Celiac Disease Frequency Is Increased in IgE-Mediated Food Allergy and Could Affect Allergy Severity and Resolution

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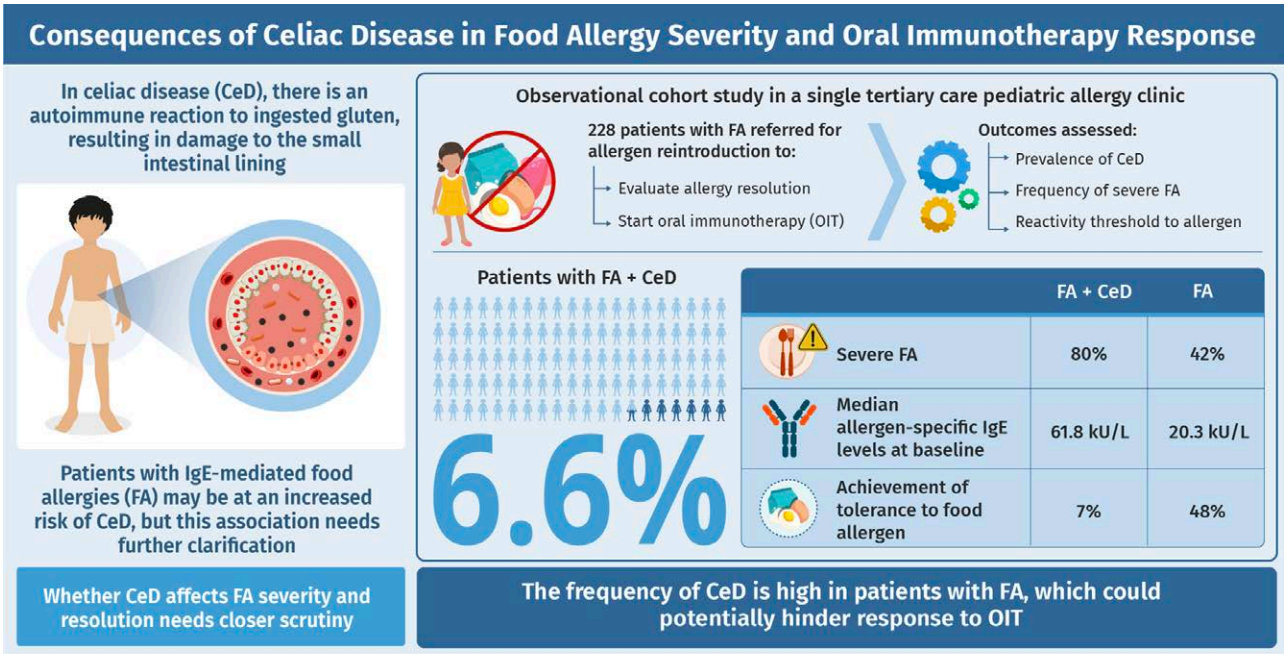
ABSTRACT

Objectives: An increased frequency of celiac disease (CeD) has been reported in severe Immunoglobulin E (IgE) -mediated food allergy (FA). This observation requires confirmation, and whether CeD affects FA severity and resolution is unknown. The study aims to estimate the prevalence of CeD in patients with FA and to investigate whether CeD affects FA severity and oral tolerance.

Methods: Consecutive patients with FA referred for allergen reintroduction, either to evaluate allergy resolution or to start oral immunotherapy (OIT), were evaluated for CeD and for FA severity. The primary outcome was the prevalence of CeD. Secondary outcomes were the frequency of severe FA and the level of clinical tolerance at study entry and at last follow-up in patients with isolated FA versus patients with FA + CeD.

Results: Two hundred twenty-eight patients were included. CeD was confirmed in 15 patients (6.6%) of whom, 8 patients had a previously established diagnosis of CeD and were on a gluten-free diet. Severe FA was observed in 12 patients with FA + CeD (80%) versus 88 patients with FA (42%) ($P = 0.006$). At baseline, patients with FA + CeD had significantly higher median allergen-specific IgE levels [61.8 kU/L; interquartile range (IQR) 11.6–279.0] compared to patients with FA (20.3 kU/L; IQR 2.9–72.7) ($P < 0.001$). Complete clinical tolerance was observed in 1 of 15 patients (7%) with FA + CeD versus 98 of 205 patients (48%) with FA ($P = 0.002$).



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What Is Known

- In a single-center retrospective cohort study, an increased risk of celiac disease was observed in patients with very severe IgE-mediated food allergy compared to the general population.
- The association between the 2 conditions needs further clarification.
- Whether celiac disease affects food allergy severity and resolution is unknown.

What Is New

- This study confirms a higher frequency of celiac disease in patients with severe or persistent food allergy compared to the general population.
- Celiac disease could negatively affect allergy severity and response to oral immunotherapy.

Conclusions: CeD is highly prevalent in patients with FA and could affect FA severity and response to OIT. CeD screening should be considered in patients with severe or persistent FA.

An infographic is available for this article at: *http://links.lww.com/MPG/C948.*

Key Words: celiac disease, IgE-mediated food allergy, immune tolerance, oral immunotherapy

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Celiac disease (CeD) is an autoimmune disorder triggered by gluten ingestion in genetically susceptible individuals that affects 1 in 100 people. CeD mainly affects the small bowel resulting in mucosal inflammation and intestinal epithelial barrier dysfunction (1). The association between CeD and IgE-mediated allergic disorders has been investigated in some studies with conflicting results (2,3). A 5-fold increased risk of CeD in patients with very severe IgE-mediated food allergy (FA) attempting oral immunotherapy (OIT) has been observed in a single-center retrospective cohort study (4). However, the association between CeD and FA has yet to be clarified and whether the coexistence of CeD has any influence on FA severity and resolution is unknown. FA is a common condition with prevalence estimates of 1%–5% of the general population. FA is thought to result from a failure of mechanisms promoting immune tolerance to specific food antigens that reside mainly in the gastrointestinal tract and skin. Milk, hen egg, and peanuts allergies are the most frequently encountered FA in children, followed by tree nuts and sesame (5,6). Though milk and egg allergy often resolve spontaneously, 20%–30% of patients do not outgrow their allergy by adolescence. A number of clinical and laboratory measures have been associated with FA persistence or resolution, however mechanisms underlying FA persistence are still poorly defined (7). FA management has historically been based on specific food avoidance. In recent years, OIT has emerged as an alternative approach. OIT involves the daily ingestion of increasing doses of specific food allergens with the goal of reaching a state of clinical non-reactivity, also defined as clinical tolerance (8), so that the patient is able to eat some or a usual portion of food as long as there is regular exposure. Whether OIT can, in the long term, induce permanent tolerance remains to be established (9,10).

The aim of the present study was to evaluate the prevalence of CeD in patients with IgE-mediated FA undergoing allergen reintroduction, either to assess allergy resolution or to start OIT, and to investigate whether the coexistence of CeD affects FA severity and response to OIT.

METHODS

This was an observational cohort study conducted at a single tertiary care pediatric allergy clinic from 2015 to 2019. Consecutive patients with IgE-mediated FA referred to our clinic for allergen reintroduction, either to evaluate allergy resolution or to start OIT, were considered for inclusion in the study. Patients with IgE-mediated wheat allergy were excluded, representing a potential source of bias for possible false negative results at CeD screening.

FA was diagnosed based on a history of immediate reaction and/or skin prick testing or serum food-specific IgE (≥0.35 kUA/L). "Severe FA" was defined as history of severe allergic reactions (Clark grade ≥ 4) (11) to any alimentary antigen at any time and/or allergen-specific IgE levels > 85 kU/L.

Patients included in the study were screened for CeD by determination of Immunoglobulin A (IgA)/Immunoglobulin G (IgG) anti-endomysium antibodies and serum IgA/IgG anti-tissue transglutaminase antibodies (normal values <7 U/I) at the time of enrollment. Patients with an already established diagnosis of CeD were also included. Susceptibility alleles for CeD were determined by Polymerase Chain Reaction (PCR) with allele-specific primers identifying HLA DQ2 and DQ8. Patients with positive CeD serology were offered to complete the diagnostic work-up for CeD. Patients with confirmed CeD were advised to start a gluten-free diet (GFD).

Food allergen reintroduction could be either through a 10-day in-hospital rush phase protocol, as described elsewhere (12), or through an open oral food challenge (OFC) at the discretion of the treating physician, based on the patient clinical history. The 10-day in-hospital rush phase was chosen in all the patients with a history of anaphylaxis within the previous year.

Clinical tolerance was arbitrarily defined as: "none," when the patient had IgE-mediated symptoms with minimal food amounts that contraindicated the continuation of OIT or that led to suspension of OIT at follow-up, "intermediate," when the patient could introduce without reactions a minimal amount of food that would allow OIT to continue at home, and "complete," when a single usual portion of food could be consumed without adverse events. Patients with intermediate clinical tolerance continued OIT at home, starting from the maximum tolerated dose during the hospital phase, followed by home dose increases on a weekly basis, as per institutional protocol. Patients with a complete clinical tolerance at OFC were advised ingesting the food without restrictions or at least periodically.

Data collected at study entry included: the occurrence of severe allergic reactions (Clark grade ≥ 4) to any alimentary antigen and the coexistence of other food allergies on personal history, allergen-specific IgE levels, total IgE levels, the level of clinical tolerance at the end of in-hospital desensitization rush phase, or at OFC. At the end of the study period, patients who continued OIT at home were contacted by phone to assess the level of ongoing clinical tolerance. The primary outcome was the prevalence of CeD. Secondary outcomes were the frequency of severe FA and the level of clinical tolerance at study entry (before hospital rush/OFC) and at last follow-up in patients with FA versus patients with FA + CeD.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Burlo Garofolo Ethics committee, Institutional Review Board (IRB 311/2011).

Written informed parental consent was obtained from the patient or legal guardian.

Statistical Analysis

For the primary outcome, a sample size of 203 patients was calculated, considering an expected prevalence of CeD in patients

with severe or persistent IgE-mediated FA of 5% and a precision of 3%. Categorical variables were summarized by frequencies and were compared across independent groups with Chi-square or Fisher exact test where appropriate; numerical variables with asymmetrical distribution were summarized by median and interquartile range (IQR) and compared by the Kruskal-Wallis test. *P* values were calculated 2-tailed, and a *P* value <0.05 was considered for significance. Statistical analysis was made using Graph-pad Prism, version 8.2.1 (LLC, San Diego, CA).

RESULTS

Study Population

A total of 232 patients were considered for enrollment during the period from January 2015 to June 2019 (Fig. 1). After excluding patients with wheat allergy, 228 patients were included in the analysis for the primary outcome. One hundred forty-two patients (62%) were males; the median age at study entry was 8 years (IQR 5–13). Baseline disease characteristics of patients included in the study are summarized in Table 1. Food allergen was reintroduced through the 10-day in-hospital rush phase protocol in 67 patients (29%) and OFC in 161 patients (71%). One hundred sixty-one patients (71%) continued OIT at home. The median time to last follow-up was 3 years (IQR 1–4).

Prevalence of CeD and Characteristics of Patients With CeD

Within the cohort, CeD was diagnosed in 15 patients (6.6%). Among these, 8 patients already had a biopsy-proven diagnosis of CeD and 7 patients tested positive for CeD serology at study entry. Of the latter, 4 patients had duodenal villous atrophy (Marsh grading 2–3) and 3 patients had either normal (Marsh 0) histology or isolated intra-epithelial lymphocytosis (Marsh 1) and were diagnosed as potential CeD as per European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines. None of the patients met the ESPGHAN criteria for a serology-based diagnosis without biopsy (13). In all of the patients, FA had been diagnosed prior to CeD. Among the patients with a previously established diagnosis of CeD, CeD screening had been prompted by the presence of symptoms (failure to thrive) in 5 patients, a family history of CeD in 2 patients, and the presence of extraintestinal autoimmune conditions (chronic urticaria) in 1 patient. Of the patients who tested positive for CeD serology at study entry, 1 patient had symptoms compatible with CeD (failure to thrive). All the patients with a previously established diagnosis of CeD were on GFD for at median 3.5 years (IQR 2.7–6.3). Of the 7 patients diagnosed with CeD at study entry, 6 patients started a GFD. One patient, diagnosed with potential CeD, who had previously undergone OIT for wheat allergy, continued to include gluten in the diet.

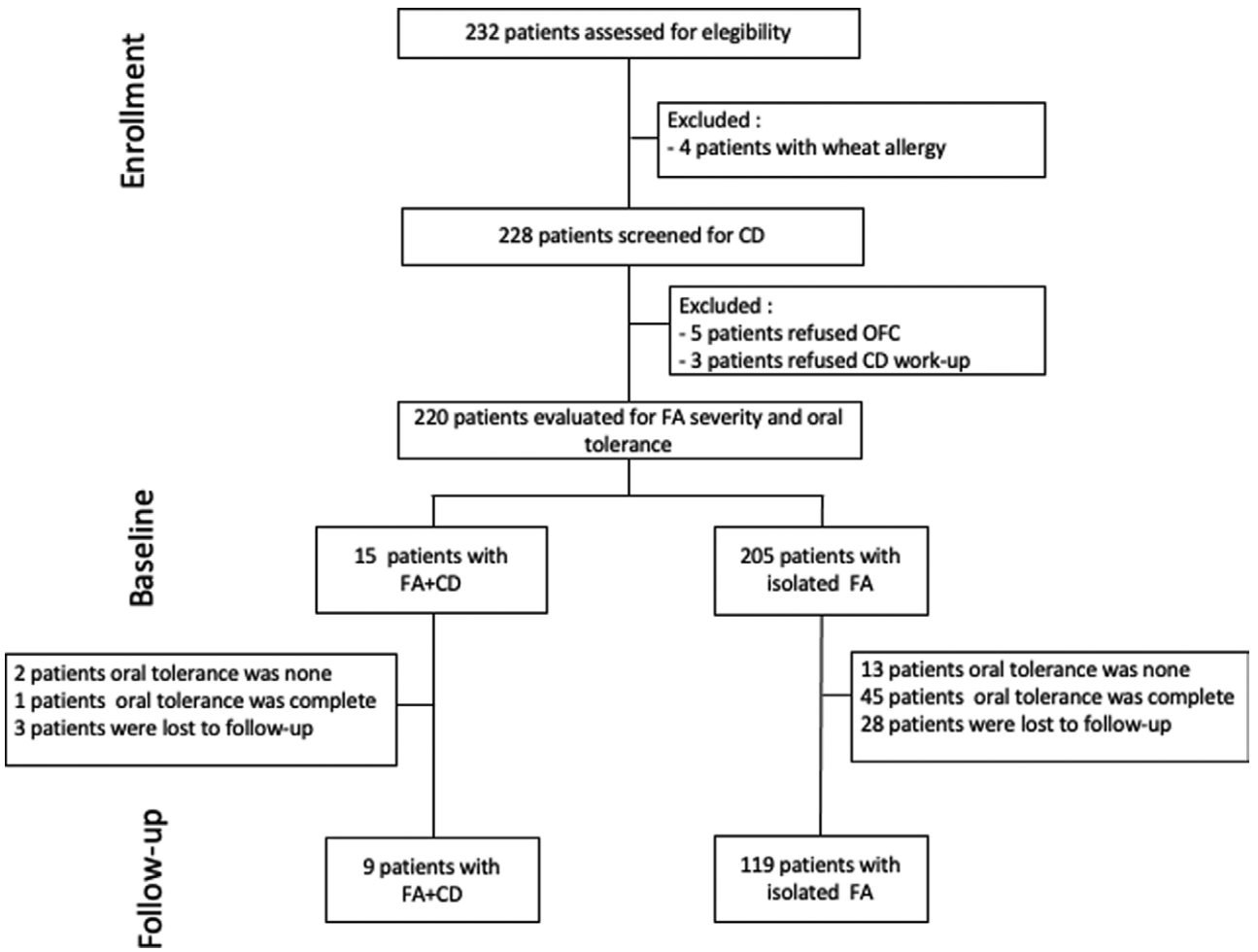

FIGURE 1. Enrollment and follow-up. CD = celiac disease; FA = food allergy; OFC = oral food challenge.

TABLE 1. Disease characteristics of patients enrolled in the study

Characteristics	Patients, n = 228
Median age, y (IQR)	8 (5–13)
Males, n (%)	142 (62)
Severe food allergy, n (%)	100 (44)
Multiple food allergies, n (%)	103 (45)
Food reintroduced	
Milk, n (%)	121 (53)
Egg, n (%)	65 (29)
Nuts, n (%)	37 (16)
Fish, n (%)	4 (2)
Legumes, n (%)	1 (0.4)
Food reintroduction modality	
In-hospital rush phase (%)	67 (29)
Oral food challenge (%)	161 (71)
Clinical tolerance*	
None, n (%)	16 (7)
Intermediate, n (%)	161 (71)
Complete, n (%)	46 (20)

IQR = interquartile range. *At oral food challenge or at the end of the in-hospital rush phase protocol.

Eight additional patients screened positive for CeD serology at study entry. The finding was not confirmed on a second serum sample in 5 patients and 3 patients refused to undergo further evaluations and were thus excluded from the following analyses.

FA Severity and Oral Tolerance in Patients With FA Versus Patients With FA + CeD

A history of severe FA was observed in 12 of 15 patients (80%) with FA + CeD versus 88 of 205 patients (43%) with isolated FA ($P = 0.006$). Ten patients (67%) in the FA + CeD group and 69 patients (34%) in the FA group had a prior severe reaction (Clark grade ≥ 4) with the food being reintroduced ($P = 0.02$).

At study entry, patients with FA + CeD had significantly higher allergen-specific median IgE levels (61.8 kU/L; IQR 11.6–279.0) compared to patients with isolated FA (20.3 kU/L; IQR 2.9–72.7) ($P < 0.001$). The type of food being reintroduced and reintroduction modalities in patients with FA + CeD and isolated FA are summarized in Table 2. Overall, complete clinical tolerance was observed in 1 of 15 patients (7%) with FA + CeD versus 98 of 205 patients (48%) with isolated FA ($P = 0.002$). At baseline, the proportion of patients according to the level of clinical tolerance did not differ significantly between the 2 groups (Fig. 2A).

At follow-up, none of the patients (0%) with FA + CeD achieved complete clinical tolerance versus 53 patients (45%) with isolated FA ($P = 0.01$; Fig. 2B).

DISCUSSION

In this cohort study, we found that approximately 7% of patients with FA reintroducing the offending food either to evaluate allergy resolution or to start OIT, had concomitant CeD. In addition, patients with CeD more frequently had clinical and biologic markers of severe allergy than patients with isolated FA, and were less likely to achieve a high level of clinical tolerance when OIT was attempted.

This result confirms 1 previous observation by the same group of a 5-fold increase risk of CeD in patients with very severe FA (defined by IgE > 85 kU/L and history of severe reactions) undergoing OIT compared to the general population (4). Other studies have been published that evaluated the prevalence of IgE sensitization in patients with CeD. These studies were focused on adult individuals and failed to show consistent findings. In one Danish cross-sectional population-based study, individuals with biopsy-proven CeD and CeD antibody-positivity had a significantly higher prevalence of IgE-mediated sensitization to food allergens, dust mite, and mugwort compared to the general population. However, when analyzing serum samples from a research biobank in the same study, the authors failed to confirm the association (2). Also, in one large Italian cohort that included more than 1000 CeD patients at the time of diagnosis, the prevalence of allergic disorders did not differ between patients with CeD and their relatives or spouses (3).

FA and CeD have been historically considered 2 antithetic conditions, driven by distinct patterns of cytokine expression. Recent experimental-based studies provided evidence of an important role of intestinal epithelial cells (IEC) and gut resident T-regulatory cells (pTreg) in the development and maintenance of oral tolerance. Although several studies support the notion that initiation of T_H2 sensitizing response to dietary antigens is mediated by skin exposure, IEC might also have a relevant role in determining the immunologic outcomes to food antigens. IEC mediate the translocation and delivery of dietary antigen from the intestinal lumen to the immune compartment in the lamina propria and induce long-lived antigen-specific pTreg that are essential for immune tolerance (13,14). Moreover, under specific circumstances IEC are able to

TABLE 2. Type of food being reintroduced at study entry and reintroduction modality

	FA, n = 205	FA + CeD, n = 15	*P* value
Type of food			
Milk, n (%)	109 (53)	9 (60)	0.8
Egg, n (%)	55 (27)	6 (40)	0.4
Nuts, n (%)	36 (17)	0	0.14
Fish, n (%)	4 (2)	0	1.0
Legumes, n (%)	1 (0.05)	0	1.0
Reintroduction modality			
In-hospital rush phase (%)	58 (28)	8 (53)	0.07
Oral food challenge (%)	147 (72)	7 (47)	0.07

CeD = celiac disease; FA = food allergy.

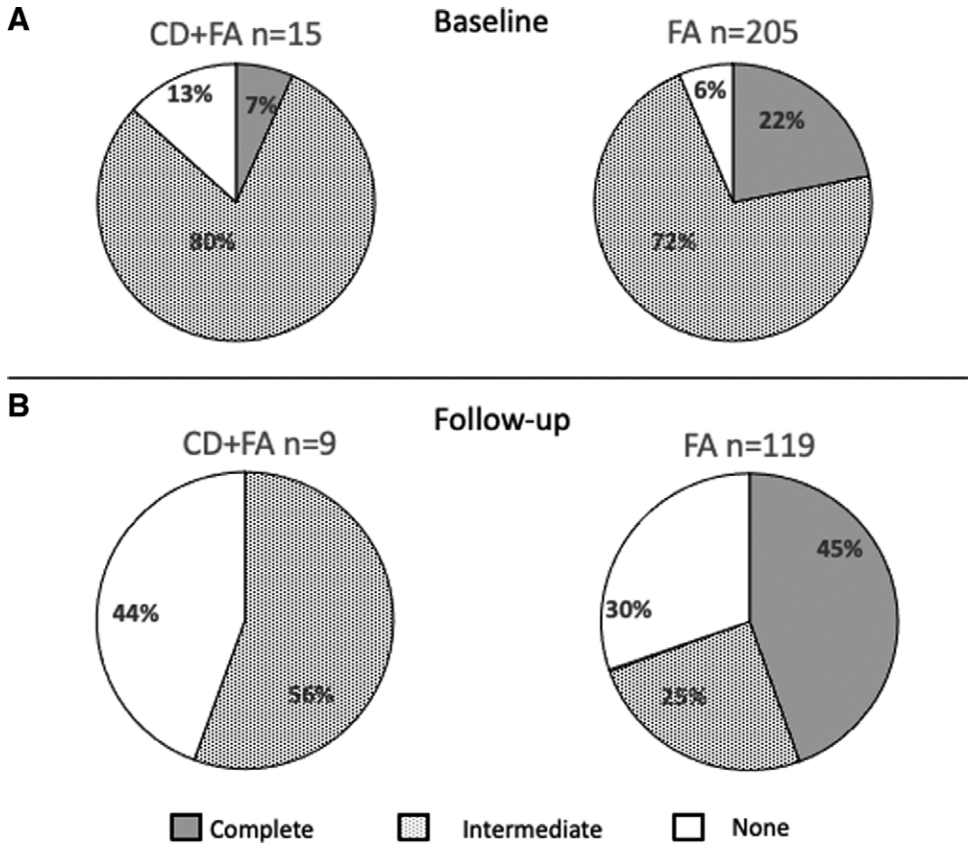

FIGURE 2. Proportion of patients according to level of clinical tolerance at baseline (A) and after oral immunotherapy at last follow-up (B). CD = celiac disease; FA = food allergy.

produce pro-type 2 cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin (13).

Small intestinal mucosal damage with villous atrophy is the hallmark of CeD. In recent years, genome-wide transcriptomic studies have shown that numerous genes are differentially expressed in IEC of CeD patients compared to healthy individuals. This dysfunctional pattern of gene expression is not simply the consequence of epithelial damage as it persists despite normalization of the duodenal mucosa upon long-term GFD (15). This observation suggests that epigenetic changes in IEC of CeD patients might be present before the development of mucosal damage.

Based on these observations, we speculate that CeD-induced dysfunction of the IEC might prevent the development of immune tolerance in children who are already sensitized to food antigens and might contribute to FA persistence and severity.

Our findings have important practical implications. Given the high prevalence, CeD screening should be considered in children with severe or persistent FA. Also, anticipating the possibility of OIT failure, adjuvant therapies might be evaluated in allergic patients with concomitant CeD, especially in patients with other risk factors for OIT failure.

Some limitations of the present study are acknowledged. The sample size was calculated for the primary outcome and the number of patients compared for the secondary outcomes is small and may have resulted in an inflation type 1 (false-positive) error. The severity of previous reactions may be confounded by the dose exposure however, in the absence of a uniform definition for FA severity (16), we based our definition of allergy severity on both clinical symptoms and allergen-specific IgE levels. The inclusion of multiple allergens implied that there was a significant heterogeneity in OIT protocols by allergen. However, for each allergen the same protocol has been applied at baseline and at follow-up. Follow-up was made by phone calls; thus, we do not have biologic markers of the degree of sensitization after OIT. Since many patients who are referred to our clinic for OIT do not live close, we anticipated that telephonic contact would reduce loss to follow-up. Major strengths of the study are the large number of patients with severe or persistent FA and relative high number of patients with concomitant CeD and FA.

CONCLUSIONS

To conclude, in this large cohort study the prevalence of CeD in patients with FA is higher than in the general population. When the two conditions coexist, failure to achieve complete oral tolerance with OIT may occur. CeD screening should be considered in patients with severe or persistent FA. Further studies with an adequate sample size are needed to confirm the effect of CeD on FA severity and to elucidate the role of CeD-induced epithelial dysfunction in preventing allergy resolution.

REFERENCES

1. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018;391:70–81.
2. Kårhus LL, Skaaby T, Madsen AL, et al. The association of celiac disease and allergic disease in a general adult population. *United European Gastroenterol J* 2019;7:78–89.

3. Ciacci C, Cavallaro R, Iovino P, et al. Allergy prevalence in adult celiac disease. *J Allergy Clin Immunol* 2004;113:1199–203.
4. Pillon R, Ziberna F, Badina L, et al. Prevalence of celiac disease in patients with severe food allergy. *Allergy* 2015;70:1346–9.
5. Longo G, Berti I, Burks AW, Krauss B, Barbi E. IgE-mediated food allergy in children. *Lancet* 2013;382:1656–64.
6. Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food allergy from infancy through adulthood. *J Allergy Clin Immunol Pract* 2020;8:1854–64.
7. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol* 2016;4:196–203; quiz 204.
8. Moran TP, Burks AW. Is clinical tolerance possible after allergen immunotherapy? *Curr Allergy Asthma Rep* 2015;15:23.
9. Kim EH, Burks AW. Food allergy immunotherapy: oral immunotherapy and epicutaneous immunotherapy. *Allergy* 2020;75:1337–46.
10. Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol* 2016;137:973–82.
11. Clark A, Ewan P. Food allergy in childhood. *Arch Dis Child* 2003;88:79–81.
12. Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008;121:343–7.
13. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr* 2020;70:141–56.
14. Newberry RD, Hogan SP. Intestinal epithelial cells in tolerance and allergy to dietary antigens. *J Allergy Clin Immunol* 2021;147:45–8.
15. Bertolini TB, Biswas M, Terhorst C, Daniell H, Herzog RW, Piñeros AR. Role of orally induced regulatory T cells in immunotherapy and tolerance. *Cell Immunol* 2021;359:104251.
16. Arasi S, Nurmatov U, Dunn-Galvin A, et al. Consensus on DEfinition of Food Allergy SEverity (DEFASE) an integrated mixed methods systematic review. *World Allergy Organ J* 2021;14:100503.