

Celiac Disease

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SUMMARY

Celiac disease is a multisystemic autoimmune disease induced by gluten in wheat, barley and rye. It is characterized by polygenic predisposition, high prevalence (1%), widely heterogeneous expression and frequent association with other autoimmune diseases, selective deficit of IgA and Down, Turner and Williams syndrome. The basis of the disease and the key finding in its diagnostics is symptomatic or asymptomatic inflammation of the small intestinal mucosa which resolves by gluten-free diet. Therefore, the basis of the treatment involves elimination diet, so that the disorder, if timely recognized and adequately treated, also characterizes excellent prognosis.

Keywords: celiac disease; pathogenesis; clinical forms; diagnostics; treatment

INTRODUCTION

Celiac disease represents an autoimmune disease induced by gliadin and related prolamins present in gluten of wheat, barley and rye grains [1-4]. It is primarily found in Caucasians (1:100), while being considerably or exceptionally rarer in the population of other races [3-8]. Similarly to other autoimmune diseases it is more frequent in females [4]. The basis of the disease and the key finding in its diagnostics is gluten-sensitive enteropathy, i.e. a nonspecific inflammation of the small intestinal mucosa that resolves by gluten-free diet [1, 2, 3, 9, 10]. Beside enteropathy, either symptomatic or asymptomatic, the disease is also characterized by different extraintestinal manifestations, as well as potentially severe complications [11, 12]. As it is disclosed in only 1:5-13 cases, today celiac disease is ranked as the most frequent chronic disease of the modern man [4, 9, 10, 13]. Owing to the up-to-date knowledge and diagnostic possibilities, over the last years the rate of verified disease, particularly atypical and subclinical form, is continually increasing both in the developed and developing countries [13-17].

PATHOGENESIS

Celiac disease belongs to the group of chronic inflammatory diseases of multifactorial nature [1-4]. Beside polygenic predisposition and exposure to gluten as the trigger of autoimmune process, some other factors also have essential participation in the expression of the disease, such as too early (<17 weeks) or too late (≥26 weeks), introduction of gluten into the child's diet, absent breastfeeding at that time, rotavirus gastroenteritis and other [6, 18-28]. In

contribution to the prevailing role of polygenic heredity in the disease occurrence speaks its highly variable frequency in different populations, as well as a high rate of its presence in one-egg twins (~100%) and first-line relatives (10-20%) [2-4, 10]. HLA class II genes play a central role in the hereditary predisposition to the disease, but also with the unavoidable participation of other genetic loci [1-4, 10, 29]. This is proved by the fact that 85-95% of examinees with celiac disease carry the HLA DQ2 haplotype, while in 5-15% the HLA DQ8 is registered [1-4, 30, 31, 32]. In addition, a correlation between these two haplotypes and celiac disease prevalence worldwide has been confirmed [4]. However, the disease expression, beside HLA DQ2 and/or DQ8 gene and exposure to gluten, also requires non-HLA genes as well as some other external factors, which is indicated by its presence in only 2-5% of carriers of these two genes, and absence of full prevalence in one-egg twins [3, 4, 8, 28].

The significance of HLA class II glycoproteins present on the antigen-presenting cells is reflected in the characteristic that, after bonding with gliadin peptide hydrolysate formed of 33 amino acids, they activate intestinal CD4⁺ T-lymphocytes which, by secreting proinflammatory cytokines, lead to the infiltrative or infiltrative-destructive inflammation of the small intestinal mucosa [1, 2, 3, 9]. This process is preceded by tissue transglutaminase-mediated deamination of the glutamine residue of gliadin hydrolysate, which increases the affinity of their bonding with HLA DQ2 and DQ8 molecules [9, 10]. In addition to T-cell immune response, humoral immunity also has an important participation in the disease pathogenesis, which is confirmed by the presence of autoantibodies to reticulin, endomysium, tissue transglutaminase and other body structures [1, 2, 3, 9].

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ENTEROPATHY

Damage of the small intestinal mucosa is most expressed in the duodenum and the proximal part of the jejunum, while progressively decreasing toward the ileum [4]. However, in some cases evident mucosal lesions can be present only in the duodenal bulb [4, 33]. According to the modified Marsh criteria inflammation of the small intestinal mucosa is classified into three basic types: infiltrative (I), infiltrative-hyperplastic (II) and destructive (III) [34]. In the first form of mucosal damage there is an increased number of intraepithelial lymphocytes with γ/δ receptor properties, as well as the lymphoplasmocytic infiltration of the stroma, while intestinal villous height and crypt depth remain intact. In the second form of damage, beside marked infiltrative changes, there is crypt hyperplasia, while in the third one, beside a marked infiltration and hyperplasia, there is villous flattening and/or loss. According to the degree of mucosal damage, destructive enteropathy is additionally classified into partial (IIIa), subtotal (IIIb) and total (IIIc) (Figure 1). Besides, a fourth form is also possible to occur, which is characterized by a total villous atrophy but without crypt hyperplasia and typical signs of mucosal inflammation.

CLINICAL FORMS OF THE DISEASE

From the clinical aspect, celiac disease is divided into two basic types: symptomatic and asymptomatic (Scheme 1) [9,

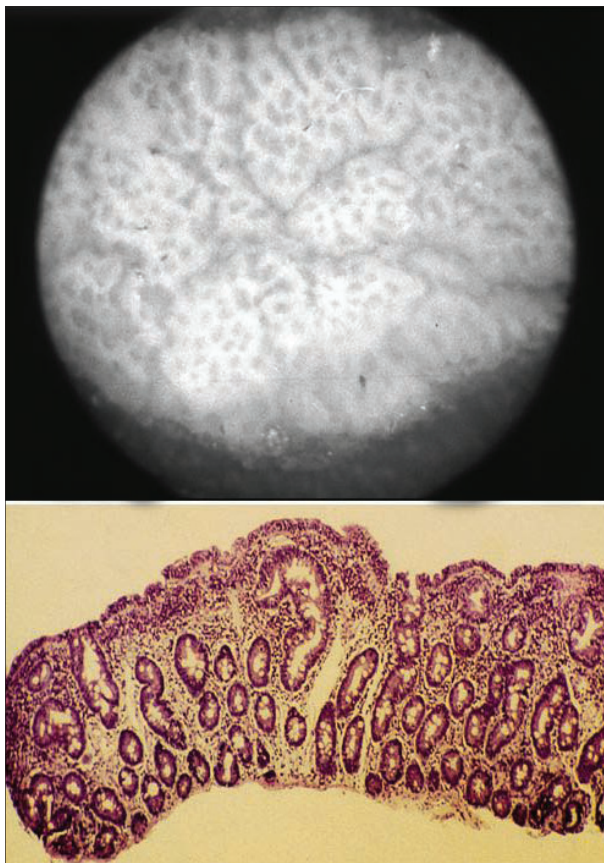
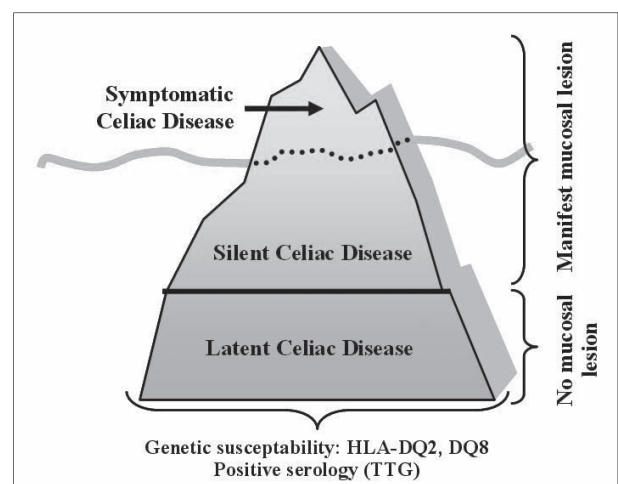


Figure 1. Stereomicroscopic and pathohistological appearance of small intestinal mucosa with most severe form of damage (Marsh IIIc)

28, 30]. Under the symptomatic form of the disease, which is much rarer, classical and atypical clinical presentation can be differentiated. The classical form of the disease is characterized by chronic diarrhea followed by malabsorption and secondary malnutrition, while the clinical features of the atypical form are predominated by extraintestinal (mono or oligosymptomatic) manifestations [1, 2, 3, 9, 30]. The classical form of the disease is mainly seen in infants and small children and atypical in later ages and in adults [1, 2, 3, 12, 28]. In the clinically manifested forms of the disease, beside evident enteropathy mostly of more severe degree, antibodies to tissue transglutaminase (AtTG) and endomysium (EMA), as well as HLA DQ2 and/or DQ8 are registered. As the small intestinal mucosa is characterized by a great functional reserve, in a considerable number of cases its inflammation can be nonmanifest, so that such a form of the disease is called subclinical (silent celiac disease) [13, 28, 30]. In addition, the asymptomatic character is also the feature of the latent (potential) celiac disease, which differs from the silent form by a normal appearance of the small intestinal mucosa [13, 28, 30].

The classical form of celiac disease is most frequently seen at age 9-36 months (Figure 2) [9, 28, 30]. Complaints develop gradually and have a progressive course, and involve chronic diarrhea, anorexia, apathy and irritability. The insufficient intake and malabsorption of nutritional substances consequentially lead to a global malnutrition followed by sideropenic anemia, fat tissue loss and bone-muscle mass reduction. The child's longitudinal growth remains preserved for a relatively long time. In view of the concurrent deficit of the organic and mineral part of bones classic rickets are rare. Hypoproteinemic edema occurs in the most severe cases of the disease. During the first 6-9 months of life the disease usually presents with a rapid and severe clinical course. In rare cases the so called celiac crisis can be seen that is characterized by a total gastrointestinal insufficiency followed by severe hydroelectrolytic and acid-base disorder, drastic loss of body weight and exudative enteropathy [1, 35, 36, 37]. Although the classical form of the disease is most frequently and best investigated entity, it is known today that it represents only the peak of the celiac iceberg and that the highest number of



Scheme 1. Clinical forms of celiac disease – the celiac iceberg [30]



Figure 2. A 15-months old boy with celiac disease during diagnostic phase (left) and after a year on gluten-free diet (right)

patients, both children and adults, present with the atypical or asymptomatic form of the disease [13, 28, 30].

In preschool children the onset and the course of the disease is mostly uncharacteristic (atypical) and more difficult to recognize [9, 28, 30]. Most frequently, gastrointestinal disorders are absent or slight. There is the presence of recurrent abdominal pain and constipation, diarrhea rarely, while frequently sideropenic anemia resistant to oral therapy with iron, delay in longitudinal growth, marked thinness, osteopenia and child's personality changes. [1, 2, 3, 30].

In later childhood and adolescence symptomatology is predominated by mono or oligosymptomatic extraintestinal disorders [9, 28, 30]. Beside the manifestations of this type that can be seen at previous age, others also develop, such as developmental delay, enamel hypoplasia, chronic fatigue, arthralgia, myalgia, ataxia, polyneuropathy, epilepsy, alopecia, vitiligo, dermatitis herpetiformis and other. Frequently occurring finding, both in these and earlier ages, involve isolated hypertransaminasemia, liver steatosis, thrombocytosis, granulocytosis, osteopenia and lymphocytic gastritis [5, 13, 38].

Possible complications of celiac disease verified with delay or inadequately treated that are seen in adult age involve T-cell small intestinal lymphoma, refractory sprue and ulcerative jejunoileitis [3]. Recent investigations have indicated that the risk of other malignancies is not as high as previously considered [2]. A potential complication of untreated celiac disease also involves infertility [4].

ASSOCIATION WITH OTHER DISEASES

In addition to a high frequency among close relatives of the diseased, particularly those of the first line, celiac disease is characterized by a high association (3-10%) with other autoimmune diseases, such as diabetes mellitus type I, au-

toimmune thyroiditis, Addison's disease, juvenile idiopathic arthritis, Sjögren's syndrome, autoimmune liver diseases, systemic lupus erythematoses, IgA nephropathy, myasthenia gravis, psoriasis, dilated cardiomyopathy and other [1, 2, 3, 30, 39]. Approximately identical prevalence of the disease is also registered in IgA selective deficit, as well as in Down, Turner and Williams syndrome [2, 9, 40].

DIAGNOSTICS

The diagnosis of celiac disease is based on enterobiopsy with pathohistological examination of the small intestinal mucosa [1, 2, 3, 41]. According to the latest recommendations of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) defined in 2010, this procedure is not necessary only in patients with symptoms and/or signs corresponding to celiac disease, but also with present IgA antibodies titer to tissue transglutaminase (AtTG) above 100 U/ml, positive anti-endomysial antibodies and "celiac HLA" (DQ2 and/or DQ8) [42, 43]. In favor of the verification of disease presence, i.e. justified introduction of gluten-free diet unpreceded by biopsy, speak the patient's clinical recovery and AtTG disappearance [42, 43]. Such attitude in the celiac disease diagnostics is based, not only on high sensitivity and specificity of IgA AtTG as a serological marker of the disease (>95%), but also on a highly significant correlation of their titer with the degree of small intestinal mucosa damage, as well as on the almost unavoidable (>98%) presence of HLA DQ2 and/or DQ8 [42, 43]. Serological indicators of the disease, such as autoantibodies to endomysium and tissue transglutaminase, and antibodies to deanimated gliadin peptides have a high sensitivity and specificity, but not also an absolute diagnostic validity [1, 2, 3, 44, 45]. Therefore, they are primarily used in the detection of asymptomatic and atypical forms of the disease, as well as in the assessment of the consistency of elimination diet in cases with already verified disease [11, 13, 45, 46]. If the diagnosis of celiac disease is exact, according to the latest ESPGHAN criteria, the provocation of gluten tolerance with a pathohistological analysis of the small intestinal mucosa is unnecessary neither in children in whom it was verified before completed second year of life [42, 43]. However, in patients on gluten-free diet introduced without a preceding enterobiopsy, as well as in cases in whom morphological mucosal damage was not typical or where samples were inadequate for a reliable interpretation, the final confirmation or exclusion of celiac disease is based on the biopsy finding during gluten tolerance provocation [41, 42, 43]. As this procedure can endanger the quality of permanent teeth, it is suggested not to be used before completed sixth year of life, and due to adverse effects on the child's growth and development neither during puberty [41].

TREATMENT

As celiac disease represents a permanent disorder, the basis of its treatment forms a life-long gluten-free diet [1, 2,

3, 47]. In addition, during the initial phase of treatment most patients, particularly those with the symptomatic form of the disease, require correction of microelements and vitamin deficit, above all iron and folates, and in a certain number of cases a temporary restriction of lactose [2, 48]. In the most severe forms of the disease, beside the stabilization of water-salt balance and edema removal, semi-elementary and/or additional parenteral nutrition is applied, and very rarely a short-term glucocorticoid therapy as well [1, 36, 37].

PROGNOSIS

The prognosis of a timely recognized and adequately treated celiac disease is excellent [49]. In fact, if all conditions are fulfilled, these persons cannot even be considered patients. Late recognition of the disease or non-adherence

to the gluten-free diet can lead to various complications, sometimes even highly severe [11, 49, 50].

CONCLUSION

Celiac disease represents a polygenically determined autoimmune disorder induced by gluten in wheat, barley and rye. It primarily occurs in Caucasians, and particularly often in close relatives of the diseased, as well as in patients with other autoimmune diseases; IgA deficit and Down, Turner and Williams syndrome. The basis of the disease and the key finding in its diagnostics are formed by the non-specific inflammation of the small intestinal mucosa that resolves by gluten-free diet. Beside enteropathy, either symptomatic or asymptomatic, the disease is also characterized by different extraintestinal manifestations. If timely recognized and adequately treated, the disease prognosis is good.

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Целијачна болест

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КРАТАК САДРЖАЈ

Целијачна болест је мултисистемско аутоимунско обољење изазвано глутеном пшенице, ражи и јечма. Одликују је полигенска предиспозиција, висока преваленција (1%), веома хетерогена експресија и честа удруженост са другим аутоимунским обољењима, селективним дефицитом *IgA* и Дауновим (*Down*), Тарнеровим (*Turner*) и Вилијемсовим (*Williams*) синдромом. Основу болести и кључни налаз у њеној

дијагностици чини симптоматско или асимптоматско запаљење слузокоже танког црева које се повлачи на дијету без глутена. Отуда и суштину терапије чини елиминациона дијета, те овај поремећај, уколико се благовремено препозна и на одговарајући начин лечи, одликује и изванредна прогноза.

Кључне речи: целијачна болест; патогенеза; клинички облици; дијагностика; терапија

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