

THE ASSOCIATION OF CELIAC DISEASE WITH OTHER AUTOIMMUNE DISEASES IN CHILDREN

Jelisaveta Maksimović¹, Zlatko Djurić^{1,2}

¹Faculty of Medicine, University of Niš, Niš, Serbia

²Children's Hospital, Department of Gastroenterology, Niš, Serbia

Abstract. Celiac disease (CD) is an autoimmune disease with estimated prevalence of 1% in European and North American population. All four components of CD autoimmunity are well known, such as: genetics, autoantigen, autoantibodies and the environmental triggers. Besides gastrointestinal manifestations, celiac disease has a wide array of extraintestinal symptoms and clinical signs. This article briefly summarizes celiac disease pathophysiology and association of celiac disease with other autoimmune diseases in children. It puts emphasis on possible protective role of gluten-free diet for the development of other autoimmune diseases in patients with celiac disease.

Key words: celiac disease, autoimmune diseases, diabetes mellitus.

Introduction

Over the last few decades increased prevalence of many autoimmune diseases in the human population has been documented. Celiac disease (CD) is one of the most common autoimmune diseases in human population and the only disease with well-known environmental triggers of autoimmunity. Patients with one autoimmune disease are more susceptible to other autoimmune diseases. Coexistence of two or more autoimmune diseases in the same individual (autoimmune polyendocrine syndrome) has been published in literature [1].

At the beginning of the twentieth century, with the advent of the highly sensitive and highly specific serological screening tests for CD, large screening studies have been put into practice with the aim of identifying CD prevalence in general population and patients suffering from other autoimmune diseases.

Celiac Disease

CD is common, lifelong disease characterized by autoimmune damage of the small bowel mucosa. Recent epidemiological studies indicate that CD affects about 1% of European and North American population [2,3]. Nowadays, all 4 components of CD autoimmunity are well known, such as: genetics, autoantigen, autoantibodies and the environmental triggers. Genetic predisposition is needed for CD occurrence. More than 95% of patients

are carriers of HLA-DQ2 haplotype (encoded by alleles DQA1 * 05 and DQB1 * 02). The rest of the patients are carriers of HLA-DQ8 (encoded by alleles DQA1 * 03 and * DQB1- 0302). The role of the genes out of the HLA system was examined by GWARS (genome-wide association studies) [4,5]. More than 115 of these genes have been involved in the regulation of the innate and adaptive immune responses. However, the importance of each individual gene outside the HLA system for the development of CD is very small.

The enzyme tissue transglutaminase (TG2) is located in lamina propria of small bowel mucosa. TG2 leads to deamination of glutamine residue of gliadin [6]. This reaction provides glutamine residue a negative charge and ability to bind to HLA DQ2 / DQ8 molecule on the antigen-presenting cells. TG2 participates in many physiological processes, such as extracellular matrix building, tissue reparation, signal mechanisms of receptors, cell proliferation, cell motility and endocytosis [7]. In addition to the small intestine, TG2 can also be found in the liver, muscles, and lymph nodes.

Dietrich et al. (1997) were the first who discovered IgA antibodies against TG2 (Anti-TG2) in the sera of CD patients [8]. Deployment of tests based on Anti-TG2 detection substantially improved the diagnostic accuracy of CD serologic testing.

Development of CD requires food intake that contains gliadin fraction of gluten from wheat or similar prolamins from rye (secalins) and barley (hordeins). There are gliadin peptides which demonstrate two different effects on small bowel mucosa: toxic and immunostimulatory [9]. Alpha-gliadin peptides (31-43, 44-55, 56-75) with toxic activity are responsible for the damage of the small bowel mucosa and initiation of the pathophysiological processes in CD. Peptides with

* Correspondence to: Jelisaveta Maksimović, M.D.
Faculty of Medicine, University of Niš, Bulevar dr Zorana Đindjića 81,
18000 Niš, Serbia
Phone: +3810603010190
E-mail: saveta17@gmail.com
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immunostimulatory effects initiate T helper 1 (Th1) response and secretion of interferon- γ . It is assumed that there are more than 50 gliadin peptides with this kind of effect.

The pathophysiology of autoimmune damage of small bowel mucosa in CD is not completely understood. It encompasses complex interactions between the innate and adaptive immune response, triggered by ingestion of gluten. At the beginning of this process paracellular permeability of small bowel mucosa is increased for gluten peptides due to peptide induced CXCR3 activated upregulation of zonulin, an intestinal peptide involved in tight junctions control [10].

Toxic gliadin peptides activate the innate immune system and increase production of interleukin 15 (IL-15) by epithelial and dendritic cells. IL-15 stimulates cytotoxic activity of intraepithelial lymphocytes through production of interferon γ (IFN γ) and stimulation of NKG2D cells. Activation of the adaptive immune response occurs after deamination of glutamine residues with TG2, their binding to dendritic cells and presentation to CD4 T lymphocytes followed by activation of the cellular (Th1) and humoral (Th2) immune response. Th1 response leads to the IFN γ induced cell death of enterocytes. Th2 response causes differentiation of B lymphocytes into plasma cells capable of producing anti-TG2 and antigliadin antibodies (AGA). It is not known whether anti-TG2 in a certain way influences the activity of the TG2. In addition to Anti-TG2 other types of auto-antibodies, such as antibodies against actin and reticulin were detected in CD [11].

CD may be manifested by typical (chronic diarrhea, loss of appetite, distended abdomen, malnutrition) and non-typical symptoms (stunted growth, refractory anemia, osteoporosis, unexplained hypertransaminasemia). The CD diagnosis is established on the basis of positive serology (anti-TG2 or anti-endomysial antibodies) and small bowel mucosa pathohistology.

Celiac Disease and Other Autoimmune Diseases

A group of autoimmune diseases is consisted of about 80 different diseases affecting 5-8% of the human population [12]. Patients with a single autoimmune disease are at 25% risk of development of other autoimmune diseases [13]. Many studies in children have reported an association between CD and various autoimmune diseases. Common genetic background is one of the predisposing factors for this association [14,15]. There is a possibility that persistent activation by proinflammatory cytokines leads to the unmasking of other autoantigens (besides TG2) and the initiation of a new autoimmune attack. Recent studies demonstrated that gut microflora plays an important role, not only in shaping the immune responses, but also in the development of autoimmunity [16].

Italian authors have found an increased frequency of organ-specific antibodies in CD patients [17]. Titer of

antibodies significantly decreased following the commencement of the gluten-free diet (GFD). On the basis of this, they hypothesized that GFD may prevent the occurrence of other autoimmune diseases. However, subsequent studies have not confirmed the protective role of GFD [18,19]. Development of other autoimmune disease is more likely if the CD is diagnosed in young individuals with positive family history of CD [20].

Celiac Disease and Diabetes Mellitus Type 1

Diabetes mellitus type 1 (DMT1) is one of the most common chronic diseases in children with increasing annual prevalence from 3% to 4% [21]. Numerous screening studies conducted around the world showed the increased prevalence of CD (2.4% -16.4%) in patients with DMT1 [22]. The only screening study of this type in Serbia revealed the CD prevalence of 5.79% in children and adolescents with DMT1 [23]. DMT1 patients with CD can be asymptomatic (60%-70% of patients) or have classical CD symptoms. It should be kept in mind that positive titer of anti-TG2 in DMT1 patients does not always mean that they have CD. In a number of serologically positive DMT1 patients who do not have symptoms of the CD, anti-TG2 disappeared spontaneously, even though they continued to use gluten containing food. In these children anti-TG2 titer levels are usually slightly lower than in asymptomatic CD patients.

Some studies suggest that patients with newly diagnosed DMT1 and CD have frequent hypoglycemic episodes, higher average value of glycosylated hemoglobin, and reduced bone mineral density [24-26]. Conflicting evidence exist as to whether a GFD significantly improves glycemic control in DMT1 patients [24,27,28].

Children and adolescents with DMT1 and CD are prone to vascular complications later in life. CD is regarded as an independent risk factor for retinopathy and nephropathy in patients with DMT1 [29].

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommended serological screening for CD in all children with DMT1 at the time of DMT1 diagnosis and every 1-2 years thereafter [30] because positive titer of Anti-TG2 can be found many years after the beginning of DMT1.

Celiac Disease and Autoimmune Thyroid Disease

Many screening studies in children with autoimmune thyroid disease (Hashimoto's thyroiditis, Graves' disease) have found an increased prevalence of CD (2.3-7.9%) [31]. CD has been more commonly found in autoimmune thyroiditis than in Graves' disease. Serologic CD screening is recommended in children with autoimmune thyroid disease by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [32].

Investigations were carried out in the opposite direction as well, with the aim of determining the prevalence of autoimmune thyroid disease in children with CD. In one Italian study autoimmune thyroid disease was found in 26.2% of pediatric patients with CD [33]. Thyroid dysfunction in CD has a negative impact not only on growth, metabolism of proteins and cholesterol, but also on cognitive function and fertility.

Celiac Disease and Autoimmune Hepatitis

In case of elevated transaminases in children with CD, autoimmune hepatitis and non-specific reactive hepatitis (celiac hepatitis) should be considered. Autoimmune hepatitis (AIH) is a chronic disease in genetically predisposed individuals in whom the autoimmunity is directed toward liver antigens. Pediatric surveys have reported a wide prevalence of CD in AIH in a range from 3.6% to 12% [34]. Although there are still no recommendations for routine serological CD screening in patients with AIH, the association between these two diseases should be considered if one of them is diagnosed. Rare cases of CD associated with other autoimmune liver diseases such as primary sclerosing cholangitis (PSC) and "overlap" syndrome (AIH / PSC) were described in children [35,36].

Celiac hepatitis is found in 26-57% of children with CD [37,38]. It is manifested by the elevation of transaminases without any symptoms of liver disease. The increased intestinal permeability in CD may ease the entry of toxins, antigens, antibodies and cytokines to the portal system leading to hepatocytes function impairment [34]. In most cases (70-100%) transaminase levels are normalized within a year on GFD. All patients with unexplained hypertransaminasemia should be serologically tested for CD.

Celiac Disease and Dermatological Diseases

CD may be associated with various skin manifestations, such as dermatitis herpetiformis (DH), psoriasis, alopecia

areata and vitiligo [39-41]. DH is most frequently found in adolescents, young and middle-aged adults. All patients with DH have some forms of enteropathy that can be found in CD. In 10-20% of DH patients, in addition to rash, there is a typical clinical picture of a CD while in the rest of 80-90% atypical or "silent" CD clinical forms are seen. GFD is standard treatment for DH with excellent clinical response. Since the reintroduction of gluten in a diet after clinical recovery on GFD triggers relapses of cutaneous and intestinal lesions, DH is regarded as skin manifestation of CD [39].

Celiac disease and rheumatological diseases

CD is found in 1.5% -2.8% of children with juvenile rheumatoid arthritis [42,43]. The prevalence of CD is less studied in other rheumatological diseases in pediatric population. Studies examining positive effect of GFD on arthritis were not conducted in children, while in adults they are very rare. Sjogren's syndrome is considered the most common rheumatological disease associated with CD (in 12% -14.4% cases) in adults [44,45].

Conclusion

CD may be associated with many diseases of autoimmune origin. Currently, there are recommendations of international societies such as ISPAD and ESPGHAN for CD serological screening only in children with T1DM and autoimmune thyroid disease. Future studies with the involvement of large number of children, including a cost-benefit analysis, are going to show whether CD screening for children with other autoimmune diseases will be justified. Despite a very promising hypothesis, there is still no scientifically based evidence that GFD has prophylactic effect on the development of other autoimmune diseases in patients with CD.

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