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Immunoglobulin E-Mediated Food Sensitization in Children with Celiac Disease: A Single-Center Experience

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Celiac disease (CD) is an autoimmune disorder of the small intestine caused by an abnormal immune response to gluten proteins and is often characterized by gastrointestinal symptoms. Food allergy (FA) is an adverse immune sensitivity to ingested food proteins leading to inflammation in various organs including the gastrointestinal tract. The relationship between CD and FA remains unclear. This study aimed to assess the prevalence and clinical relevance of immunoglobulin E (IgE)-mediated food sensitization in children with CD.
Methods: Fifty-nine children diagnosed with CD were reviewed for clinical symptoms and evidence of IgE-sensitization to food and airborne allergens using the PolyCheck method.
Results: IgE-mediated sensitization has been diagnosed in 20.3% of children with CD (CD/A). In the CD/A group, 58.3% of children were sensitized to food and 66.7% to airborne allergens. Further, 41.7% of patients with CD and allergy reported gastrointestinal tract symptoms associated with the ingestion of sensitizing foods. Analysis of the clinical status revealed that the incidence of other allergic disorders in the CD/A group was as follows: atopic dermatitis (33.3%), asthma (25.0%), and allergic rhinitis (16.7%). The percentage of eosinophils was significantly higher in the CD/A group than in the CD group (0.33±0.25 vs. 0.11±0.09; p=0.006).
Conclusion: The diagnosis of CD does not exclude FA. The gastrointestinal symptoms in children with CD may be the result of both CD and FA; therefore, children with CD should be evaluated for the presence of FA regardless of age.

Keywords: Food hypersensitivity; Celiac disease; Child

INTRODUCTION

Celiac disease (CD) and food allergy (FA) are immunologic diseases, but the relationship between them has not been thoroughly investigated. Although there are many similarities in their pathophysiology, trigger factors, disease course, and treatment, their coexistence is rarely reported [1,2].

CD is a long-term autoimmune disorder that occurs in genetically predisposed children. Ingestion of gluten proteins from cereals causes abnormal immune response inducing

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the production of several different autoantibodies such as anti-tissue transglutaminase, antiendomysial, and anti-deamidated gliadin peptide (anti-DGP) that affect many different organs, primarily the small intestine leading to villous atrophy. The damage to the intestinal villi is the cause of the malabsorption of nutrients. CD typically presents with gastrointestinal (GI) symptoms such as abdominal bloating and pain, chronic diarrhea, vomiting, constipation, foul-smelling or fatty stool, weight loss, delayed growth, and puberty. Although CD mainly affects the small intestine, other organs such as the skin and nervous system can also be involved [3].

In comparison to CD, FA is an adverse immune hypersensitivity (immunoglobulin E [IgE] or non-IgE-mediated) to ingested food proteins leading to inflammation in various organs and systems including the GI tract. The most common symptoms include abdominal pain, vomiting, and/or diarrhea. Recent hypothesis on the pathogenesis of GI FA indicates the crucial role of the epithelial barrier damage on non-characteristic endoscopic changes (diffuse and/or hemorrhagic inflammation, without or with involvement of the ileum and atrophy of the intestinal villi) [4,5].

FA affects 4–6% of children, with the most common harmful food allergens being cow milk, eggs, peanuts, tree nuts, seafood, shellfish, soy, and wheat. IgE-mediated FA is a specific type of immediate hypersensitivity, which develops in individuals genetically predisposed to the production of IgE antibodies [4,6].

Clinical symptoms and biochemical abnormalities ameliorate after the elimination diet in both conditions. A lifelong gluten-free diet and a diet with temporary elimination of harmful food allergens are prescribed in CD and FA, respectively. It is also known that dysfunction of the immune system, disturbances in gut microbiota together with a genetic predisposition may promote the development of CD and FA [7,8].

Although the relationship between CD and allergic diseases seems to be very interesting, only a few studies on this topic have been conducted on the general adult population [1,2,9]. The published data in the pediatric population focused on the association of CD with allergic symptoms or wheat sensitivity and other non-celiac gluten-related disorders [10,11].

The study aimed to evaluate the prevalence and clinical relevance of IgE-mediated food sensitization in children with CD.

MATERIALS AND METHODS

This retrospective study was conducted on a group of 59 children hospitalized with CD over three years (2016–2018). The patients with concomitant diseases that could be a cause of villous atrophy were excluded from the analysis [12].

The diagnosis of CD was based on the results of IgA anti-tissue transglutaminase antibodies (IgA-tTGA) evaluated by immunoenzymatic ELISA method (considered as positive, if IgA-tTGA >10 U/mL) and confirmed by villous atrophy in the duodenum biopsy. Patients with low serum IgA were screened for anti-DGP [13]. The diagnosis of CD was always done before the implementation of dietary treatment.

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All individuals were tested for the presence of IgE-sensitization to 20 major food and airborne allergens evaluated using a multiparameter immunoblot PolyCheck method (Biocheck GmbH, Münster, Germany) according to the manufacturer's instructions. The detection limit of the system is 0.35 kU/L IgE; measurable specific IgE was defined as positive if the level was >0.7 kU/L. Some participants, with doubtful results, underwent skin prick tests (SPT) with major native food allergens (milk, egg, soy, wheat, pork, cod, citrus fruits, and peanuts) and airborne allergens (standardized test by Allergopharma and Nexter).

Patients with negative results on allergic tests served as a control group. The final diagnosis of IgE-mediated FA was based on the history of patients who experienced the reaction following ingestion of specific food and on the increased concentration of serum food-specific IgE antibodies and/or the SPT outcome.

The medical history was analyzed with attention to clinical features suggestive of CD and allergy. Subjects were also reviewed for co-morbidities, anthropometric parameters, and family history; all data were finally collected using a standardized questionnaire.

Ethical approval

The study was approved by the Local Ethics Committee of the Medical Univeristy of Bialystok (R-I-002/381/2019). The patients' data were de-identified.

Statistical analysis

Statistical analysis was performed using the STATISTICA 13 software (TIBCO Software Inc., Palo Alto, CA, USA). The comparison of quantitative variables was carried out using the Student's *t*-test for normally distributed data and the Mann–Whitney test for nonparametric data. A p-value<0.05 was considered statistically significant.

RESULTS

Fifty-nine children (27 boys, 32 girls), aged 10 months-17 years (mean 8.1±4.4 years), with CD, were recruited to the study.

IgE-mediated sensitization had been diagnosed in 12 (20.3%) children with CD (CD/A) and 58.3% of them were sensitized to food and 66.7% to airborne allergens. Some of them had both food and inhalant allergies (**Fig. 1**).

The data of sex, age, anthropometric parameters, and allergy prevalence in relatives are summarized in **Table 1**. CD was presented more often in the first-degree relatives of children with CD and allergy, but no significant differences were found between CD and CD/A groups.

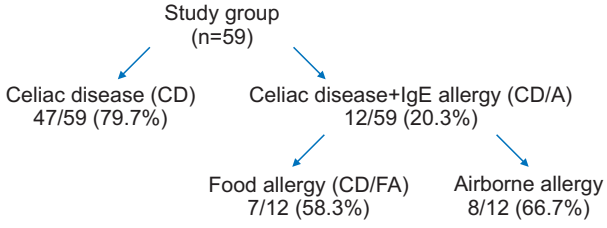

Fig. 1. Study design.
IgE: immunoglobulin E.

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Table 1. Clinical features of the investigated children

Patient	CD/A (n=12)	CD (n=47)	*p*-value
Sex, boys	6 (50.0)	21 (44.7)	ns*
Age (mo)	84.1±58.1	100.9±51.2	ns
BMI (kg/m^2)	16.7±3.1	15.6±3.5	ns
Co-morbidities			
Anemia	3 (25.0)	3 (6.4)	ns
Malnutrition	2 (16.7)	14 (29.8)	ns
Gastroesophageal reflux	1 (8.3)	5 (10.6)	ns
Lactose intolerance	1 (8.3)	5 (10.6)	ns
Constipation	0	2 (4.3)	ns
Family history			
Allergy	10 (83.3)	2 (4.3)	ns
Celiac disease	4 (33.3)	7 (14.9)	ns
Hemoglobin (g/dL)	12.0±1.4	12.4±1.0	ns
Eosinophils (10^3/μL)	0.33±0.25	0.11±0.09	0.006

Values are presented as number (%) or mean±standard deviation.
CD: celiac disease, CD/A: CD+immunoglobulin E allergy, BMI: body mass index.
*No statistically significance.

Other clinical features such as co-morbidities, clinical symptoms, and morphic and infection parameters were analyzed based on the patient's documentation.

Analysis of the clinical status in the CD/A group revealed that the percentage of other allergic diseases were as follows: atopic dermatitis (AD, 4/12; 33.3%), asthma (3/12; 25.0%), allergic rhinitis (2/12; 16.7%) (**Fig. 2**). The percentage of eosinophils was significantly higher in the CD/A than in the CD group (0.33±0.25 vs. 0.11±0.09; *p*=0.006). Anemia has been diagnosed more often in CD/A patients (3/12; 25.0%) than in the CD group (3/47; 6.4%), but the prevalence and mean concentration of hemoglobin did not show statistical differences (**Table 1**).

The analysis of the results of specific IgE to the main food and airborne allergens has shown that most of the children were sensitized to one food allergen: mainly peanuts (5/12; 41.7%). Other common food allergens were cow milk proteins (3/12; 25.0%), egg white (2/12; 16.7%), respectively. Half of the patients were sensitized to more than one food allergen; some of them presented with co-existing airborne sensitization (**Fig. 3**). The association of symptoms from GI tract (abdominal pain, chronic diarrhea, and bloating) with the ingestion of sensitizing foods was reported in 41.7% of children with diagnosed IgE-mediated allergy. No anaphylactic reactions were registered in the CD/A group. The exacerbation of AD along with FA was noticed in five children.

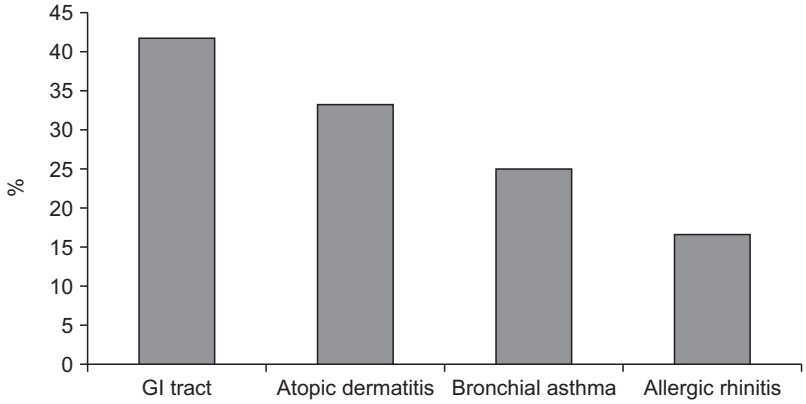

Fig. 2. Clinical manifestation of allergy in study group.
GI: gastrointestinal.

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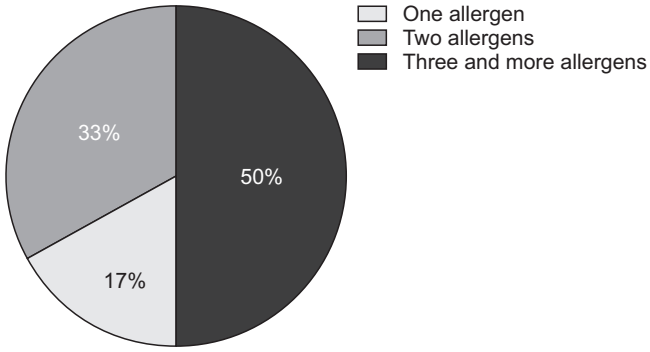

Fig. 3. Prevalence of sensitization to food and airborne allergens in study group.

Analysis of the relationship between sensitization to airborne allergens and clinical expression in the CD/A group has shown that children were mainly sensitized to mites (6/12; 50.0%), grass pollen (5/12; 41.7%), and birch (4/12; 33.3%). Asthma has been diagnosed in three (25.0%) children and allergic rhinitis in two (16.7%). These diseases were the most common clinical expression of airborne sensitization.

DISCUSSION

CD and immediate-type FA are immunological responses to ingested foods and their treatment is based on the elimination diet [1,3]. The relationship between them is not clear and the coexistence of the two disorders is rarely reported. Some studies show CD to be more frequent in patients with atopy [4]; while others documented atopy to be more frequent in those with CD [1].

The published data indicate that allergy prevalence in adult patients with CD was 16% and is similar to their relatives and spouses [2]. To our knowledge, there are no studies on allergy frequency in children with CD, except for single case reports concerning IgE-mediated FA to wheat or soy [10,14]. Therefore, the strength of our research is that this is the first publication in children with CD.

In our study, IgE-mediated sensitization was confirmed in more than 20% of children with CD and seven from this group had documented food sensitization. Although assessment of specific IgE is not a standard in CD patients, since the symptoms are similar all our patients underwent this test during hospitalization. It is worth noticing that this frequency is higher compared to the pediatric population, where the prevalence of FA is estimated to be 4–6% according to the age [15], in correlation with the previous report of increased respiratory and FA in children with CD [16]. The concept of this phenomenon is that both, CD and FA, are linked to T helper 1 and 2 lymphocytes, but the pathogenesis of the two diseases are different and there is no common pathway [16,17]. It is also known that altered permeability of the damaged intestinal mucosa and the passage of antigens throughout the intestine is the pathogenetic basis for the increased IgE-sensitization in patients with CD [5]. Contrarily, Ciacci et al. [2] did not find a significant difference between individuals with CD compared with their relatives without CD with regard to allergy prevalence. Other studies also found no association between self-reported allergy and CD-related autoantibodies [18].

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We excluded patients with suspected non-IgE-mediated FA, which occurs more often in infants with GI complaints due to the lack of specific symptoms and lab tests. Diagnosis of non-IgE-mediated FA is difficult and time-consuming [19].

We consider IgE-mediated allergy for another reason also. This type of hypersensitivity has a high risk of anaphylaxis and patients sensitized to wheat proteins, especially omega-5 gliadin, can develop systemic allergic reactions [20]. Mennini et al. [21] demonstrated the association of IgE-mediated allergy to wheat and CD in a young boy with CD, who experienced an anaphylactic reaction, after occasional unexpected ingestion of gluten. Confirmation of wheat sensitization is crucial for differentiating the cause of symptoms and the patient's cooperation in dietary restriction. In the investigated group of children, no episodes of food anaphylaxis were registered.

Gluten intake is the cause of GI symptoms in patients with CD and FA. More than 40% of children in our study had GI complaints, such as abdominal pain, chronic diarrhea, and bloating associated with the ingestion of sensitizing foods. Interestingly, almost half of them were sensitized to nuts, while, according to the published studies, cow milk proteins have a crucial role in FA in infants and young children [22]. The mean age of the investigated group was 8.1±4.4 years; therefore, it can be suspected that a significant number of children have grown out of allergy to milk. Another cause seems to be the change in nutritional habits in our country and increased consumption of nuts, citrus fruits, etc.

The association between CD and wheat allergy is being discussed [23,24], but the epidemiological data are not available. Interestingly, IgE-mediated allergy to wheat was confirmed in 16.7% of individuals. It seems to be high, but not as common as it is suspected in patients with CD. Nwaru et al. [24] conducted a systemic review on the prevalence of FA. They reported wheat allergy to be the third most frequently self-reported FA, with a prevalence of 3.6%, but 0.1% after verification with an oral food challenge [24]. According to published data, gluten-related disorders affect approximately 5% of the population, but a self-prescribed gluten-free diet is estimated to be followed by 12-25%. Therefore, appropriate diagnostic protocols are required to verify gluten-related symptoms [25].

There are also other studies on reverse dependencies, the prevalence of CD in patients with severe FA, suggesting that individuals with severe FA seem to be at a five-fold increased risk of CD and that routine screening for CD should be recommended for patients with severe FA [9]. The diagnosis of co-existing FA is important for the effectiveness of CD treatment. Syrigou et al. [14] published a case report of a young girl with CD and allergy to soy. Diagnosis of soy allergy was crucial for the treatment of CD because there were persistent or recurrent GI symptoms and villous atrophy despite strict adherence to a gluten-free diet for at least 6–12 months when other causes of non-responsive CD had been excluded [14]. This concerns not only soy but also other food allergens, which should be eliminated from the diet of patients with CD, in case of sensitization [4].

The cause of skin lesions in those with CD and AD may be multifactorial and may include food sensitization as well as other immune-mediated disorders. Although the coexistence of AD and CD has been reported in some described cases, only a few controlled studies have investigated the association between the two conditions [26,27]. In the last published cross-sectional observational study, Shalom et al. [27] indicated that AD was associated with a significantly higher prevalence of CD. They concluded that individuals with AD need

timely screening for GI morbidities to prevent long-term complications [27]. Ress et al. [26] reported an estimated CD prevalence of 1.4% among pediatric patients from Estonia with AD, which was four-fold higher than the rate of CD in the general pediatric population from the same region. In our study, AD was reported in one-third of investigated children, but food allergens were the cause of symptoms only in five of them. Other skin disorders, such as urticaria and herpetiform dermatitis, may be considered as a specific form of CD following gluten ingestion [28].

We are aware that our study has some limitations. First, the group size; second, the inclusion of the patients with IgE-mediated food sensitization. But the main purpose of this study was to indicate that FA should be considered, even if the CD had been diagnosed previously. The clinicians should consider appropriate screening tests for allergy in children with CD, because the GI symptoms may be misleading.

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