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Food allergy in children with hypogammaglobulinemia

Alergia pokarmowa wśród dzieci z hipogammaglobulinemią

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ABSTRACT

Introduction: Antibody production defects may predispose children to inflammatory pathologies and therefore we hypothesized that this group of immune deficiencies may be associated with food allergy. **Objective of the study:** To better characterize the interrelated pathomechanisms of food allergy coexisting with hypogammaglobulinemia in children and to define the relationship between clinical manifestation of antibody production defects and food allergy. **Material and methods:** Twenty-three children aged from 8 to 88 months regularly followed-up in the pediatric pneumonology, allergology and immunology clinic due to hypogammaglobulinemia concerning one or more major immunoglobulin isotypes were retrospectively reviewed in terms of incidence and manifestation of concomitant food allergy. Information regarding the patient's history of allergic diseases and laboratory data concerning serum levels of immunoglobulins, including total IgE, were obtained from chart review. **Results:** Clinical symptoms of food allergy were identified in 17 of 23 (74%) children studied. The mean age of onset of clinical symptoms was 2.7 months. Eczema was the most frequent manifestation present in 16 children, diarrheas and abdominal cramps were noted equally in 3 children, gastroesophageal reflux disease was diagnosed in 2 children as well as vomiting was observed in 2 children. Atopy was revealed in 8 of 17 children (47%) with food allergy. **Conclusions:** Food allergy is a common health problem coexisting with antibody production defects in infants and young children. Clinical symptoms correlate better with low immunoglobulin levels than with serum IgE, that is not a suitable diagnostic criterion for allergic disease in patients with hypogammaglobulinemia.

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Introduction

Antibody production defects are the most common primary immunodeficiencies. The hallmark of this pathophysiologically, clinically, and genetically heterogeneous group of

immunodeficiencies is a defect in mounting the antigen-specific antibody response that is an indispensable condition for the effective adaptive immunity to pathogens. A broad spectrum of diseases represents this group of immune disorders, ranging from often asymptomatic selective IgA deficiency (sIgAD) and IgG subclass deficiencies (IgGsD) to

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severe agammaglobulinemias in which the production of all immunoglobulin isotypes is severely impaired [1]. The onset of clinical manifestation falls predominately on the second half of the first year of life due to the protective effect of transplacentally obtained maternal IgG antibodies over the first 3–6 months. Hypogammaglobulinemia in infancy and early childhood may signal a congenital profound antibody production defect or may be a result of maturational delay of antibody production. However, the symptomatology of these two initially clinically indistinguishable conditions may be convergent and not necessarily associated with infections, but in subgroups of children affected, symptoms of allergy, autoimmunity or lymphoproliferation may predominate.

Multidirectional interactions and precise control of elements of the immune system determine the homeostasis between the effector mechanisms and tolerance. The overlapping mechanisms of allergic background and defects of antibody biosynthesis as well as their reciprocal impact on different clinical entities can make the diagnosis of both an allergic disease and an immune deficiency an essential challenge [2]. The gastrointestinal tract is the largest immunological organ of the human body, constantly exposed to a wide variety of exogenous antigens. The fundamental role of its mucosal immune response is both to prevent effectively the entry of invading pathogens whereas simultaneously its exposition to the external environment and to a high antigenic load elicits immune tolerance. In this context, food allergy is considered to result from a breakdown of this homeostasis between the activation and suppression of the immune response. Several exo- and endogenous biological factors, such as nature and dose of antigen, the frequency of its administration, age at first antigen exposure, maternal dietary exposure during pregnancy and breastfeeding, as well as genetic background and immunological status of the child determine the immune response profile [3].

As the organ-specific inflammatory immunopathology may be a result of mutual relationships between allergy and immunodeficiency, we hypothesize that food allergy may be responsible for a variety of symptoms presented by children with antibody production defects.

Objective of the study

The aim of the study was to better understand the pathophysiological background of the association between hypogammaglobulinemia and food allergy in children and to characterize clinical manifestation that occur in children with antibody production defects and may signal the coexisting food allergy.

Material and methods

Medical records of 23 children, aged from 8 to 88 months (mean age 29 months) with hypogammaglobulinemia regularly followed-up in the pediatric pneumonology, allergology and immunology clinic were retrospectively analyzed. The study group was relatively homogeneous in terms of clinical manifestations. All children studied had been initially referred

to our department for the evaluation of their immunological status because of recurrent episodes of respiratory tract infections and one child had suffered from meningitis accompanied by sepsis prior he has been referred to our department.

Clinical data regarding the patient's history of allergic diseases as well as the results of laboratory investigations were obtained from chart reviews. The onset of first symptoms as well as the type of patient's clinical manifestations were noted. The overall nutritional status of all participating children was assessed through measurements of body weight carried out during the visit in our clinic and through reference to percentiles of normal values for age and gender.

Serum levels of major immunoglobulin isotypes and IgG subclasses were measured with the use of immunoturbidimetric method and total IgE concentrations were assessed by nephelometry in all children studied.

Results

The study group of 23 children was divided into 4 subgroups depending on the number and type of the impaired production of one or more major immunoglobulin isotypes. The universal feature for all participating children was a decrease in immunoglobulin G serum level, that in 6 patients was an isolated disorder. In next 17 children IgG hypogammaglobulinemia was accompanied by one isotype, namely IgM in 3 children or IgA in 7 children. Defective production of all antibody isotypes was identified in next 7 children. In all children peripheral blood lymphocyte immunophenotyping with the use of flow cytometric method allowed for exclusion of agammaglobulinemia, of which a hallmark is a lack of mature B cells in the peripheral blood. In any of the children studied, a significant decrease of the relative value or number of class-switched memory B cells was not demonstrated that might suggest an early onset of common variable immunodeficiency with poor prognosis. Hence, in all children studied, clinical and laboratory findings suggested transient hypogammaglobulinemia of infancy (THI); however, this diagnosis may be reliably established only retrospectively and these children require periodic monitoring to determine the type of immunodeficiency definitely.

Of 23 participating children with hypogammaglobulinemias, in 17 of them the manifestations of food allergy were noted. Eczema was a predominating symptom, that was demonstrated by as many as 16 of 17 children with food allergy. This was followed by recurrent episodes of diarrheas and abdominal cramps, both noted in 3 children, and 2 children demonstrated vomiting. Based on pH-metry of the esophagus that was carried out in next two children because of regurgitations, the diagnosis of gastroesophageal reflux disease was established (Fig. 1). The major allergic diseases associated with eczema were asthma, that had been diagnosed in 5 children, and allergic rhinitis demonstrated by 2 children.

The age of onset of clinical symptoms ranged from 1 month to 8 months of life (mean age 2.7 months) and most frequently (in 7 children) their initial appearance was within the third month of life (Fig. 2).

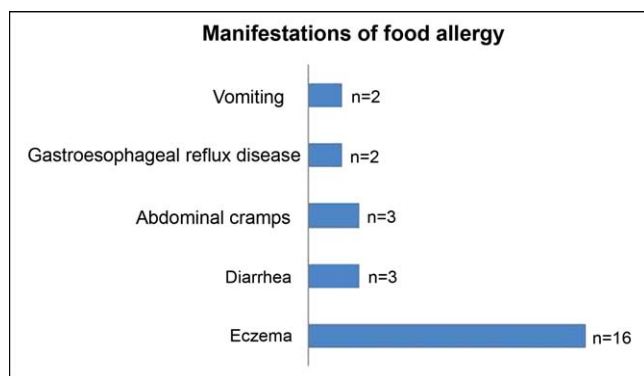


Fig. 1 – Manifestations of food allergy in children with hypogammaglobulinemia

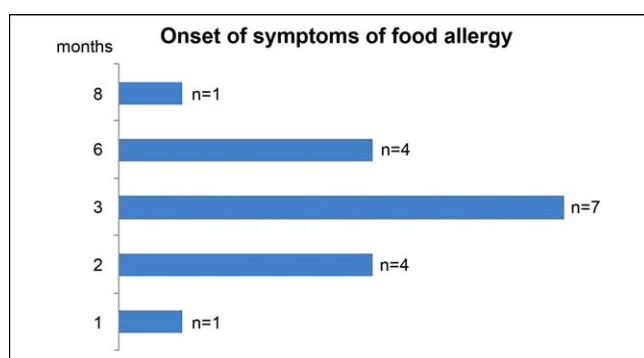


Fig. 2 – The age of onset of food allergy symptoms

The nutritional status of all children studied was assessed based on measurement of the body weight and its correlation with the age- and gender-matched distribution in Polish pediatric population, elaborated by Palczewska and Niedźwiecka [4]. The body weight of participating children was

distributed between the 3rd and 90th percentiles and in any of these children a low-for-age weight was not assessed (Fig. 3).

The total serum IgE levels, compared to age-matched range of normal values, were increased in 8 of 17 children (47%) with food allergy from the study group. These IgE levels ranged from 2.0 kU/l to 8180.0 kU/l (Fig. 4) and it was the highest in a 21-month-old child manifesting severe atopic eczema/dermatitis syndrome. In 2 children, in whom the levels of allergen-specific IgE antibodies against cow's milk proteins were also assessed, the results of these investigations were positive and fell above 0.35 kU/l.

Discussion

Food allergy in children with antibody production defects has not been hitherto extensively researched despite large numbers of observational studies suggesting that the incidence of allergic diseases may be increased in children with this type of immune deficiencies. In 1987 in his epidemiological study on immunoglobulin A deficiency, Klemola [5] draw attention to the clinical problem of concomitant occurrence of allergic diseases and hypogammaglobulinemia in children and reported symptoms of atopic diseases in 50% of children with sIgAD. It is worth noting that the incidence of food allergy in the group of children studied was 74% and was significantly higher than in the above cited study. Furthermore, in the context of the heterogeneity of antibody production defects in children studied, food allergy was present in all these 14 patients in whom IgA levels were below the age-matched normal values. These findings are consistent with both the previous [6] as well as the current knowledge in the field of involvement of mucosal secretory IgA in the gut epithelial barrier function and immunological homeostasis, including antibody-mediated immune exclusion of microbial components [7] and tolerance mechanisms to foods [8–10]. It has also been demonstrated that serum antigen-specific IgA and IgG antibodies play an important role in protection against severe IgE-mediated food allergy, including anaphylaxis induced by

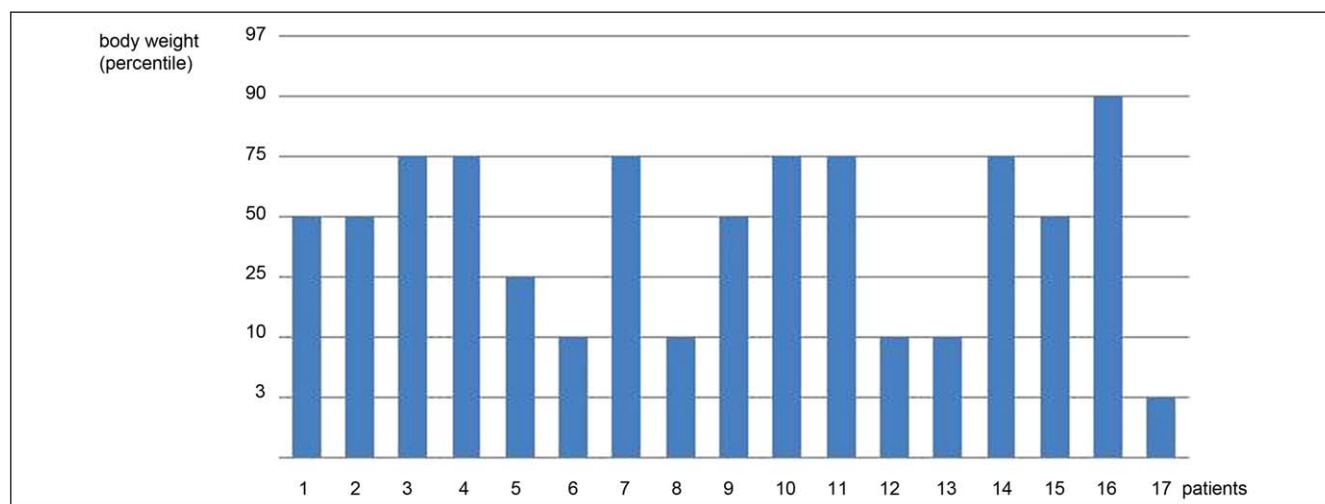


Fig. 3 – Nutritional status of children with food allergy and hypogammaglobulinemia

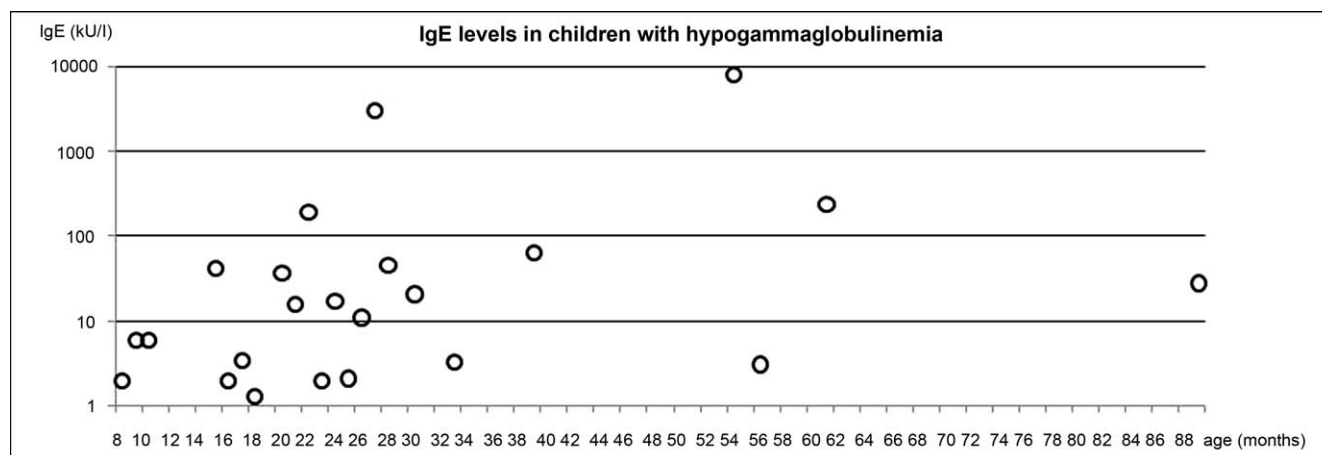


Fig. 4 – Total serum IgE levels in children with food allergy and hypogammaglobulinemia

ingested antigens [11]. This might imply that decreased serum neutralizing IgG and IgA antibody levels that occurs in patients with hypogammaglobulinemia, may predispose to increased intestinal mucosal permeability and systemic absorption of ingested antigens, thus posing the risk of severe food allergy. In particular, atopic children might be at high risk of systemic IgE-mediated reactions to alimentary allergens and in our study group increased levels of serum total IgE was demonstrated in 8 of 17 (47%) children with food allergy. Moreover, in 2 children high serum IgE levels (8180.0 and 3140.0 kU/l) correlated with positive (class 2 >0.7 kU/l) results of measurement of allergen-specific IgE against cow's milk proteins, alpha-lactalbumin and casein. Albeit the percentage of atopic children with food allergy in the study group was significant, but there must be emphasized that not in all children clinical manifestations of hypersensitivity to alimentary allergens was reflected by increased serum total IgE. Likewise, in the study by Dorsay and Orange [12] who reviewed retrospectively a group of 24 children with THI, as much as twenty patients carried at least one atopic diagnosis despite elevated IgE levels in 7 patients. These findings are supported by other authors' opinions that patients with hypogammaglobulinemia and concomitant allergic diseases may show poor correlation between clinical symptoms and results of serum total and allergen-specific IgE tests [13–15]. Therefore, serum IgE levels cannot be considered as suitable diagnostic criteria for allergic disease in patients with defective antibody synthesis.

Interestingly, an early onset of clinical manifestations of food allergy that in 16 of 17 children falls on the first 6 months and in 12 children even on the first 3 months of life supports the initial hypothesis that hypogammaglobulinemia, among others genetic and environmental factors, may substantially contribute to the development of food allergy in children. The first symptoms of allergic disease are thus present in infants in parallel to the breakdown of protective maternal transplacentally obtained IgG antibodies and resulting hypogammaglobulinemia.

In these considerations on reciprocal pathomechanisms of low serum immunoglobulin levels and breakdown of tolerance to alimentary antigens one should also take into account the protein loss through the inflamed gastrointestinal mucosa

and the enteropathy secondary to food allergy as the primary cause of hypogammaglobulinemia [16–18].

As the immune competence later in life is affected by the ability to mount an appropriate immune response upon infection as well as to develop tolerogenic immune mechanisms, the immunomodulatory role of breastfeeding in shaping the immune maturation must be stressed [19, 20].

This study has several limitations, namely a relatively small study group and its retrospective character that does not enable to define either prognosis in terms of hypogammaglobulinemia or the outcome of food allergy. The natural history of early allergy to milk, egg, wheat and soy is generally associated with development of spontaneous clinical tolerance in food-allergic individuals [10], but there is a lack of one universal parameter that might enable to predict the spontaneous immunocorrection and resolution or progression of allergy. These issues might be the subject of further case-controlled prospective studies.

Conclusions

Antibody production defects in infants and young children may be associated with health problems beyond just hypogammaglobulinemia, but pose the increased risk of allergy to alimentary antigens. Symptomatology of food allergy correlates better with serum IgG and IgA deficiency than laboratory markers of atopy. Dysregulation of the immune response contributing to defective antigen elimination in predisposed immunodeficient individuals might be considered as a critical risk factor accompanying development of allergy. The reciprocal pathomechanisms of hypogammaglobulinemia and food allergy, involving defective intestinal and systemic immune response and breakdown of tolerance to alimentary antigens implicate a “vicious circle” hypothesis.

Authors' contributions/Wkład autorów

A. Szczawińska-Popłonyk – study design, data collection and interpretation, literature search, A. Bręborowicz – acceptance

of final manuscript version, L. Ossowska – data collection and interpretation.

Conflict of interest/Konflikt interesu

None declared.

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