases (when known). The manufacturers of SPT solutions used for wheat (followed by center) included Allergopharma (Guy's London and Guildford), ALK Abello

(Liverpool), and Allergy Therapeutics (plain flour 10%) (Cambridge). Rye, barley, and oat (10%) were from Allergy Therapeutics (Cambridge). Wheat isolate was Alyostal 1000 IC/mL (Cambridge). Specific IgE measurements were performed using ImmunoCAP (Thermo Fisher, Waltham, Mass). WDEIA reaction severity was graded using the Brown anaphylaxis grading: grade 1—mild reaction affecting skin and subcutaneous tissues only; grade 2—moderate reaction with features suggesting respiratory, cardiovascular, or gastrointestinal involvement, including dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain; grade 3—severe reaction resulting in hypoxia (cyanosis or oxygen saturation as measured by pulse oximetry [SpO_2] $\leq 92\%$), hypotension (systolic blood pressure < 90 mm Hg), or neurological compromise (including confusion, collapse, loss of consciousness, or incontinence). Statistical analyses were performed using GraphPad Prism software (GraphPad Software, La Jolla, Calif) and were documented next to each figure.

RESULTS

The age range of our omega-5 gliadin allergy cohort was 19 to 74 years, comprising 59% males (78 of 132) and 41% females (54 of 132). Atopy was present in 46% (61 of 132) of individuals. The mean age of males at the time of diagnosis was more than that of females (43 years vs 37 years) and this was statistically significant ($P = .0104$). The median age at the time of diagnosis was 41 years in the cohort.

From the clinical history, wheat was correctly suspected by the clinician and/or patient as the allergen in 82% of cases at initial consultation. Most patients (61%) reported 1 cofactor, 28% reported more than 1, and 11% were unable to identify a cofactor (Figure 1, A). Exercise was the commonest cofactor identified (80%), followed by alcohol (25%), NSAIDs (9%), and heat (5%) (Figure 1, B).

Of those patients for whom data were available (84%), 39% had a reaction in less than 30 minutes from wheat ingestion, 56% between 30 and 60 minutes, and 5% in 1 hour or longer (Figure 1, C). Most of the presentations were severe (66%), followed by moderate (10%) and mild (24%) severity using the Brown anaphylaxis grading (Figure 1, D). Our data showed no significant difference between the mean specific IgE level of those with grade 1, 2, or 3 severity (Figure 1, E), even when corrected for sex. When documented, mast cell total tryptase level rose acutely in omega-5 gliadin allergic reactions (Figure 1, G).

There were significant delays in diagnosis of more than 1 year in two-thirds of the patients (Figure 1, F), despite most patients presenting with severe anaphylaxis. The lack of identification of wheat as an allergen from medical history or the lack of an identifiable cofactor did not cause delays in diagnosis.

Half the patients had wheat SPT, of whom 52% had positive result. Only 11% had wheat isolate testing for omega-5 gliadin, of whom 67% were positive (Table I). All patients tested positive for omega-5 gliadin IgE because this was part of the inclusion criteria. However, some patients were also tested for wheat and gluten specific IgE, demonstrating sensitivities of 59% and 76%, respectively (Table II). A minority of patients had specific IgE testing to other cereals such as rye, barley, and oat (Table III). More than two-thirds of those tested were positive to rye, and roughly one-third were positive to each of barley and oat.

The dietary/lifestyle advice given to patients with omega-5 gliadin allergy was not uniform across the different centers. We

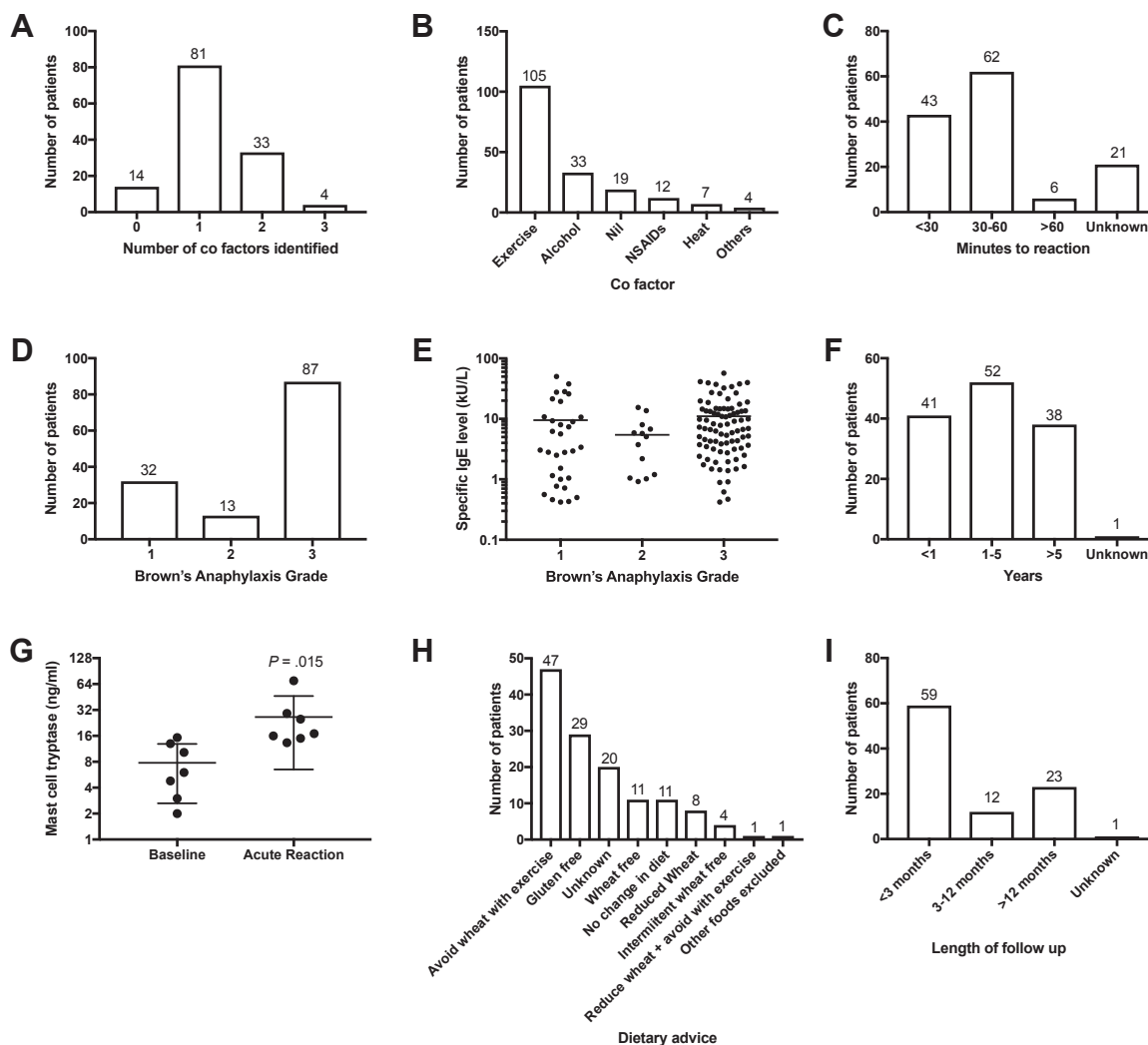


FIGURE 1. Characterization of 132 patients with omega-5 gliadin allergy. (A) Cofactors identified during allergic reactions. (B) Types of cofactors. (C) Timing from wheat ingestion to allergic reaction. (D) Allergic reaction severity using the Brown anaphylaxis grading. (E) Omega-5 gliadin specific IgE as a function of the Brown anaphylaxis grading ($n = 132$; $P = .0616$ [Kruskal-Wallis test]). (F) Delay in omega-5 gliadin allergy/WDEIA diagnosis. (G) Baseline and acute total tryptase measurements ($n = 7$; $P = .015$ [Wilcoxon signed rank test; data are assumed to be nonparametric as too small to test for normality]). (H) Dietary advice given to patients postdiagnosis. (I) Length of follow-up postdiagnosis.

had postdiagnosis dietary records available for 112 patients (85%). The commonest management strategy was to avoid wheat in combination with exercise; however, the advice was variable with some advised to avoid wheat 4 hours before exercise, some to avoid 2 hours after and 2 hours before exercise, and others advised just to avoid with exercise, with the time not specified (Figure 1, H). Most of the advice was given by an allergy/immunology clinician, with only 27 patients (20%)

receiving dietician input. Most patients ($n = 59$ [45%]) had follow-up for less than 3 months in allergy clinics after diagnosis, 12 (9%) had follow-up for 3 to 12 months, and 23 (17%) had follow-up for more than 1 year (Figure 1, I).

Seventy patients had documentation of reactions pre- and postdiagnosis (Table IV). There were statistically significant differences between the different dietary advice groups' outcomes on future allergic reactions ($P = .0266$). A gluten-free diet and the avoidance of wheat in combination with exercise yielded the largest reductions in future omega-5 gliadin allergic reactions of 67% and 69%, respectively (Table IV).

DISCUSSION

Omega-5 gliadin allergy is a rare allergic disorder typically presenting as anaphylaxis after wheat ingestion in combination with exercise, but symptoms can range from mild urticaria to

TABLE I. Sensitivity of wheat and wheat isolate SPT

SPT	Patients with positive SPT result (sensitivity)	Patients with negative SPT result
Wheat	34 of 65 (52%)	31 of 65 (48%)
Wheat isolate	10 of 15 (67%)	5 of 15 (33%)

TABLE II. Specific IgE testing for omega-5 gliadin, wheat, and gluten

Blood test	Omega-5 gliadin	Wheat	Gluten
Number of patients with data	132	106	37
Positive IgE (>0.35 kU/L)	132 (100%)	63 (59%)	28 (76%)
Negative IgE	0	43 (41%)	9 (24%)
Positive result analysis			
Minimum	0.42	0.37	0.39
Maximum	56.9	20.3	22
Median	6.245	1.26	3.165
Mean (95% CI)	10.34 (8.372-12.31)	3.14 (2.09-4.19)	4.895 (2.73-67.05)

TABLE III. Specific IgE measurements for oat, barley, and rye

Blood test	Oat IgE	Barley IgE	Rye IgE
Number of patients	10	15	13
Number of samples	10	15	13
Positive IgE (>0.35 kU/L)	3 (30%)	4 (27%)	10 (77%)
Negative IgE	7 (70%)	11 (73%)	3 (23%)

severe anaphylaxis with hypotension and loss of consciousness (Figure 1, D).

In the past, the name “wheat-dependent exercise-induced anaphylaxis” was used for this condition. However, “omega-5 gliadin allergy” may now be a more appropriate name for the disorder because we do not always identify exercise as a cofactor or in fact any cofactor in a minority of cases. In addition, although omega-5 gliadin is the main wheat allergen in WDEIA, there are other wheat allergens that can cause WDEIA. Therefore, referring to omega-5 gliadin allergy may help remove any confusion for clinicians and patients and so we have preferentially used this term throughout our article.

Our study population broadly reflects previous smaller studies,⁹ with a male predominance of 59% (78 of 132) and a history of atopy in 46% (61 of 132) of patients. The mean age of males at the time of diagnosis was more than that of females (43 years vs 37 years) and this was statistically significant ($P = .0104$). This is unlikely to be related to severity of presentation (which was not statistically different) and may be related to sex dimorphism or to cultural factors.

Diagnosing omega-5 gliadin allergy has long been recognized as challenging.⁶ From the clinical history alone, wheat was identified as the allergen in 82% of patients at the initial consultation. The initial consultation could have been, for example, in an emergency department or with their family doctor who may not consider omega-5 gliadin allergy in the differential diagnosis. This may be because allergic reactions may not occur after every wheat consumption, leading to difficulties in identifying wheat as the allergen by both the physician and the patient.

Most patients (61%) reported 1 cofactor, 28% reported more than 1 cofactor, and 11% were unable to identify a cofactor (Figure 1, A). Exercise was the commonest cofactor identified (80%), followed by alcohol (25%), NSAIDs (9%), and heat (5%) (Figure 1, B). Regarding cofactors, previous studies have shown increased absorption of wheat from the gut during exercise, by measuring circulating plasma gliadin peptides.⁵ In addition, exercise is thought to increase tissue transglutaminase

activity, whose enzymatic processing of omega-5 gliadin increases its immunogenicity demonstrated by increased IgE cross-linking *in vitro*.^{5,7} Similarly, NSAIDs and alcohol have been shown to facilitate allergen absorption from the gastrointestinal tract, thus increasing levels of circulating gliadin peptides in patients with WDEIA.⁵

Importantly, it has been shown that if wheat intake is high enough, the cofactor requirement can be removed,⁶ suggesting that cofactors mainly reduce thresholds for wheat reactions, offering a possible explanation why cofactors are not always identified. Furthermore, it is difficult to know what is quantified as exercise by individual patients.

Only half the patients tested positive on SPT for wheat, and of the limited number who received wheat isolate SPT, two-thirds tested positive. Most patients with WDEIA have specific IgE antibodies to gliadins, most commonly omega-5 gliadin (Tri a 19),^{2,8} and this was considered in our diagnostic criteria. The American chemist Thomas Burr Osborne defined 4 wheat fractions (also known as the Osborne fractions) that are extracted sequentially in water (albumins), dilute saline (globulins), alcohol (gliadins), and alcohol with reducing and disaggregating agents (glutenins). The gliadins are divided into groups depending on their electrophoretic potential: alpha/beta (fast), gamma (medium), and omega (slow).¹⁰ Other wheat subunits such as glutenins and gamma-gliadins have been identified as rare causes of WDEIA, but tests for these are not yet routinely available in clinical practice.^{2,8} Omega-5 gliadin is an ethanol-soluble cereal prolamin, which is the major storage protein found in wheat. This protein is rich in proline and glutamine, and there is some sequence homology with prolamins in rye and barley, but not in oats, which belong to a different group in the grass family.¹¹

Testing for wheat and gluten specific IgE in our cohort showed sensitivities of 59% and 76%, respectively. It would be useful to further evaluate both wheat isolate SPT and specific IgE to wheat and gluten in patients with WDEIA who have negative omega-5 specific IgE. However, wheat isolate SPT is not widely available nor is the extract standardized.

Of the minority of our patients who had specific IgE testing to other cereals, more than two-thirds were positive to rye, and roughly one-third were positive to each of barley and oat (Table III), suggesting *in vitro* cross-reactivity in a small number of patients. Specific IgE to oat was a surprise finding given the low level of structural homology. ELISA inhibition studies in patients with WDEIA have shown greater affinity to omega-5 gliadin than to gamma-secalins (in rye) or gamma-hordeins (in barley), suggesting that omega-5 gliadin is the primary sensitizer.¹¹ However, we advocate taking a specific history for

TABLE IV. Patients experiencing WDEIA reaction pre- and postdiagnosis with dietary advice

Dietary advice given	Number of patients (%)		
	Reactions prediagnosis	Reactions postdietary advice	No reactions postdietary advice
Wheat and exercise avoidance	26 (100%)	8 (31%)	18 (69%)
Gluten-free	21 (100%)	7 (33%)	14 (67%)
Wheat-free	7 (100%)	5 (71%)	2 (29%)
Reduced wheat and exercise avoidance	1 (100%)	1 (100%)	0 (0%)
Intermittent wheat-free	3 (100%)	3 (100%)	0 (0%)
Reduced wheat	8 (100%)	6 (75%)	2 (25%)
No change	4 (100%)	3 (75%)	1 (25%)

Note. There were statistically significant differences between the different dietary advice groups' outcomes on future allergic reactions ($P = .0266$) performed using a χ^2 test.

consumption of rye, barley, and oats, and making patients aware of the potential cross-reactivity with other cereals.

In cases of diagnostic uncertainty and for research purposes, physicians have started suggesting food challenges for these patients to confirm diagnosis and investigate cofactor thresholds using different combinations of cofactors. Given the severity of the reactions in this particular group of patients, frequently grade 3, this would be hard to implement as a standard procedure. However, food challenges could be considered if the diagnosis is doubtful, that is, if the patient has negative specific IgE to omega-5 gliadin or doubtful clinical history. As we know, patients can also react to other gliadins (alpha-, beta-, and specifically gamma-gliadin) and to high-molecular-weight glutenins, which are not currently routinely tested for.^{8,12} Patients may require both a gluten-free diet trial and a food challenge testing. However, not all patients are easily diagnosed on exercise testing with wheat⁶ and therefore expert immunology/allergy input is needed.

The dietary/lifestyle advice given to patients with omega-5 gliadin allergy is not currently standardized (Figure 1, *H*). In addition, patients have a variable follow-up time in clinic post-diagnosis. (Figure 1, *I*). In patients with a positive specific IgE to omega-5 gliadin and/or a strong clinical suspicion (because a minority of patients may react to other wheat components that are not clinically tested for), advice to maintain a gluten-free diet or to avoid wheat (and possibly other cereals) and exercise (if exercise is a cofactor) should be given while waiting to see an expert. In our cohort, this led to the greatest decrease in the risk of subsequent allergic reactions (Table IV). Both management strategies do not eliminate the risk of further reactions completely, and approximately 30% of patients in both dietary groups still had allergic reactions. The frequency of recurrences in the aforementioned dietary groups suggests difficulties with adherence because, unlike celiac disease, exposure to wheat does not always induce a reaction. It may also reflect the interaction of cofactors other than exercise, such as alcohol and NSAIDs. Therefore, we believe it is imperative that patients continue to carry antihistamines and an epinephrine autoinjector because the risk of further allergic reactions remains high.

Interestingly, a wheat-free diet led to only a 29% reduction in future reaction risk, whereas a gluten-free diet and the avoidance of wheat in combination with exercise led to reductions in future omega-5 gliadin allergic reactions of 67% and 69%, respectively.

It is possible that a gluten-free diet excluded other cereals (cross-reacting with wheat, eg, rye). Gluten-free products may be more available than wheat-free products. The wheat-free group

was also small when compared with the other 2 groups (Table IV). A wheat-free diet rather than a gluten-free diet could be a sign of wanting a less strict diet and it may be easier than regulating the diet by analyzing wheat consumption and cofactors every day. These patients may be at more risk of an accidental exposure around the time of a cofactor in comparison with the wheat avoidance with exercise group that specifically looks out for this risk. There are many potential reasons for this huge difference.

There were significant delays in diagnosis of more than 1 year in two-thirds of patients (Figure 1, *F*), which is of concern given that most patients present with severe anaphylaxis. The reasons for delay are unclear, but the lack of awareness of the condition in emergency departments and primary care settings might be a contributing factor.

CONCLUSIONS

We present the largest study of patients with omega-5 gliadin allergy. Omega-5 gliadin allergy commonly presents with severe anaphylaxis in about 30 to 60 minutes after wheat ingestion. Common exacerbating cofactors include exercise, alcohol, and NSAIDs; however, a minority of patients will have no identifiable cofactor. Lack of awareness, rather than the absence of history of wheat ingestion or of cofactors, affects time to diagnosis, which is delayed beyond 1 year in two-thirds of cases. To reduce the delay in omega-5 gliadin allergy diagnosis in all adults with unexplained anaphylaxis, we recommend that specific IgE to omega-5 gliadin should be tested at the same time as mast cell tryptase. As expected in anaphylactic reactions, mast cell tryptases also rise acutely in anaphylaxis associated with omega-5 gliadin (Figure 1, *I*). Simple dietary intervention such as gluten avoidance or avoiding wheat-based meals and exercise is effective in stopping reactions in only about 70% of cases, and so epinephrine autoinjectors and antihistamines should continue to be prescribed to patients with this rare, but serious, immunological disorder. Finally, all patients presenting with anaphylaxis should be referred to a specialist immunology/allergy center.

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