

Wheat food allergy in adults has a favorable prognosis

Short title: Wheat allergy in adults

Scibilia J¹, Rossi CM¹, Losappio LM¹, Mirone C¹, Farioli L², Pravettoni V³, Pastorello EA¹

¹Unit of Allergology and Immunology, Dipartimento Medico Polispecialistico, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

²Department of Laboratory Medicine, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

³Clinical Allergy and Immunology Unit, Foundation IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy.

Corresponding Author:

Elide Anna Pastorello, MD

Unit of Allergology and Immunology, Dipartimento Medico Polispecialistico

ASST Grande Ospedale Metropolitano Niguarda

Piazza Ospedale Maggiore, 3

20162 Milan, Italy

Phone: +39026442751

Fax: +39026442082

e-mail: elide.pastorello@ospedaleniguarda.it

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ABSTRACT

Background: Wheat ingestion can lead to different disorders such as IgE-mediated food allergy and wheat-dependent exercise-induced anaphylaxis (WDEIA), associated with impaired quality of life and significant morbidity. Allergy to wheat is relatively benign in children, however its natural history in adults is still unknown.

Objective: We evaluated the natural history of wheat hypersensitivity in atopic patients with adult-onset wheat- allergy assessed by placebo-controlled-challenge.

Methods: We enrolled 13 patients from an initial cohort of adult patients (mean age 40 years) with IgE-mediated wheat allergy. After diagnosis the patients observed a wheat-free diet and were followed as outpatients for 5-years to evaluate for wheat-exposure. At the end of the follow-up, wheat-IgE titers were determined and a second wheat-challenge was performed.

Results: 10 out of 13 patients took part in the study. The mean period of wheat avoidance was 4.2 years. 3 patients had spontaneously re-introduced wheat before the second evaluation, after a mean of 28 months (IQR 18-36 months), with only mild gastrointestinal discomfort at wheat reintroduction. At the end of follow-up, 9/10 patients were wheat-tolerant. 2 patients had a history WDEIA. A reduction of IgE levels, median IgE from 2.77 kU/l (IQR 0.35-100 kU/L) at diagnosis to 0.88 kU/l (IQR 0.1-20.8 Ku/L) was observed. No statistical correlation was found between IgE and negative challenge outcome.

Conclusion: IgE-mediated wheat allergy in adults is benign and represents a temporary break in the gastrointestinal tolerance. Future studies may improve our knowledge of wheat allergens, routes and factors leading to sensitization and prognostic biomarkers.

Key words: Wheat allergy. Adult food allergy. Food tolerance. Double-blind placebo-controlled food challenge.

RESUMEN

Introducción: La ingesta de trigo puede originar varias patologías como alergia alimentaria mediada por IgE y la anafilaxia inducida por ejercicio previa ingesta de trigo. Todas ellas originan un descenso en la calidad de vida y una importante morbilidad. La alergia a trigo es relativamente benigna en niños, sin embargo, su historia natural en adultos es aún desconocida.

Objetivo: Evaluamos la historia natural de la hipersensibilidad al trigo de inicio en la edad adulta en pacientes atópicos confirmado mediante pruebas de exposición oral.

Métodos: Se incluyeron 13 pacientes de una cohorte de pacientes adultos (edad media 40 años) con alergia a trigo mediada por IgE. Tras el diagnóstico los pacientes siguieron una dieta exenta de trigo y fueron seguidos durante 5 años para valorar su tolerancia tras la exposición al trigo. Al final del seguimiento se determinaron los valores de IgE específica a trigo y se realizó una segunda provocación oral con trigo.

Resultados: 10 de los 13 pacientes tomaron parte en el estudio. La duración media del periodo de no ingesta de trigo fue de 4,2 años. 3 pacientes reintrodujeron por iniciativa propia la ingesta de trigo antes de la segunda evaluación, después de un periodo medio de 28 meses (RIQ 18-36 meses), presentando solo leves síntomas gastrointestinales. Al final del seguimiento, 9/10 pacientes toleraron la ingesta de trigo. 2 pacientes tenían historia de anafilaxia inducida por ejercicio. Se observó una disminución de los valores de IgE específica desde una mediana de 2,77 kU/l (RIQ 0.35-100 kU/L) en el momento del diagnóstico hasta 0.88 kU/l (RIQ 0.1-20.8 Ku/L) al final del seguimiento. No se observó correlación entre los valores de IgE específica y los resultados de la tolerancia final.

Palabras clave: Alergia a trigo. Alergia alimentaria en el adulto. Intolerancia alimentaria. Provocación alimentaria doble ciego con placebo control.

INTRODUCTION

Wheat is one of the most widely cultivated cereals due to its easy growth and resistance to environmental stresses, and its high nutritional value makes it the basis of the diet worldwide. As a result, it is unsurprising that its consumption has been associated with a wide array of disorders that on the basis of individual atopic background may be IgE-mediated, cell-mediated or both.

Classic food allergy and wheat-dependent exercise-induced anaphylaxis (WDEIA) illustrate IgE-mediated forms of wheat disorders brought on by wheat ingestion, whereas Baker's asthma is caused by protein inhalation. Moreover wheat protein contact urticaria is provoked by skin exposure; in particular, an IgE-mediated reaction has been observed in subjects sensitized to Glupearl 19S, a wheat hydrolysed protein present in soaps [1].

Among cell-mediated reactions, celiac disease and dermatitis herpetiformis have been described as autoimmune disorders. Recently, the so-called non celiac gluten sensitivity, where gluten exerts its pathogenetic role with a still unknown mechanism, and the irritable gut syndrome, where fermentable wheat carbohydrates may significantly worsen the clinical picture, have received growing attention.

If one focuses on IgE-mediated wheat allergy one finds that in pediatric populations the prevalence varies from 0.5 to 1% as demonstrated by double-blind placebo-controlled food challenge (DBPCFC) studies published in US and Europe [2,3]. Moreover, wheat food allergy seems to be more frequent in some countries for partially unknown reasons, such as in Japan and other eastern countries as well as in Northern Europe, where wheat is the most relevant cause of WDEIA.

Wheat allergy is rarer in adults. It is conceivable that wheat, with its peculiar chemical-physical features and immunogenic peptides and several routes of sensitization, can induce a break in the oral tolerance in a subset of atopic adult patients. In a previous study we described a series of atopic patients with adult-onset IgE-mediated wheat food allergy, as assessed DBPCFC [4].

It is interesting to note that while the majority of children outgrow food allergy to milk and egg in adolescence and rarely outgrow allergy to nuts, the case of wheat allergy seems to stand between these two extremes with almost half of the patients becoming tolerant by the age of eight years [5]. Moreover, pediatric subjects with higher titers of wheat-specific IgE and more severe clinical manifestation of wheat allergy have shown less favorable outcomes and a more delayed development of wheat tolerance [4-6]. There is very little data in the literature as regards the natural history of allergy to wheat in adult patients. The aim of this study is therefore to analyze the outcome of wheat allergy through a prospective follow-up study of a previously described cohort of patients with adult onset wheat allergy [4]. Indeed, we foresee that the knowledge of the natural history of wheat allergy in adults can carry significant and possibly divergent implications as regards the therapeutical approach in patients with food allergy, i.e. watch and wait for the allergy to pass or subject the patient to an extended and unneeded wheat elimination diet.

In children however, avoidance is not the only approach, active intervention with oral immunotherapy has been recently reported [6] in this cohort of 6 patients sensitized to alpha-amylase a rapid tolerance was safely obtained in 83% of patients with only a minority of doses (6.25%) associated with mild adverse reaction in the up-dosing phase.

METHODS

We enrolled 13 patients with a positive DBPCFC challenge with raw wheat flour from the original cohort of 27 patients (24 Italian and 3 Danish) with suspected wheat allergy, as previously described [4].

Patient characteristics and diagnostic challenge results are reported in the original study [4]. In brief, all of the patients reported a history of symptoms shortly after the ingestion of wheat products; patients were selected on the basis of clinical history and positive wheat skin test or specific IgE; grass pollen allergy status was not adopted as a selection criterion. Clinical and laboratory assessments were performed. Specific IgE antibodies (CAP-FEIA; Pharmacia-Upjohn, Uppsala, Sweden) to wheat, Pru p3 and omega-5-gliadin were determined according to manufacturing standards. Immunoblotting of the three Osborn's fractions (albumin/globulin, gliadins and glutenins) of raw and cooked wheat was performed according to manufacturing standards as described in [15]. Tri a14 was initially determined by immunoblotting and later by CAP when the latter became available. Anti-transglutaminase antibodies were used to screen for celiac disease prior to undergoing wheat DBPCFC.

The symptoms manifested during the initial DBPCFC were typical of IgE mediated reactions, with the majority of symptoms involving the skin, mucosa and the gastro-intestinal tract (urticaria in 8 patients, pruritus in 4, angioedema in 3, oral allergy syndrome in 5, abdominal pain in 5); a smaller number of patients showed respiratory manifestations (asthma in 3, persistent cough in 3 and rhinitis in 1). Patients originally identified as wheat allergic by DBPCFC were placed on a wheat-free diet and were discharged with scheduled clinical follow-up visits at six months, 1, 3 and 5-years with wheat status being monitored as regards voluntary or inadvertent wheat introduction and tolerance. In the case of cancelled visits, patients were interviewed by telephone at 12-24 month intervals. None of the patients underwent allergen immunotherapy.

Wheat status was ascertained after a 5-year interval with a second wheat DBPCFC prior to retesting negative to anti-transglutaminase antibodies. The second DBPCFC was carried out with raw wheat. Specific IgE for were also repeated after 5 years of wheat avoidance.

The challenge procedure is reported in the original paper [4]. In brief, the test meals were prepared by expert dieticians using wheat flour, potato starch, water, cocoa, partially cooked minced rice, sugar and lemon aroma syrup; allergies to these foods were excluded prior to testing. Twenty-five grams of raw wheat flour was used in the active meal. Doses were administered at 20 minute intervals. A minimum starting dose of 100 mg of raw wheat was administered, doses were increased until symptoms were reported/observed or until the entire test meal was eaten (incremental doses were 100 mg, 500 mg, 1 gr, 1.5 gr, 3 gr, 6 gr and 12 gr).

RESULTS

Ten Italian patients took part in the follow-up study as three out of the 13 selected patients were lost to follow-up (2 Danish and 1 Italian patient). Wheat status assessment revealed that the majority of patients originally diagnosed as truly allergic to wheat [3] continued to avoid wheat after 5 years even if accidental wheat ingestion had occurred without any allergic reaction.

Table 1 shows the demographic data, wheat-specific IgE, and grass sensitization status. Patient characteristics were distributed as follows for sex and age: 7 female, 3 male; the median age of wheat diagnosis was 40 years. The mean period of wheat avoidance was 4.2 years. As shown in table 1, most of the patients presented adult-onset food allergies, mainly to fruit and vegetables; one patient was also allergic to barley and rye, and one patient to rice and corn. As far as the pattern of sensitization is concerned, the majority of patients test positive for alpha-amylase inhibitors. Three patients were sensitized to Pru p 3 and Tri a 14, whereas only 1 patient was sensitized to omega-5-gliadin and one to low-molecular-weight glutenin.

Patients 1, 2 and 3 had reintroduced wheat spontaneously after having avoided it for 18, 30 and 36 months, respectively. These 3 patients complained mild gastro-intestinal symptoms at reintroduction, however they maintained wheat in the diet. These patients were not re-tested by wheat DBPCFC.

Patients 4-10 continued to avoid wheat during the follow-up period and, despite inadvertent introduction of small amounts of wheat was reported, no relevant allergic manifestation had occurred. None of the patient developed new illnesses or new allergic conditions. Seven patients were once again tested for wheat specific IgE and wheat DBPCFC using raw wheat flour [patients 4-10]. Table 1 shows the clinical history for wheat challenge before and after wheat avoidance. Six of the 7 patients passed wheat DBPCFC and were instructed to introduce cooked wheat openly on a daily basis (25 grams of cooked pasta or bread). Four of the seven patients were sensitized to grass pollen. Patient 5 was the only patient that retained wheat allergic status, see Table 1 for challenge symptoms. The patient was advised to continue on a wheat-free diet.

Nine of the ten patients (90%) with challenge-proven wheat allergy were confirmed to have reacquired wheat tolerance.

At the re-evaluation the exercise test was not carried out since one patient, patient 3, declined to undergo the stress test and patient 7, who had passed the second wheat challenge, referred that after the challenge she performed strenuous exercise without reporting symptoms.

Wheat avoidance was associated with a reduction in wheat-specific IgE values as compared to the values detected at the time of initial diagnosis in all of the patients reviewed: range 0.35 – 100 kU/L (median 2.77 kU/L) at the time of diagnosis and 0.1 -20.8 kU/L (median 0.88 kU/l) after wheat elimination. The magnitude of the reduction did not vary according to grass pollen sensitisation. See Table 1 for wheat specific IgE levels in these subjects before and after wheat reintroduction.

Regardless of the fact that wheat specific IgE had decreased in patient 5 (6.3 to 2.5 kU/L), we found no change in the wheat provocation dose delivered (25 gr) during both challenges, even if challenge symptoms were reported to be less severe when compared to the first wheat DBPCFC. Patient 5 was sensitized to Pru p 3 and grass pollen.

The wheat tolerance status was subsequently confirmed with an additional follow-up of 7 years.

DISCUSSION

Our main finding is that in a cohort of prospectively-evaluated wheat-allergic adult patients, wheat allergy ceased in 90% of the patients after a mean period of 4.2 years. We are therefore brought to conclude that adult-onset wheat allergy seems to be a transient form of food allergy with a very favorable prognosis.

We underline that all of the wheat-allergic patients described herein were diagnosed by DBPCFC using a standardized meal; all of the patients that developed wheat tolerance were of Italian origin and had taken part in a multicentre-study [3]. Most of these subjects displayed coexisting plant and food allergies and manifested true adult-onset wheat allergy inasmuch as they had always tolerated wheat and became allergic to this cereal at some point in adult life (mean age 41.6 years).

Wheat allergy in adults is rather uncommon despite the frequency of wheat sensitization due to its cross-reactivity with grass pollen. The most frequent form of clinical wheat allergy diagnosed in the adult is WDEIA in which wheat has a pivotal role for yet unknown reasons in both adults and children. Two of our patients also showed exercise-induced wheat allergy (patients 3 and 7).

Other factors that can exert an influence on the development of food allergy in adults are various, e.g. the use of anti-acids that alter protein digestion, in particular, these drugs have been shown to be important in conditioning the development of allergy to fish and melon [9]; the use of NSAIDS that alter protein absorption in the gastrointestinal tract; and alcohol intake. As far as wheat is concerned one can conjecture that the incomplete digestibility that distinguishes some wheat fractions, such as gliadins, may be a factor which partially favors the development of some wheat related immunological disorders in the adult such as eosinophilic esophagitis, where wheat seems to play a prevalent role [10].

Another possible explanation for the development of wheat allergy in patients with eczema could be related to the cutaneous sensitization generated by the use of soaps that contain hydrolyzed wheat protein (HWP). Recently in Japan, there have been several reports of wheat sensitization via the skin after having used soap bars that contained HWP, most patients had used the soap bar named "Cha-no-Shi-zukuTM"; these patients manifested anaphylaxis or other allergic reactions in association with exercise and NSAIDS [9].

Indeed, wheat displays complex physico-chemical properties. According to the Osborne classification, there exist several fraction of wheat proteins, water and salt-soluble (namely albumins and globulins, which are mainly responsible for Baker's asthma) as well as alcohol and acid/alkaline soluble (namely gliadins and glutenins, which are related to WDEIA and wheat allergy). The most important wheat allergens are alpha-amylase inhibitors, gliadins and glutenins. Among gliadins, omega-5 (Tri a 19) is implicated in WDEIA and food allergy. In the Mediterranean area, Tria a 14, a non specific lipid transfer protein (nsLTP), is mainly implicated in wheat allergy and WDEIA but also in baker's asthma [12]. Interestingly, in addition to the complex chemico-physical features of wheat, several gliadin peptides that are rich in proline residues (such as the 33-mer peptide) have been shown to be particularly resistant to proteases and therefore undergo incomplete digestion in the gastrointestinal tract and retain their immunological features [13]. The majority of patients in our cohort display sensitization to alpha amylase inhibitors. The remaining patients tested positive to Tri a 14, a LTP, or omega-5 gliadin. One patient displayed a co-sensitisation to both alpha-amylase inhibitor and omega-5 gliadin. One patient displayed a co-sensitisation to both alpha-amylase inhibitor and low molecular weight glutenin.

We therefore speculate that an atopic individual under the influence of additional risk factors, some of which specified above, can become allergic to wheat, which *per se* is difficult to digest. These subjects need to be considered as a distinct population set apart from the pediatric population.

As far as the prognosis of wheat allergy in children is concerned, in the available series evaluating the natural history of IgE-mediated allergy, including both prospective and retrospective analyses and challenges performed with clinical supervision or at home, wheat allergy is outgrown in the majority of patients subject to an elimination diet after a median period of 6.5 years. Moreover, other favorable prognostic factors have been shown to be a low titer of wheat-specific IgE at the time of diagnosis, higher specific IgE levels at an early age and the absence of IgE against gliadin [5-6,8].

Prognostic factors in adult populations remain largely unknown. Despite the fact that all of our patients showed a decrease in wheat specific IgE we could not identify a statistical correlation between a decrease in specific IgE levels and a negative challenge outcome. This is likely due to the small patient population, however, it may reflect a unique feature of adults patients with wheat allergy. With the exception of patients 2, 3 and 4, all of the patients who became wheat tolerant continued to display wheat-specific IgE albeit at low levels (i.e. < 3kU/L). This finding could be explained only partially by serological cross-reactivity between wheat and grass pollen inasmuch as only 40% of the patients were grass sensitized (patients 5, 8-10) in our series, as compared to 70% in the one described by Nilsson [8]. Of note, patients 1-4, 6 and 7 showed no sign of grass sensitization and continued to show positive IgE for wheat, even after having developed wheat tolerance. This finding may be accounted for by different observations. The knowledge of wheat allergen is still far from complete and solutions adopted for commercial wheat SPT display a mixture of the more common allergens without covering the entire spectrum. Besides, it is possible that the nature of epitopes recognized by the antibodies (conformational versus sequential) is different in adult patients that developed wheat tolerance as compared to those who do not outgrow it, as is the case of allergies to milk and eggs [14]. In contrast, Patient 5 continued to show clinical wheat allergy despite the decrease in wheat specific IgE.

Moreover, the sensitization pattern could have role. It is noteworthy that in our cohort of adult patients, the only one who did not extinguish the allergy to wheat was positive to LTP (Tri a 14 and Pru p3), however the small number of patients hamper definitive conclusions to be drawn as far as the correlation of outcome and molecular sensitization is concerned.

Patients 3 and 7 had a history of wheat dependent exercise induced urticaria and both patients became wheat tolerant. Patient 3 no longer manifested urticaria after wheat or after wheat ingestion and exercise; we advised the patient to undergo wheat and exercise challenge but the patient declined inasmuch as symptoms were no longer present. However, the small number of patients with presumed exercise-induced urticaria hampers any definite conclusion.

Of note, the three patients that had spontaneously reintroduced wheat were not sensitized to grass pollen, whereas the only patient that maintained wheat allergic status was grass pollen sensitive and allergic to peach lipid transfer protein. The three patients that had spontaneously reintroduced wheat (patients 1-3) originally complained of gastrointestinal symptoms upon wheat challenge, as compared to only one patient in the group of patients that continued to avoid wheat (patient 6). Thus, it may be that the presence of gastrointestinal symptoms at the time of diagnosis could be utilized as a prognostic marker of a more rapid acquisition of tolerance as has been reported in children [6].

In conclusion, in our study IgE-mediated wheat food allergy showed excellent prognosis in a small population of Italian adults. Although wheat specific IgE titers could not be used in our population to estimate the likelihood of having developed wheat tolerance, wheat-allergic adults should be re-evaluated periodically inasmuch as wheat tolerance can be expected in the vast majority of patients after a variable period of wheat avoidance. Wheat allergy ceased in 90% of the Italian patients included in our cohort, thus adult-onset wheat allergy seems to be a transient form of food allergy with a very favorable prognosis. The robustness of this finding is further substantiated by the additional 7-year follow-up period during which none of the patients showed relapse of wheat food allergy.

The mechanisms of natural tolerance to food allergen are largely unknown, so further studies are needed.

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Table 1. Demographic data, wheat-specific IgE and challenge results before and after wheat avoidance, grass sensitization.

	Sex	Age*	Wheat specific IgE at diagnosis (kU/L)	Wheat specific IgE at re-evaluation (kU/L)	Wheat DBPCFC 2004	Wheat DBPCFC 2009	Wheat status	Wheat avoidance (yrs)	Age of wheat tolerance (yrs)	Grass pollen sensitization	Pattern of sensitisation
P1	F	54	1.4	0.53	AE, GI	NP	T	1.5	55.5	-	alpha- AI
P2	F	16	>100	20.8	AD, U, GI, R	NP	T	2.3	18.3	-	omega 5-gliadin, alpha-AI
P3	M	42	17.2	5.7	EIU, GI, AE	NP	T	3	45	-	alpha-AI, LMW-glutenin
P4	M	44	38.7	9.22	A, GI,	Negative	T	5	51	-	Tri a 14, Pru p3
P5	F	50	6.3	2.49	A, R, OAS P,	E, Pr	A	5	-	+	Tri a 14, Pru p3
P6	F	45	<0.35	<0.1	E, GI, AE	Negative	T	5	50	-	alpha-AI
P7	F	37	1.97	0.23	EIU	Negative	T	5	42	-	Tri a 14, Pru p3
P8	F	60	3.57	1.23	OAS, U	Negative	T	5	65	+	alpha-AI
P9	M	40	0.54	0.18	A	Negative	T	5	45	+	alpha- AI
P10	F	28	0.89	0.48	U	Negative	T	5	33	+	alpha- AI

A: Asthma; AD: atopic dermatitis; AE: angioedema; C: cough; E: erythema; GI: abdominal colic; V: emesis; U: urticaria; H:

headache; OAS: oral allergy syndrome; Pr: pruritus; U: urticaria, EIU: exercise-induced wheat urticaria; *Age: age of wheat allergy diagnosis; NP: not performed; T: tolerant; A: allergic.

Alpha-AI: alpha amylase inhibitor, LMW-glutenin: low molecular weight glutenin.

Other food allergies in the study patients: tomato (4,8,9), carrot (8), fennel (4), soy (8), peach (2,4,5), cherry (2), grape (4,5), melon (8), apple (2,4), hazelnut (2,8), chestnut (5,8), barley and rye (4), corn and rice (5).

Pattern of sensitization to wheat allergens: alpha-amylase inhibitor (7 patients), Tri a14 and Prup 3 (3 patients), Tria a 19 or omega-5-gliadin (1 patient).

Pattern of sensitization to other cereals: barley (5 patients), rye (5 patients), rice (2 patients), corn (1 patient).

Pru p 3 and omega -5 gliadin were assessed by CAP, alpha-amylase inhibitor and Tri a 14 by immunoblotting , the latter was subsequently confirmed on stocked sera by CAP when this became available.