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Celiac Disease and Sensitization to Wheat, Rye, and Barley: Should We Be Concerned?

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Celiac disease · Allergy · Immunoglobulin E · Wheat · Sensitization

Abstract
Background: Concomitance of celiac disease (CD) and IgE-mediated wheat allergy is described in some case reports. The objective was to evaluate the frequency of sensitization to wheat, rye, barley, and malt in children and adolescents with CD. ***Methods:*** Measurement of serum levels of specific IgE to wheat, rye, barley, and malt (ImmunoCAP; sensitization IgE ≥0.35 kUA/L) in CD patients followed in specialized clinics to verify allergy history, general characteristics, small bowel biopsy characteristics, compliance with gluten-free diet (GFD), and occurrence of symptoms in case of noncompliance. ***Results:*** We evaluated 74 patients; the median of age and age at diagnosis of CD were 8.6 years (5.0–12.8) and 3.6 years (1.6–7.0), respectively. Median time of GFD was 3.5 years (1.4–5.8). History of asthma occurred in 17.3% of subjects, allergic rhinitis in 13.5%, and AD in 5.4%. Frequency of sensitization was 4% for wheat, 10.8% for rye, 5.4% for barley, and 2.7% for malt. There was no association between wheat sensitization and age at diagnosis, time of GFD, small bowel biopsy characteristics, allergy history, and gluten consumption. There was no relationship between sensitization to wheat and occurrence of immediate symptoms when not complying with GFD. ***Conclusion:*** In conclusion, the frequency of sensitization to wheat, rye, barley, and malt in CD patients was 4, 10.8, 5.4, and 2.7%, respectively. Therefore, to ensure that cutaneous and respiratory contact with wheat is safe, we advise patients with CD to investigate their sensitivity to wheat, rye, and barley because not all patients with CD are allergic to these cereals.

Introduction

Celiac disease (CD) is a systemic disease mediated by T helper type 1 (Th1) lymphocytes, which occurs in genetically predisposed individuals exposed to gluten and other environmental factors [1, 2]. The result of this interaction of factors generates an inflammatory reaction that causes damage to the intestinal mucosa [1, 2]. The

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only effective treatment is removing wheat, rye, barley, and the byproduct of barley, malt, from diet [1, 2]. Wheat allergy (WA) is characterized as an immunological reaction in which manifestations will depend on the route of exposure and immunological mechanisms involved [3, 4]. Wheat, rye, and barley may cause allergy through inhalation, ingestion, and skin contact [3–5]. In WA, activation of type 2 T helper lymphocytes (Th2) in the gastrointestinal mucosa promotes two mechanisms that lead to allergic reactions: IgE-mediated food allergy that stimulates immunoglobulin E (IgE) production and non-IgE-mediated food allergy that can lead to a chronic cellular inflammation, often characterized by the presence of T cell and eosinophils, which is a much less understood pathogenetic mechanism [5]. Treatment consists of avoiding contact with wheat and eliminating it from diet [3–5].

Studies show a higher occurrence of atopic dermatitis (AD), asthma, and rhinitis in CD patients [6–8]. Concomitance of CD and IgE-mediated WA, including anaphylaxis, is described in case reports and coexistence of Th1 and Th2 lymphocyte-mediated diseases is still under debate [8–15]. A Finnish study showed a high frequency of wheat sensitization (WS) (specific IgE ≥0.35 kUA/L) in CD patients, that is, 11.9% [8]. Some authors question whether exclusion of foods from diet could lead to loss of tolerance, favoring mediated IgE reactions [13, 14, 16].

There are social media reports of CD patients exhibiting symptoms from topical or inhaled gluten contact, suggesting that they also avoid these routes of exposure. We then question the frequency of sensitization to wheat, rye, barley, and malt in CD patients.

We decided to conduct this study due to the scarcity of studies and the need for more reliable data to inform CD patients about sensitization to wheat, rye, barley, and malt. The objective of this work was to evaluate the frequency of sensitization (serum specific IgE) to wheat, rye, barley, and malt in children and adolescents with CD at a referral clinic.

Materials and Methods

This is a descriptive, cross-sectional study of patients diagnosed with CD from a Pediatric Gastroenterology Celiac Disease Clinic of Paulista School of Medicine – Federal University of São Paulo. We included patients aged from 1 to 20 years old, followed-up at the clinic, and who were evaluated at the time of consultation during the data collection period.

Diagnosis of CD was based on the presence of a suggestive clinical history of CD, or an asymptomatic patient with first-degree relatives with CD, positive antibodies to transglutaminase or endomysial with small bowel mucosal villous atrophy (Marsh III) at the time of diagnosis, and mucosal's normalization after 1 year of a gluten-free diet (GFD). It is worth mentioning that after 1 year of diet, all patients undergo a new small bowel biopsy. All biopsies were evaluated and classified according to Marsh [17] criteria modified by Rostami et al. [18].

Symptoms at the diagnosis, general characteristics, and allergy history manifested by the report of specialist follow-up and/or treatment of asthma, rhinitis, AD, food allergy, urticaria, and eosinophilic esophagitis were obtained by retrospectively reviewing the medical record. We evaluated if the GFD was being followed and looked for symptoms to be triggered if the restrictive diet was not obeyed. Voluntarily consumption of gluten was considered present when there was a report from 6 months of the beginning of GFD until the closest consultation to obtain specific IgE (sIgE). Symptoms were classified as immediate (medical record, when it was present within 24 h of voluntary gluten consumption) or late (when it was present after 24 h of voluntary gluten consumption up to 30 days). All data were collected using a standardized questionnaire at the time of blood collection. Peripheral blood samples were collected for measurement of serum sIgE levels (enzymatic fluorescence test; ImmunoCAP®, Thermo Fisher Scientific) on wheat, rye, barley, and malt. Levels ≥0.35 kUA/L were considered positive.

Age at diagnosis, age at collection, follow-up of GFD, and sIgE values were presented as median and 25–75 percentiles. These variables were compared according to the presence or absence of sensitization using Mann-Whitney test. χ^2 test was used in the evaluation of the possible association between the degree of villous atrophy and the occurrence of sensitization to the evaluated allergens. Fisher's exact test was used in the evaluation of sensitization and its relation with allergy history, as well as the noncompliance with GFD and the time intervals of GFD. Significance level was set at 0.05. IBM SPSS Statistics 22® software was used for statistical calculation.

The study was approved by the Research Ethics Committee of Federal University of São Paulo under number 035.714/2013. Those responsible signed term of consent, and patients signed term of assent.

Results

Of 123 screened patients, 74 were included in the study, 55.4% being female. Associated comorbidities were Down syndrome (n = 2), type 1 diabetes mellitus (n = 2), deficiency of immunoglobulin A (n = 3), Crohn's disease and hepatopathy (n = 1), vitiligo (n = 1), congenital megacolon and intestinal volvulus (n = 1), Evans syndrome (n = 1), and cystic fibrosis (n = 1). One patient had suspected Marfan syndrome, and 12.2% (9/74) of the patients were first-degree relatives of individuals with CD. Frequency of sensitization to wheat, rye, barley, and malt among CD patients was 4, 10.8, 5.4, and 2.7%, respectively (Table 1). Only 2.7% (2/74) of the patients were sensitized simultaneously to wheat, barley, rye, and malt. Of

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Table 1. Clinical and laboratory characteristics of patients, according to the presence of sensitization to wheat, rye, barley, and malt

	WS			Rye sensitization			Barley sensitization			Malt sensitization		
	yes *n* = 3 (4%)	no *n* = 71 (96%)	*p* value	yes *n* = 8 (10.8%)	no *n* = 66 (89.2%)	*p* value	yes *n* = 4 (5.4%)	no *n* = 70 (96.4%)	*p* value	yes *n* = 2 (2.7%)	no	*p* value
Median age, years	9.4 (9.3–12.2)	8.3 (4.9–12.5)	0.397*	11.7 (9.4–14.1)	8.1 (4.9–12.5)	0.062*	11.2 (8.9–14.1)	8.3 (4.9–12.5)	0.241*	11.2 (9.3–13.1)	8.6 (4.9–12.6)	0.433*
Median age at diagnosis, years	6.1 (3.0–7.5)	3.6 (1.6–7.2)	0.612*	4.4 (1.7–8.7)	3.6 (1.6–6.9)	0.875*	6.4 (3.3–8.7)	3.6 (1.6–6.9)	0.416*	4.9 (1.8–8.0)	3.7 (1.6–7.1)	0.907*
Small intestine biopsies												
Marsh IIIa	2	11	0.156**	3	10	0.282**	2	11	0.843**	1	12	0.645**
Marsh IIIb	0	11	NC	1	10	>1**	0	11	NC	0	11	NC
Marsh IIIc	1	49	0.488**	4	46	0.460**	2	48	0.782**	1	49	>1**
Median time of GFD, years	3.3 (1.8–9.2)	3.6 (1.4–5.8)	0.742*	7.5 (4.2–10.1)	3.3 (1.3–5.4)	0.028*	4.8 (2.5–8.5)	3.3 (1.4–6.2)	0.437*	6.3 (1.3–11.2)	3.5 (1.4–6.0)	0.629*
Specific IgE												
≤0.35 kUA/L		71			66			70			72	
0.36–0.69 kUA/L	0			5			2			0		
0.7–3.49 kUA/L	1			0			1			1		
Gluten consumption	2	43	>1***	6	39	0.642***	3	42	0.974***	1	44	>1***
Immediate symptoms	0	2	NC	0	2	NC	0	2	NC	0	2	NC
Late symptoms	1	12		1	13		1	13		1	12	
Without symptoms	1	29		5	24		2	27		0	30	

NC, non-calculable; WS, wheat sensitization; GFD, gluten-free diet. * Mann-Whitney test. ** χ^2 test. *** Fisher's exact test.

Table 2. Frequency of allergy history and the occurrence of sensitization to wheat, rye, barley, and malt

	WS $n = 3$			Rye sensitization $n = 8$			Barley sensitization $n = 4$			Malt sensitization $n = 2$		
	yes	no	*p* value*	yes	no	*p* value*	yes	no	*p* value*	yes	no	*p* value*
Asthma	0	13	NC	0	13	NC	1	12	>1	0	13	NC
Rhinitis	1	9	0.715	2	8	0.588	1	9	0.896	1	9	0.254
AD	1	3	0.311	1	3	0.747	0	4	NC	0	4	NC
Urticaria	0	1	NC	0	1	NC	0	1	NC	0	1	NC
Food allergy	0	6	NC	0	6	NC	0	6	NC	0	6	NC
Eosinophilic esophagitis	0	1	NC	0	1	NC	0	1	NC	0	1	NC

NC, non-calculable; AD, atopic dermatitis; WS, wheat sensitization. * Fisher's exact test.

the 3 patients with WS, 2 were sensitive to all of the allergens and 1 was also sensitive to rye. Median serum level (25–75 percentile) of sIgE was 15.3 kUA/L (4.5–18.9 kUA/L) to wheat, 0.63 kUA/L (0.5–20.0 kUA/L) to rye, 0.7 kUA/L (0.4–10.0 kUA/L) to barley, and 5.5 kUA/L (0.8–10.1 kUA/L) to malt. There was no statistically significant difference in the proportion of sensitization among the studied allergens, $p = 0.160$.

Regarding the personal history of allergic diseases, history of asthma was present in 17.6% (13/74) of patients, rhinitis in 13.5% (10/74), and AD in 5.4% (4/74). One patient reported a history of urticaria using ibuprofen. Regarding the previous history of food allergy, 8.1% (6/74) of the patients presented allergy to milk and/or to soy. One patient had a history of eosinophilic esophagitis.

Table 2 presents the frequency of allergy history and presence of sensitization to the studied allergens. One of the 10 patients with allergic rhinitis presented sIgE above 3.5 kUA/L for wheat (15.3 kUA/L), rye (17.4 kUA/L), barley (19 kUA/L), and malt (10.1 kUA/L). Concerning AD, only one of the 4 patients presented sensitization to wheat (sIgE 20.1 kUA/L) and barley (22.5 kUA/L); the symptoms of AD disappeared after GFD.

Concerning gluten consumption, 60.8% (45/74) reported noncompliance with GFD. Among these, who voluntarily consumed gluten, 2/45 had WS – sIgE 15.3 kUA/L with late symptoms and 20.1 kUA/L without symptoms (Table 1). When median time of GFD and sensitization were evaluated, GFD time of rye-sensitized patients was statistically longer than non-sensitized ($p = 0.028$).

Only 2.7% (2/74) of the patients had immediate symptoms after consumption of gluten, one manifested diarrhea, and the other experienced pain, bloating, and vomiting. None of these patients with immediate symptoms were sensitized to wheat, rye, barley, and malt. Patients who presented late symptoms after gluten consumption (17.6%, 13/74) reported abdominal pain, vomiting, diarrhea, and abdominal distension. Of the total number of patients that consumed gluten, 66.7% (30/45) had no symptoms after consumption.

Discussion/Conclusion

In this study, sensitization frequencies of wheat, rye, barley, and malt were 4, 10.8, 5.4, and 2.7%, respectively. Frequency of WS in CD was reported in two pediatric studies [8, 19]. One of them evaluated 57 children between 3 and 6 months of age with a history of growth retardation, gastrointestinal, or cutaneous symptoms related to the introduction of cereals in the diet. The authors observed villous atrophy (Marsh III) in 36 of them, and 4 of these (11.1%) were sensitized to wheat and 3 to barley (8.3%). Two of 3 wheat-sensitive patients were sensitive to barley [19]. Other study reported WS in 5 out of 42 (11.9%) children with CD, assessed by sIgE measurement [8].

Other studies evaluating sensitization to wheat and/or rye, barley, and malt in CD patients did so as case reports ($n = 9$) [9–15]. Anaphylaxis episodes have been reported in 3 patients [12, 14, 15], 1 of whom died [12]. In these reports, sIgE levels for wheat ranged from 2.99 to 100 kUA/L, for barley between 11.3 and 15.1 kUA/L, and for rye between 1.91 and 33.9 kUA/L [9–15]. The sIgE for malt was evaluated in only one patient and reached 24.5 kUA/L [9]. Seven of the 9 patients described that they had a history of allergy [9–15]. In the present study, one patient with AD was sensitized to wheat (20.1 kUA/L) and barley (22.5 kUA/L), and another patient with rhinitis

was sensitized to wheat (15.3 kUA/L), rye (17.4 kUA/L), barley (19 kUA/L), and malt (10.1 kUA/L).

Regarding sensitization to wheat in general population, a systematic review with European data reported a prevalence of 3.9%, based on studies involving the ages from 2 to 17 years [20]. In a Finnish study with 5-year-old children, the frequency of sensitization was 5% [21], and in a Swedish study with 4-year-old children, it was 4% [22]. In our study, the frequency of sensitization to wheat is similar to that in these studies. On the other hand, another pediatric study that evaluated 10 years old children in the UK found 15% wheat sensitivity [23]. Brazilian and Latin American studies are scarce. Two Brazilian multicentric studies evaluated WS in atopic patients and controls [24, 25]. The first one observed a frequency of 20.1% among atopic patients and 8.1% among controls [24]; the other study, 12 years later, observed an increase of these proportions, which were 23.4 and 9.4%, respectively [25].

Regarding the presence of WS and duration of a GFD, in our study, we did not observe this association. Verkasalo et al. [8] reported an average GFD time of 3 years in wheat-sensitized patients and an average of 9.1 years of diet in non-wheat-sensitized patients [8].

It is hypothesized that the food elimination diet in children could lead to mediated IgE reaction [16] and an increase in wheat sIgE and anaphylaxis [15]. In the present study, there was no history of anaphylaxis related to gluten consumption. Proportion of patients who consumed gluten was very high (60.8%), but the frequency of sensitization to wheat was equal to 4%. It is important to note that the 2 patients with immediate symptoms after gluten consumption did not present sensitization to wheat, rye, barley, or malt. Interestingly, in our study, the frequency of rye sensitization was high (10.8%), and these patients had a higher median GFD time (7.5 years).

Micozzi et al. [13] suggested 3 possible explanations for WS in patients on a GFD. First, WS could be masked by symptoms of CD, so gastrointestinal symptoms could be due to WA and not just CD. Second, CD patients could be previously sensitized to wheat and after a GFD would lose tolerance to wheat, developing an allergy. The last explanation would be that sensitization could occur during GFD by intermittent and inadvertent consumption of gluten. The same authors also point out that increasing the permeability of the mucosa could facilitate the passage of allergens and promote sensitization in contact with small amounts of these. It is worth noting that patients who did not follow GFD and presented WS were the same ones who had allergic rhinitis and an elevated sIgE level to wheat (15.3 kUA/L), rye (17.4 kUA/L), barley (19 kUA/L), and malt (10.1 kUA/L), and those with AD, with an sIgE of 20.1 kUA/L and 22.5 kUA/L for wheat and barley, respectively.

In our study, 17.3% of patients had asthma, 13.5% had allergic rhinitis, and 5.4% had AD. A Finnish cohort study demonstrated a significantly higher cumulative incidence of asthma among patients with CD (24.6%) as compared to those without CD (3.4%), at 7 years of age [26]. An Italian study in adults with CD evaluated the prevalence of asthma, rhinitis, and AD using a questionnaire and comparing them to their spouse or relatives living in the same residence. Among those with AD, there was the highest prevalence (3.8%) in relation to relatives (2.3%) and spouses (1.3%) [6]. Ellul et al. [7], using a questionnaire, evaluated the occurrence of asthma and rhinitis in patients with CD in Malta. Of 86 evaluated patients, 28.8% were asthmatic, while the frequency of asthma in the general population, established in another study, was 11%, a statistically significant difference. The same was observed with allergic rhinitis, where the proportion of patients with rhinitis and CD was higher (44%) than previously established in the general population (32.3%) [7]. Verkasalo et al. [8] evaluated 42 children with CD per questionnaire and reported a higher occurrence of AD (45%), gastrointestinal allergy (5%), and asthma (7.1%). In AD, there was a statistically significant difference as compared to the control group of students [8]. In our study, the frequency of asthma history in CD patients was higher when compared to a Brazilian multicentric study, whose frequency was 11.9% [27]. On the other hand, the frequency of AD and rhinitis in our study was lower when compared to the same study: 27.6 and 10.2%, respectively [27].

It should be emphasized that not all patients with a sIgE ≥ 0.35 presented an allergy; it is possible to evaluate only the sensitization and not the food allergy [2]. However, since the patients evaluated had CD, the oral food challenge for allergy diagnosis would not be possible due to ethical reasons. However, the presence of symptoms could be evaluated in patients who voluntarily consumed gluten although it cannot be considered an oral food challenge. There was no association between symptoms in 24 h after the consumption and the presence of sensitization to gluten – wheat, rye, barley, and malt.

Studies have attempted to establish sIgE levels that would be predisposed to positive triggering. Komata et al. [28] demonstrated a relationship between the probability of positive triggering and a sIgE concentration in wheat. Reaction to wheat with lower sIgE levels was higher in younger children [28]. Pourpak et al. [29] reported that 91.6% of patients with positive triggering presented a pos-

itive wheat sIgE. Another study established a cutoff value for wheat of 26 kUA/L at 90% specificity, which showed 61% sensitivity and 92% specificity in predicting allergic patients [30].

In our opinion, there are no grounds for the current movement, according to social networks, that all patients with CD should avoid cutaneous and inhalation exposure to wheat. Based on the frequency of sensitization to wheat in patients with CD equaled 4% in our study, it is still a lower proportion than the general population of the same country that was equal to 9.4% [25]. It is also important to note that most patients who had sensitization to wheat did not show symptoms when they did not follow GFD.

Limitations of our study refer to the data collection regarding allergy history, the occurrence of noncompliance with GFD, and no dosage of sIgE at the time of diagnosis. The absence of a dosage of total IgE is another limitation, whereas a high level of total IgE could show false positive results against sIgE. Further prospective studies should be performed to identify the presence of allergies, such as asthma, rhinitis, and AD, the dosage of serum levels of sIgE for wheat, rye, barley, and malt at the time of diagnosis, and total IgE dosage. Serum sIgE levels of these allergens along GFD are also suggested to evaluate the influence of diet on sensitization to these cereals.

In conclusion, the frequency of sensitization to wheat, rye, barley, and malt in CD patients was 4, 10.8, 5.4, and 2.7%, respectively. Therefore, to ensure that contact with wheat, both cutaneous and respiratory, is safe, we advise CD patients to investigate their sensitivity to wheat, rye, and barley because not all patients with CD are allergic to these cereals.

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Statement of Ethics

Study was approved by Research Ethics Committee of Federal University of São Paulo under number 035.714/2013. Those responsible signed term of consent, and patients signed term of assent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Camila Marques de Valois Lanzarin: substantial contributions to the conception, acquisition, analysis, and interpretation of data. Drafting the work. Final approval of the version to be published. Natalia Oliveira e Silva: acquisition, analysis, and interpretation of data for the work. Drafting the work. Final approval of the version to be published. Maissara Obara Venturieri: acquisition, analysis, and interpretation of data for the work. Drafting the work. Final approval of the version to be published. Dirceu Solé: Substantial contributions to the conception and design of the work. Revising it critically for important intellectual content. Final approval of the version to be published. Ricardo Palmero Oliveira: acquisition, analysis, and interpretation of data for the work. Drafting the work. Final approval of the version to be published. Vera Lucia Sdepanian: substantial contributions to the conception and design of the work. Analysis and interpretation of data for the work. Revising it critically for important intellectual content. Final approval of the version to be published.

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