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Wheat dependent exercise induced anaphylaxis: is this an appropriate terminology?

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ABSTRACT

Background The presentation of wheat dependent exercise induced anaphylaxis (WDEIA) can be variable. A high index of clinical suspicion is required to initiate the investigation pathway. Double blind placebo controlled food-exercise challenge is the gold standard investigation but the practicality of this test limits its application.

Aim To critically analyse the symptoms of WDEIA and their correlation with serum specific IgE (sIgE) to ω -5-gliadin.

Methods 17 patients were tested for serum sIgE to ω -5-gliadin. The clinical response to a diet/exercise intervention protocol was used to assess specificity of a positive sIgE to ω -5-gliadin. Length of time to diagnosis, clinical likelihood scores, exercise intensity involved and the severity of allergic reactions were examined retrospectively.

Result 8/10 patients with positive sIgE to ω -5-gliadin had a confirmed diagnosis of WDEIA. Half of the WDEIA patients had a prolonged time lag to diagnosis (32–62 months) and were initially diagnosed with idiopathic anaphylaxis or chronic idiopathic urticaria and angioedema. Only three patients had experienced life threatening symptoms (Mueller grading 4). A close association was observed between requirements of lower exercise intensity to provoke a reaction and diagnostic delay.

Conclusion Specific IgE to ω -5-gliadin can provide supportive evidence for WDEIA without the need of a food-exercise challenge. The wheat-exercise association is not obvious in many patients, highlighting the need to consider WDEIA in the differential diagnosis of all patients presenting with idiopathic systemic reactions. The term anaphylaxis may be inappropriate and it is therefore worth considering an alternative terminology such as 'activity dependent wheat allergy' to describe this condition.

INTRODUCTION

Wheat dependent exercise induced anaphylaxis (WDEIA) is a distinct clinical entity characterised by development of an allergic reaction triggered when ingestion of wheat is followed by physical activity.¹ The clinical presentation of WDEIA can be extremely variable with respect to the threshold of the quantity of wheat ingested and intensity of exercise. Furthermore, patients may not show clinical reactivity each time they are subjected to the triggers, raising the possibility for a role for other unidentified factors in the pathophysiology. It has been reported that alcohol and non-steroidal anti-inflammatory drugs may potentiate allergic responses in this condition.^{2–4} Given that wheat represents a dietary staple food worldwide, this condition may be mistaken for exercise induced anaphylaxis and idiopathic anaphylaxis, and a high index of clinical suspicion is required to make an accurate diagnosis. Double blind placebo controlled food-exercise challenge is the gold standard inves-

tigation for this condition,⁵ but the practicality of this test limits its application in routine clinical practice.

In recent years, the specific antigenic epitopes for WDEIA have been identified.^{6–8} Measuring serum specific IgE to these antigens appears to offer a suitable alternative to food-exercise challenge. Matsuo *et al* reported that serum specific IgE to recombinant ω -5-gliadin (Tri a 19) [ω -5-gliadin] by enzyme immunoassay has a sensitivity and specificity of 80% and 96%, respectively in WDEIA.⁹

The objective of this case series is to evaluate the diagnostic utility of serum sIgE to ω -5-gliadin in routine clinical practice, particularly in centres not equipped with facilities to undertake food-exercise challenges, as well as to perform a critical analysis of symptoms and their correlation with sIgE to ω -5-gliadin.

METHODS

Identification of patients with WDEIA

All patients who were tested for serum sIgE to ω -5-gliadin between March 2008 and September 2009 in our laboratory were included in the analysis (8 women, 9 men; age 32.8 ± 12.4 years). The clinical characteristics of those patients were collated from clinical notes and electronic patient records.

In the absence of a double blind placebo controlled food-exercise challenge, the clinical response to a diet/exercise intervention protocol was used as a surrogate standard to assess specificity of a positive sIgE to ω -5-gliadin. Patients with positive sIgE to ω -5-gliadin were advised not to undertake any significant physical activity for at least 4 h following consumption of wheat containing foods and keep a diary of their reactions for at least 6 months. The diagnosis of WDEIA was made if there was a $\geq 75\%$ reduction in the frequency of systemic reactions over a 6-month period following institution of the diet/exercise intervention protocol. The diagnosis of WDEIA was excluded if: (a) allergic reactions occur in the absence of wheat; (b) an alternative food allergy was found with supporting sIgE testing; or (c) an alternative non-allergy diagnosis was made (eg, mastocytosis). One patient (patient 4) reported type 1 hypersensitivity to wheat with mild urticaria but with significant exacerbation if this was followed by physical activity, for example walking. She has excluded wheat completely from her diet and has not experienced any further allergic reactions. This patient's presentation is atypical but was included in our analysis.

Since this was not a clinical trial, a diet/exercise intervention protocol was not applied to patients without demonstrable sIgE to ω -5-gliadin.

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Table 1 Classification of the severity of allergic reaction²⁰

Mueller grading*	Clinical features
Grade I	Generalised urticaria, itching, malaise, anxiety
Grade II	Any of the above plus two or more of the following: angioedema, chest constriction, nausea, vomiting, diarrhoea, abdominal pain, dizziness
Grade III	Any of the above plus two or more of the following: dyspnoea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
Grade IV	Any of the above plus two or more of the following: fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis

*The severity of clinical manifestation was graded using the modified Mueller classification (Mueller, 1990). The patient's most severe reaction was used to determine their grading.

Specific IgE antibodies to recombinant ω -5-gliadin

Specific IgE to ω -5-gliadin in the patients' sera was determined by ImmunoCap according to the manufacturer's instructions (Phadia, Uppsala, Sweden) and was measured in kilo units of antibodies per litre (kUa/l).

Defining the time to diagnosis and evaluating the possible reasons that could influence time to diagnosis

The length of time (in months) from the first clinic visit to documented diagnosis of WDEIA was used to define time to diagnosis. A clinical likelihood score for WDEIA in each patient was given by two independent allergy specialists following review of the summary of clinical presentation without knowledge of the laboratory data. The scoring system used was as follows: (1) will not consider as a differential diagnosis; (2) will consider as an unlikely differential diagnosis and will adopt a 'wait and watch' policy; (3) will consider as a top three differential diagnosis and will actively investigate; or (4) highly suggestive. The exercise intensity required to trigger a reaction was graded as: (1) mild: walking <15 min; (2) moderate: walking >15 min, walking uphill, jogging, light dancing; or (3) high: heavy lifting, intense cardiovascular training and competitive sport (football, hockey, rugby etc). The severity of allergic reaction was graded according to the Mueller classification (table 1).

Table 2 Characteristic of subjects

Patient no.	Gender	Age of presentation	*Clinical likelihood scores (total of 2)	Total IgE (kU/l)	Specific IgE to ω -5-gliadin (kUa/l)	No. of allergic reactions per 6/12 before modified exercise dietary test	No. of allergic reactions per 6/12 after modified exercise dietary test	Diagnosis
1	M	25	4/3 (7)	323	29.6	4	1	WDEIA
2	M	41	3/1 (4)	358	17.7	2	0	WDEIA
3	F	47	2/4 (6)	3617	17.9	4	0	WDEIA
4	M	53	3/3 (6)	203	6.46	12	1	WDEIA
5	F	31	4/4 (8)	176	12.0	26	2	WDEIA
6	M	52	3/3 (6)	Not done	3.89	12	0	WDEIA
7	M	30	4/4 (8)	100	5.96	3	1	WDEIA
8	M	20	3/2 (5)	46	0.96	24	6	WDEIA
9	M	44	2/3 (5)	1172	6.62	8	6	EIA
10	F	26	1/1 (2)	109	0.53	6	5	CIUA
11	F	22	3/4 (7)	Not done	0.14	—	—	Prawn allergy
12	F	25	1/1 (2)	21	0.00	—	—	CIU
13	M	51	2/3 (5)	986	0.02	—	—	IA
14	F	8	1/1 (2)	Not done	0.00	—	—	IBS
15	F	24	1/3 (4)	283	0.03	—	—	Wheat allergy
16	M	20	3/3 (6)	1947	0.05	—	—	IA
17	F	17	1/1 (2)	134	0.00	—	—	CIUA

*The scoring system for clinical likelihood score is as follows: (1) will not consider as a differential diagnosis at all; (2) will consider as an unlikely differential diagnosis and will adopt a 'wait and watch' policy; (3) will consider as the top three differential diagnosis and will actively investigate for the condition; or (4) highly suggestive.

CIUA, chronic idiopathic urticaria and angioedema; CIU, chronic idiopathic urticaria; EIA, exercise induced anaphylaxis; IA, idiopathic anaphylaxis; WDEIA, wheat dependent exercise induced anaphylaxis; ≥ 0.35 kUa/l, positive sIgE to ω -5-gliadin.

Statistics

The Mann–Whitney U test was used to analyse the statistical significance between the differences of the clinical likelihood scores among groups with or without WDEIA. A two-tailed p-value of <0.05 was considered significant. All statistical calculations were performed by Graphpad Prism software version 5.00.

RESULTS

Eight of ten patients with sIgE to ω -5-gliadin ≥ 0.35 kUa/l had a confirmed diagnosis of WDEIA following a successful trial of diet/exercise intervention protocol. Table 2 summarises the clinical characteristics of all patients. All patients with sIgE to ω -5-gliadin of <0.35 kUa/l had an alternative confirmed diagnosis.

sIgE to ω -5-gliadin in this cohort was shown to have a high specificity and positive predictive value, particularly when the 'cut-off' value was set at 0.89 kUa/l as in a previous study.⁹

Time taken to reach the diagnosis of WDEIA

Four (1, 2, 4 and 6) of eight WDEIA patients had a prolonged time lag to diagnosis (32–62 months). The average time to diagnosis for all WDEIA patients was 28.5 months (range 2–62 months). Although patient 2 was given a diagnosis of food dependent exercise-induced anaphylaxis after 12 months, the association with wheat could not be ascertained until a later date despite maintaining a good food–exercise diary. Three patients (3, 5 and 8) were diagnosed within 1 year of their first clinic visit. Patient 7 was diagnosed in 15 months but the predominant reason was his failure to attend clinic appointments. Table 3 summarises the characteristics of patients with WDEIA.

Factors that may influence time to diagnosis

Patients who were diagnosed <18 months had a primary diagnosis of either WDEIA or exercise induced anaphylaxis. However, those four subjects with prolonged time lag to diagnosis (≥ 32 months) had a primary diagnosis of either idiopathic anaphylaxis or chronic idiopathic urticaria and angioedema.

Table 3 Clinical characteristics of patients with confirmed wheat dependent exercise induced anaphylaxis (WDEIA)

Patient no.	Atopic diseases	Intensity of exercise needed for a reaction	Severity of reaction (Mueller grading)	Systemic reaction may trigger by alcohol/NSAIDs without exercise	Time to diagnosis from first visit in months	Primary diagnosis made at first presentation
1	Asthma	Mild	2	Yes	32	Idiopathic anaphylaxis
2	Nil	Mild	3	Yes	52	Chronic idiopathic urticaria and angioedema
3	Asthma, SAR	High	2	No	2	WDEIA
4	Nil	Mild	4	No	59	Idiopathic anaphylaxis
5	Nil	Mild	3	Yes	4	WDEIA
6	Nil	Mild	4	No	62	Chronic idiopathic urticaria and angioedema
7	Nil	Mild	4	No	15	WDEIA
8	Nil	Moderate	3	No	5	Exercise induced anaphylaxis

SAR, seasonal allergic rhinitis.

Higher clinical likelihood scores were observed among subjects with WDEIA than subjects with alternative diagnosis (WDEIA vs non-WDEIA (median (IQR), 6 vs 4, $p=0.027$)). Among those eight patients with WDEIA, seven had a clinical likelihood score of ≥ 5 compared to 4 (out of 9) with an alternative diagnosis.

A close association was observed between requirements of lower exercise intensity to provoke a reaction (subjects 1, 2, 4, 5, 6 and 8) and the prolonged time lag to diagnosis of WDEIA. Patients 3 and 8 required high and moderate intensity of exercise, respectively, to trigger their reactions; both were diagnosed in <6 months.

DISCUSSION

Our data show that sIgE to ω -5-gliadin is specific for WDEIA when used in the appropriate clinical context. This finding is consistent with previous studies on adult WDEIA.^{9–11} Matsuo *et al* demonstrated that the specificity of sIgE to ω -5-gliadin was 68% when the 'cut-off' value was set at 0.35 kUa/l, but improved to 96% when this was reset to 0.89 kUa/l.⁹ However, the evidence in children is less clear.¹² Palosuo *et al* have shown that sIgE to ω -5-gliadin can also be found in children with wheat allergy.¹¹ Beyer *et al* reported that sIgE to ω -5-gliadin cannot distinguish between wheat sensitisation and clinical reactivity in children.¹³

High molecular weight-glutenin is another major antigenic determinant for WDEIA.^{7, 14} Despite being specific, it is only found in 20% of WDEIA patients. It was therefore proposed as a useful adjunct to sIgE to ω -5-gliadin.¹⁰ The simultaneous detection of sIgE to ω -5-gliadin and High molecular weight glutenin can improve the sensitivity to 97%.¹⁰

There was a significant diagnostic delay of ≥ 32 months in 4/8 patients with WDEIA in our study. It is likely that this may at least in part be related to relatively milder levels of physical activity involved in provoking systemic reactions, thus not raising the possibility of WDEIA (or other food dependent EIA) even as a differential diagnosis at initial presentation. The term WDEIA may be misleading given that *mild* physical activity that may not be considered as exercise was sufficient to provoke a systemic reaction and that cardiorespiratory compromise was not seen in the majority of patients in our cohort. Anaphylaxis is defined as a severe life threatening systemic reaction characterised by significant cardiac and/or respiratory compromise.^{15, 16} A case series of Japanese children with WDEIA reported the clinical symptoms of pruritus (90%), urticaria (86%), angioedema (72%), flushing (70%), shortness of breath (51%), dysphagia (34%), chest tightness (33%), syncope (32%), profuse sweating

(32%), headache (28%) and other gastrointestinal and upper airway symptoms.¹⁷

Wheat represents a dietary staple and considering the inconsistency of allergic responses associated with WDEIA, it becomes an important diagnostic consideration in all patients presenting with recurrent anaphylaxis or mild–moderate systemic reactions without an obvious allergenic trigger. It follows that a careful history and scrutiny of the patient's food–activity diary documenting all the episodes is invaluable in arriving at this diagnosis.

We did not identify any associations between the severity of reaction, exercise intensity and the level of sIgE to ω -5-gliadin as reported previously.^{6, 18, 19} The clinical presentation can also be influenced by concurrent exposure to non-steroidal anti-inflammatory drugs and/or alcohol, both shown to trigger a systemic reaction in the absence of exercise in WDEIA.^{2–4} This was observed in a third of our cohort. Interestingly, one patient reported mild urticaria to wheat ingestion per se, that was exaggerated if this was followed by physical activity.

Limitations to our case series include relatively smaller sample size, retrospective analysis of clinical symptoms and failure to subject the patients to wheat–exercise challenge. We also did not examine the clinical application of sIgE to high molecular weight glutenin and further work will be needed to clarify this.

This case series analysis is the first report describing the clinical application of sIgE to ω -5-gliadin in a routine clinical practice and assesses patients' response to diet/exercise intervention.

In conclusion, a high index of clinical suspicion is required to avoid diagnostic delay in WDEIA. The wheat–exercise association may not be obvious in many patients, highlighting the need to consider this in the differential diagnosis of all patients presenting with idiopathic allergic reactions and exercise induced

Take-home messages

- A high index of clinical suspicion is needed to avoid underdiagnosis and diagnostic delay of wheat dependent exercise induced anaphylaxis (WDEIA).
- WDEIA should be considered in the differential of idiopathic anaphylaxis or systemic reactions.
- Beware of the misleading terminology of 'wheat dependent exercise induced anaphylaxis'; a more appropriate description is 'activity dependent wheat allergy', since some patients develop milder symptoms and strenuous exercise may not be involved.

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anaphylaxis. It may also be worth considering an alternative terminology such as 'activity dependent wheat allergy' to describe this condition more accurately. Specific IgE to ω -5-gliadin can provide supportive evidence for clinicians to make the diagnosis without performing a food-exercise challenge. Raising the clinical awareness and using targeted sIgE testing will be central to the diagnosis of this condition.

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Competing interests None.

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