Recieved: 10 April 2015/ Accepted: 20 April 2015/ Published online: 15 June 2015

# Celiac Disease: Pathomorphology and Clinical Picture

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## ABSTRACT

Celiac disease, also known as gluten enteropathy or "flour disease" – is a chronic autoimmune disease that affects the small intestine. The disease is widespread in Kazakhstan, since the climatic conditions favor the harvest of cereal corps this is due to favorable climatic conditions for the harvest of cereal crops; the latter are subsequently used in the food industry. Scientists, experts and doctors all over the world are actively engaged in searching ways of further development and treatment of this disease, which promising results.

## KEYWORDS

Gluten Enteropathy, Malabsorption Syndromes, Atrophy, Pathology

## INTRODUCTION

Celiac disease (CD) – is an immune-mediated enteropathy caused by gluten intolerance. This pathology is found frequently in genetically susceptible individuals. CD is a chronic disorder of the digestive system, in which damage to the mucous membrane of the small intestine leads to malabsorption of nutrients and minerals [1, 2].

### History

In the first century AD Aretaios the Cappadocian and Aurelian described chronic diarrhea and steatorrhea in children and women and they called the disease «Morbus coeliacus». The classic symptoms of CD in children - diarrhea, emaciation, anemia and developmental delay - described in 1888 by Samuel Gee, doctor in Bartolomey's Hospital in London. He also drew attention to the delay of physical development in children, lack of muscle and bloating [3]. In 1950, a Dutch pediatrician W.K. Dicke found and identified the cause of CD of children with gluten - soluble in alcohol fraction of protein contained in wheat . In 1952, G. McIver and J. French successfully applied the gluten-free diet for the treatment of this disease [4].

### Epidemiology

Currently, CD is one of the most common autoimmune pathologies characterized by various systemic manifestations. Women are affected more often than men (in most cases, the ratio of 2: 1). Numerous studies have reported the prevalence of CD, ranging from 1: 200 to 1: 100 among people belonging to the risk groups, and 1:10 among close relatives. This frequency among newly or already diagnosed is 1: 7 [5]. CD's frequency varies greatly in different regions, such as Europe varies from 1: 300, in Western Ireland,1: 267 in Sweden and 1: 10000 in Denmark, averaging 1: 1000-1: 2000. According to the T. K Isabekova CD detection in Kazakhstan is very high and ranges from 1: 250 to 1: 300 children, with ratios of overt and covert forms of 1: 6. CD prevalence among children in Kazakhstan is 1: 262, at a ratio typical to atypical forms of 1: 5. [6, 7]. At the international conference on CD (Belfast, 2004) the official rate of patients with CD in the world was defined at - 1: 184. Thus, the average prevalence of 0.5-1% of the total population of the planet. CD is considered a rare and less common diseases among Africans, the Japanese, the Chinese, who prefer to give food millet, rice and sorghum. [8].

### Pathogenesis

Gluten is a group of proteins that are found in wheat, barley, oats and rye as gluten. The most toxic component is alpha-gliadin. According to scientific views prevailing during the XX century, CD is a genetically determined disease associated with one of the fractions of vegetable protein gluten, gliadin. In Individuals with a tendency in developing CD, gliadin damages the mucosa of the small intestine and leads to atrophy and severe malabsorption. There is a disorder in the structure of HLA-region on chromosome 6. It is assumed to be an autosomal dominant character passed down with incomplete penetrance. The importance of genetic factors confirms the changes revealed by

duodenal biopsy in 10-15% of close relatives. Over 97% of patients have CD histocompatibility markers HLA-DQ2 and / or DQ8, compared with a 40% in the general population (high predictive value). Abnormal sensitivity to gluten causes damage to the small intestinal mucosa and the inflammatory response, which in the long run leads to a gradual atrophy of the villi. Gluten is associated with epithelial specific receptors, deterministic HLA genes and (or) damaged by viruses and activates Th1-mucosal immune response. The number of lymphocytes and plasma cells that produce antibodies antigliadin and specific for gliadin T-lymphocytes in the lamina propria are increased. As a result, intolerance in various nutrients develops due to damage of the glycocalyx, and of the brush border membrane of enterocytes where certain enzymes reside including lactase, sucrase, maltase, isomaltase. The result of the compromised small intestine enzyme activity and the disrupted mucous membrane permeability is that there are undisgested nutritional moieties (di-, tri- saccharides/ peptides). Changing the composition of the normal flora in lower parts of the small and large intestine, leads to disruption of the metabolism of fatty acids, cholesterol, bile acids, reduced synthesis of vitamin K and B, reduced fermentation of indigested food residues, increased absorption of toxic substances produced in the gut as a result of microbial metabolism ( histamine, cadaverine) [8, 9].

## MAIN BODY

### Clinical manifestations

The classic manifestations of CD - malabsorption syndrome (malabsorption): chronic diarrhea, bloating, weight loss, hypoproteinemia, signs of deficiency of vitamins and minerals. It is necessary to pay attention to the appearance of swelling, bloating and a satiety feeling [9, 10].

The clinical forms or variants of celiac disease are the following:

- A typical form of the disease occuring in early childhood diarrhea polifekalia and steatorrhea, anemia, metabolic, malabsorption hereditary syndrome of stage 2 or 3.

- Torpid (refractory) form - heavy current, lack of effect of conventional treatment, and therefore requires the use of glucocorticoid hormones.

- Latent form - long subclinical disease, first appearing in adulthood and even in old age. The rest of the clinical picture is similar to the typical form.

- Potential C - this form has been recently proposed, it affects the relatives of the patients; they may have normal small intestinal mucosa, but there is an increase in the content of intraepithelial lymphocytes having a cytotoxic effect. In the blood are determined specific to CD antibodies.

- Oligosymptomatic (erased) shape - in the majority of the patients, changes in the small intestine mucosa may be limited to a short section of thin lesion (duodenal) ulcers, some deepening of crypts, and / or increasing the number of intraepithelial lymphocytes in the mucosa.

However, in many cases, intestinal symptoms may be absent or at all, or have a more insidious progress, giving way to extraintestinal manifestations dominating the clinical picture [10-13]. (Table 1).

### Diagnostics

One of the most reliable methods of diagnosing and confirming the diagnosis D are serological tests and a biopsy of the proximal small intestine. Seroimmunological markers of CD include antigliadin antibodies (AGA-IgA, AGA-IgG) and an antibody to components of connective tissue, reticulin (ARA-IgA), endomysial (EMA-IgA, EMA-IgG); tissue transglutaminase (anti-tTG-IgA, anti-tTG-IgG). Antigliadin antibodies have been the classic serological marker of CD, but now the use of this test is not recommended due to low sensitivity and specificity (70-80%). Reticulin antibodies test is also not widely used. Thus, the current serological diagnosis of CD is based on the detection of antibodies in tissue transglutaminase and (or) endomisial antibody, antigen, which is also a tissue transglutaminase. At the present time, the use of plasma-citrulline as a marker for CD [14], is widely used, as well as the question about the improvement of serogenetical methods for diagnostic purposes [15, 16].

Histological methods are the “gold standard” in the diagnosis of CD. Biopsy should be obtained from the distal part of the duodenum and jejunum. The pathological report should indicate the degree of crypt hyperplasia and villous atrophy, as well as the number of intraepithelial lymphocytes. The inflammation onset is signified by infiltration of lymphocytes in the

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| **Typical symptoms** | malabsorption, diarrhea, bloating, weight loss, intolerance to dairy products, steatorrhea |
| **Atypical symptoms** | nonspecific - chronic fatigue, weakness, fatigue |
| **Hematological symptoms** | anemia (iron, folievodefitsitnoy, B12-deficient), bleeding, a tendency to bruise, hyposplenism |
| **Neurological symptoms** | peripheral neuropathy, cerebellar ataxia, epilepsy |
| **Metabolic symptoms** | bone pain, osteoporosis, osteomalacia, short stature, signs of vitamin deficiency |
| **Gynecological symptoms** | delayed puberty, amenorrhea, infertility, recurrent miscarriages |
| **Gastrointestinal symptoms** | constipation, irritable bowel syndrome, dyspepsia, gastroesophageal reflux disease, hypertransaminasemia |
| **Mental disorders** | depression, psychosis, schizophrenia |
| **Dermatological symptoms** | atopic dermatitis, alopecia, follicular keratosis |
| **Others symptoms** | rthralgia, aphthous stomatitis, hepatitis, type 1 diabetes |

Table 1. Clinical picture of CD

epithelium of the intestinal wall. In the future, there will be shown a significant increase of mitosis in the epithelium of the crypts, and noticeable flattening of enterocytes [13]. Some degree of villous atrophy is needed to confirm the diagnosis of CD. The presence of intraepithelial lymphocytes in combination with crypt hyperplasia without "blunting" villi, is less specific [14].

Thus, in addition to inflammatory processes, atrophy can also be observed. Atrophy of the mucous membrane in the CD has a hyperregenerative character. Manifestations of the atrophy include the shortening and thickening of the villi, the elongation (hyperplasia) of the crypts. Important for diagnosing CD is a change of attitude villus height to the depth of the crypt. His assessment is only possible with the correct orientation histologic preparation, the criterion of representativeness which is the presence of at least three adjacent cut lengthwise villi and crypts. The main morphological manifestation of CD is the development of hyperregenerative atrophy of small intestinal mucosa, which includes reducing of the height or the complete absence of intestinal villi and deepening of crypts with increased proliferative activity of enterocytes. Along with increased cell proliferation in the crypts, there is lack of formation of high-grade villi. This is due to disruption of proliferation and differentiation of cells and tissues. Inflammatory infiltration of the mucosa includes infiltration of surface epithelial lymphocytes and lymph plasmocytic infiltration of the lamina propria.

The average content of intraepithelial lymphocytes (IEL) in the epithelium of the villi of the small intestine does not exceed 30 per 100 epithelial cells. A typical histological manifestation of CD is the increase IELcontent. However, increased infiltration of lamina propria lymphocytes, plasma cells has no independent diagnostic value and may be considered only if other histologic evidence of disease co-exist. Among the cells which infiltrate both lamina propria and epithelium, neutrophils and eosinophils can be detected in large quantities.

To standardize the pathological findings of CD Marsh's criteria (1999) are used:

**Marsh I** – Infiltration of the villus epithelial lymphocytes- the earliest histological manifestation of celiac disease. Infiltration of epithelial lymphocytes is maintained at all stages of CD, but during the later (atrophic) stages (Marsh IIIB-C) it can be difficult to assess the content of intraepithelial lymphocytes, due to severe dystrophic pseudo stratified regenerative epithelium.

**Marsh II** - Extension of the crypts (hyperplastic stage of CD) - the first manifestation of hyperregenerative atrophy of small intestinal mucosa. In this step, the ratio of length to villi crypt depth is reduced to 1: 1. In parallel with the extension of the crypts there is some expansion of the villi. There remains the infiltration epithelial lymphocytes. Evaluation of the ratio of the villi to the depth of the crypt should only be correctly oriented in the preparation.

**Marsh III** - The following (atrophic) stage of CD is a gradual shortening of the villi and expand in combination with the deepening of the crypts (Marsh IIIA), subtotal villous atrophy and crypt hyperplasia (Marsh IIIB) up to the full (total) disappearance of the villi (Marsh IIIC). In such cases, the structure of small intestinal mucosa resembles colon. This stage is also characterized by changes in the surface epithelium associated with damage and an attempt of recovery: an increase in cell size, cytoplasm basophilia, increasing the size of the nucleus; enlightenment of nuclear chromatin, loss of nucleus basal orientation (pseudo stratified epithelium), blurred and fuzzy brush border.

**Marsh IV** (hypoplastic atrophy) - an irreversible atrophy with a sharp thinning of the mucous membrane of the small intestine. Very rare [15, 16].

In 2005 G.R. Corazza, V. Villanacci was quite a new three-stage classification system diseases, which builds on the relative values (the ratio of villus height and crypt depth). Corazza classification does not reflect the pathological and morphogenesis (staging) disease, but the simplicity, brevity and ease of use it provides a gradual replacement of the classification of Marsh. It is necessary to consider that the degree of A corresponds to the stage of Marsh I; degree B1 comprises the steps Marsh IIIA and IIIB due to the fact that in practice it is impossible to distinguish them; B2 level corresponds to stage march IIIS [11].

European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 1990 revised criteria for the establishment of a definite diagnosis of CD [17].

**Therapy**

The principles of treatment are based on the CD consultation of experienced physicians - general practitioner, pediatrician, gastroenterologist and nutritionist, as well as regular diagnostic observation. Methods of treatment include malabsorption lifelong gluten-free diet compliance, drug therapy and infusion therapy [2]. According to experts, the ways to prevent CD are complete elimination of gluten from a protein diet, as well as, long-term breastfeeding delays the manifestation and the further disease progression. This is due to the immunomodulatory properties of milk, as well as positive effects on child eubiosis [18, 19].

The basic principles of a gluten-free diet in celiac disease: elimination of foods containing gluten - wheat, rye, barley and oats, as well as products and substances that enhance fermentation and putrefaction; complete diet with high protein and calcium salts; limitation of mechanical and chemical stimuli of the intestinal mucosa, as well as dishes that stimulate the secretion of gastric and pancreatic cancer. Diet includes exception of wheat, rye and barley, which contains gluten peptides. Even small amounts of gluten can be undesirable since an amount of 0.1-2 g / day may lead to the disease progression. In marked malabsorption syndrome healthy food should contribute to the correction of disturbed protein, fat and carbohydrate metabolism, and to the elimination of deficiency of vitamins and minerals (calcium, iron, phosphorus, potassium, zinc, and others) [18, 20].

*Drug therapy*: Correction of vitamin, mineral deficiencies, osteoporosis, including iron deficiency, calcium, phosphorus, folate, vitamin B12, and fat-soluble vitamins. In severe forms are shown the following drugs: Calcium gluconate is 5-10 g / day, Ergocalciferol 0.01-1 mg / day (up to 2.5 mg / day. in severe malabsorption), Ferrous sulfate 300 mg / day, Folic acid 5-10 mg / day and multivitamin formulas.

*Infusion therapy:* protein preparations, fat emulsions, glucose solution, correction fluid and electrolyte balance and acid-base balance. If a patient is in critical condition, he ought to be fed with parenteral nutrition.

In refractory CD (found in 15% of cases), Glucocorticoids such as prednisone 20 mg / day can be administered for 6 weeks. Therapeutic indications are the lack of prednisolone effect on gluten-free diet for 3-6 weeks, the absence of other inflammatory diseases of the small intestine accompanied by the malabsorption syndrome, no complications (lymphoma of the small intestine, ulcerative jejunocolitis) [19, 20].

In addition, during relapses a number of treatments are prescribed including antibiotic therapy, to restore the intestinal microflora ("Alpha normiks", Ciprofloxacin, Metronidazole, Tetracycline); hormone therapy (Prednisolone), if the patient continues to eat flour and cereal products; the use of symptomatic drugs (white clay, bismuth, chalk, Dermatol, Bilignin). Patients with CD must be in constant medical supervision of a gastroenterologist [20-22].

## CONCLUSION

CD (gluten enteropathy) is a disease caused by a genetic predisposition of patients with eating foods containing gluten. This pathology is accompanied by atrophy of the villi of the mucosa and crypt hyperplasia of the small intestine. The basic principle of the diagnostic for this disease is to analyze the positive response serological, histological and clinical tests. Histological method today is the "gold standard" of research. Patients are advised to lifelong adherence to a gluten-free diet leads to remission in the majority of individuals.

CD (gluten enteropathy) is a chronic autoimmune disease affecting the digestive tract of genetically predisposed (HLA - DQ2, HLA - DQ8) persons who have intolerance to basic protein cereal (gluten).

Morphological identifying of mucosal atrophy, which has hyper regenerative character. The main pathologic manifestations are the following features:

- shortening and thickening of the villi;

- elongation (hyperplasia) of the crypts;

- changing attitudes to the height of the villus crypt depth;

- early inflammation is characterized by infiltration of lymphocytes in the epithelium of the intestinal wall;

- increase in the number of IEL;

- increase in the number of lymphocytes and plasma cells in the lamina propria.

Treatment is based on a lifelong gluten-free diet; drug therapy, based on the clinical course of the disease; infusion therapy; antibiotic therapy; Hormone therapy and traditional use of symptomatic agents. Meanwhile, breastfeeding delays the manifestation of CD at children.

## ACKNOWLEDGEMENTS

None

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