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The Most Common Complications of Celiac Disease and the Impact of a Gluten-Free Diet on Their Course

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Abstract

Introduction and Purpose:

Celiac disease is a gluten-sensitive, immune-mediated enteropathy that occurs in people with a genetic predisposition and leads to inflammation in the small intestine. During its course, characteristic antibodies are produced, which together with histopathological examination of material taken from the intestine, are the main elements of the diagnostic process. Depending on the symptoms present and microscopic changes, we distinguish classical, non-classical, subclinical and potential forms. The most typical presentation, in the form of gastrointestinal symptoms includes diarrhea, abdominal pain and weight disturbances. Atypical symptom, which may involve multiple other systems, are also increasingly observed. The cornerstone of treatment is a lifelong gluten-free diet that excludes all products containing wheat, barley and rye. In most cases, it helps alleviate or resolve symptoms and regenerate the intestinal mucosa. The long diagnostic process, non-adherence to the diet and resistance to treatment pose a high risk of complications at various stages of the disease, so it is important for the patient to cooperate appropriately with the doctor and nutritionist. The purpose of this paper is to review the most common complications of celiac disease and evaluate the impact of an appropriate diet on their course.

State of knowledge:

The most commonly observed complications of celiac disease involve the gastrointestinal, hematopoietic, reproductive, osteoarticular, and neurological systems. Although in some cases the etiology of complications is not fully understood and the association of celiac disease with other diseases is not completely certain, the need for early diagnosis and rapid implementation of a gluten-free diet is still emphasized. This significantly reduces the risk of dangerous consequences. If they occur, exclusion of gluten improves the clinical situation of the patient. Undoubtedly, the most frequently observed complications include the effects of impaired absorption, such as anemia, growth disturbances, and osteoporosis. Among the hematological diseases associated with celiac disease, in addition to anemia, we find IgA deficiency, coagulation disorders, and hyposplenism. Osteopenia, osteoporosis and the associated risk of fractures mainly affect those with delayed diagnosis, severely advanced lesions on histopathological examination and those who do not adhere to the diet. The most dangerous complications during the course of celiac disease appear to be malignant lesions of the small intestine. The greatest co-occurrence has been shown between intestinal T-cell lymphoma and adenocarcinoma. The prognosis in such patients is

usually poor. The effects of visceral disease can be particularly felt by women in their reproductive years. In addition to menstrual disorders, obstetric complications in the form of miscarriages, premature labor, fetal growth disorders and infertility are also observed. Neurological symptoms such as gluten ataxia, peripheral neuropathy, headaches although less frequently observed can be a major problem for the patient.

The implementation of a gluten-free diet proves to be a major financial and psychological burden for the patient.

Conclusions:

Celiac disease is one of the diseases that pose many diagnostic and treatment challenges. In addition to the typical gastrointestinal symptoms, many other symptoms and extraintestinal complications are possible. A gluten-free diet plays a key role in the treatment process. It helps to alleviate the symptoms of the disease, rebuild the small intestine and reduce the risk of dangerous complications. Unfortunately, the introduction of changes often proves to be heavily burdening for the patient, so close cooperation with a nutritionist and psychologist is necessary.

Keywords: celiac disease, gluten-free diet, anemia, lymphoma, osteoporosis, infertility, depression, gluten ataxia, neuropathy

Introduction and purpose

Celiac disease (CD) is a gluten-sensitive immune-mediated enteropathy that occurs in genetically predisposed individuals, which is associated with the presence of HLA-DQ2 and/or HLA-DQ8 antigens. Gluten consumption induces the production of specific IgA class antibodies against: tissue transglutaminase (tTG), deamidated gliadin peptide (a-DGP), endomysium (EMA). The autoimmune reaction results in inflammation within the small intestine which is histopathologically manifested by intraepithelial lymphocytosis, crypt hyperplasia and villous atrophy [1,2]. The disease is estimated to affect 1% of the population with a prevalence in women. An increased risk of celiac disease affects first-degree (5-10%) and second-degree relatives, people with other autoimmune diseases, and some genetic diseases, such as trisomy of chromosome 21 (Down syndrome) [3].

Most patients exhibit symptoms during childhood. However, more than 70% of individuals are diagnosed only after the age of 20. In the diagnostic process, we mainly take into account the patient's clinical picture, serological tests and histopathological examination [3]. The key to

diagnosis in adults is histopathological evaluation of material taken from the duodenum and assessment of lesions according to a modified Marsh scale, also known as the Marsh-Oberhuber scale [4]. In 2011, the Oslo CD classification identified the following clinical presentations: classic, non-classic, subclinical, potential and refractory [5].

The cornerstone of celiac disease treatment is a lifelong gluten-free diet, which should be established and reviewed in collaboration with a dietitian [1]. This diet is based on the exclusion of all products containing wheat, barley and rye. According to the Executive Order of the European Union Commission products are considered gluten-free if they contain less than 20mg/kg of gluten in the form sold to the consumer [6].

The increased risk of complications of celiac disease is associated with various factors. The main ones are late diagnosis, lack of patient cooperation with doctors and failure to follow dietary recommendations, which are crucial in the treatment process [7]. Delayed diagnosis may be due to the fact that typical symptoms of celiac disease such as diarrhea, abdominal pain, weight loss and abnormal weight gain are not always present. On the contrary, atypical symptoms related to completely different systems may dominate [8]. Introducing new dietary habits and maintaining a consistent diet is a significant challenge and can result in low patient compliance. Eliminating the appropriate products not only reduces the symptoms of the disease but also allows for the regeneration of the intestinal mucosa and in many cases, prevents the development of complications [3]. Unfortunately, in some patients despite a restrictive gluten-free diet the improvement is only temporary and in some cases it does not occur at all. If this condition persists for more than 12 months, it is referred to as refractory celiac disease (RCD). It is also a factor that increases the risk of developing complications [7]. It is important to exclude lactose intolerance and fructose intolerance in patients who do not respond to a gluten-free diet, as they may be the cause of treatment failure [9].

The purpose of this review is the most common complications of celiac disease and to assess the impact of the gluten-free diet and the time of diagnosis on their development.

State of knowledge

Both symptoms and complications in the course of visceral disease can vary widely. The problems of such patients are very complex and can sometimes be non-obvious, which causes additional diagnostic difficulties. In many cases, timely treatment is able to protect the patient from dangerous consequences. Mainly for this reason, vigilance on the part of the patient and the specialists to whom they report is very important. The crucial role of a specialized dietitian is emphasized,

as their task is to teach and advise the patient on which products are prohibited and how to structure a balanced diet [3].

Among the most commonly mentioned systems where complications occur are the gastrointestinal, hematopoietic, genitourinary, neurological, and musculoskeletal systems [10].

1. Gastrointestinal system

Numerous dietary restrictions and damage to the intestinal villi leading to impaired absorption result in micro- and macronutrient deficiencies in the body. Specifically, these include iron, folic acid, zinc, calcium, copper, vitamin B6 and vitamin D. Patients with coexisting lactose intolerance are particularly at risk of low vitamin D levels due to the additional elimination of dairy products [11]. Strict dietary adherence can compensate for these abnormalities but sometimes supplementation is necessary. Due to the need to eliminate many gluten-containing products, there is a risk of disrupting the proper proportions of consumed simple sugars, fats, and proteins.

The reduced intake of fiber can result in constipation [3]. In order to increase the diversity and nutritional quality of diets it is recommended to replace the banned grain groups with a group of gluten-free cereals called pseudo-cereals. These include amaranth, quinoa, millet and buckwheat [11].

Malignant diseases that are more common in patients with celiac disease include non-Hodgkin's lymphoma (NHL), adenocarcinoma of the small intestine and squamous cell carcinoma of the esophagus and throat [9].

Among the neoplastic changes, special attention is given to the occurrence of non-Hodgkin lymphoma, for which an increased risk was already shown in studies at the end of the 20th century [12].

A particular association has been noted between celiac disease and the development of intestinal T-cell non-Hodgkin lymphoma also known as enteropathy-associated T-cell lymphoma (EATL). It accounts for only 1% of all NHLs (non-Hodgkin's lymphomas) [13]. The cells of this lymphoma probably arise from clonal proliferations of abnormal intraepithelial lymphocytes (IELs). The lack of CD8 expression by IELs is typical of early EATL. Observations suggest that the risk of developing EATL is particularly high in cases of refractory celiac disease and approximately 80% of cases exhibiting an abnormal clonal population of IELs [14].

Although the risk of EATL lymphoma among all lymphomas is the highest, the total number of B-cell lymphomas and extranodal T-cell lymphoma in the course of celiac disease is higher [13]. The possibility of EATL should be ruled out if the patient reports abdominal pain, fever, weight

loss, gastrointestinal bleeding. A dangerous complication of lymphoma, which can lead to death, is gastrointestinal obstruction or bowel perforation. The treatment regimen for NHL is based primarily on chemotherapy and is largely no different from typical treatment regimens. Other methods used for eligible patients include bone marrow transplantation and surgical procedures [3].

One study published in 2018 showed an increased incidence of celiac disease comorbidity in patients with T-cell lymphoma, small intestinal adenocarcinoma and esophageal squamous cell carcinoma. The study sample consisted of 301,425 people diagnosed with lymphoma or gastrointestinal cancer between 1994 and 2014. Data were taken from the Dutch national population-based pathology database (PALGA) [15].

An increased relative risk (RR) was found in celiac disease patients for:

- T-cell lymphomas (RR = 35.8)
- duodenal adenocarcinoma (RR = 10.2)
- distal adenocarcinoma of the small intestine (RR = 14.4)
- squamous cell carcinoma (SCC) of the esophagus (RR = 3.5) [15].

Additionally, a study conducted in the years 1998-2000 in the United Kingdom collected information about new cases of primary small bowel cancer. The results of the study showed that celiac disease was also present in 13% of adenoma cases and in 39% of lymphoma cases [16].

The effectiveness of a gluten-free diet and early detection of celiac disease in relation to cancer is uncertain and still under discussion. It is suggested that the risk of EATL decreases ≥1 years after the implementation of an appropriate diet [15].

The prognosis at the time of diagnosis is usually unfavorable due to the advanced stage of the disease [3]. Despite the existing increased risk of this cancer, it is not high enough to warrant screening for the disease in people with celiac disease [17].

2. Hematopoietic system

Common hematologic complications of celiac disease include anemia and hyposplenism. Less common are thrombocytopenia, thrombocytosis, thrombotic events, IgA deficiency, and lymphoma [18].

Anemia is the most common hematologic complication of celiac disease and results primarily from malabsorption of micronutrients such as iron, vitamin B12 and folic acid. It is frequently observed phenomenon and may be the only symptom present in the patient [19].

When iron levels are reduced, microcytic anemia, low serum iron and ferritin levels are observed. A characteristic feature of iron deficiency anemia is the lack of improvement after oral iron preparations. Intravenous supplementation is then required [18]. This condition is more commonly observed in cases of refractory celiac disease. Due to the fact that vitamin B12 absorption occurs mainly in the ileum, which is less frequently affected by inflammation, vitamin B12 deficiency anemia is less common, although it is still estimated to affect up to 40% of patients with untreated celiac disease. In the case of vitamin B12 or folic acid deficiency, macrocytic anemia is observed [19].

When deficiencies of these elements overlap, normocytic anemia can also occur. In rarer cases, celiac disease can be associated with anemia of chronic disease and aplastic anemia [18].

Hyposplenism

The prevalence of hyposplenism in adults with celiac disease is estimated to be about 30%, but it can rise to as high as 80% in patients who are not properly treated. A peripheral blood smear may show characteristic Howell-Jolly bodies in erythrocytes and red blood cells containing characteristic depressions (wells) in the cell membrane, visible on phase-contrast interference microscopy [20]. Due to impaired splenic function, there may be hyperplasia and increased susceptibility to infections, especially those associated with *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis* infections. As part of the prophylaxis, additional vaccinations against these bacteria are recommended for such patients [18].

IgA deficiency

The coexistence of IgA deficiency and celiac disease is observed in about 2-3% of patients during the diagnostic process. To avoid false-negative results, it is recommended to assess the total IgA antibody level in the serum together with the measurement of celiac-specific antibodies. Determining anti-tTG in the IgG antibody class may also be helpful. Patients with known IgA deficiency have an increased risk of chronic parasitic infections and inflammatory bowel disease [18]. In the case of visceral disease, this risk is about 10-20 times higher [3].

Thrombotic-embolic events are considered a rare complication of celiac disease. However not all studies show a correlation between these conditions [21]. The potential cause is believed to be elevated homocysteine levels in the blood serum and a deficiency of proteins C/S. Hyperhomocysteinemia may result from acquired folic acid and vitamin B12 deficiencies. It is thought that its presence may not only affect the increased frequency of thrombotic incidents, but may also have a negative impact on pregnancy outcomes and the development of osteoporosis [22].

3. Reproductive system

The reproductive system complications of celiac disease primarily include obstetric complications such as more frequent miscarriages, reduced fetal birth weight, preterm labor, and infertility. Other gynecological complications include delayed menarche, amenorrhea, and premature menopause [23]. The previously described malabsorption leading to multiple deficiencies, weight disorders and endocrine disruption are considered potential causes. In addition, adverse effects of anti-TG2 antibodies on placental development and function are also considered. These problems primarily affect women with diagnosed untreated or improperly treated celiac disease [24].

According to a Danish cohort study, which included all single live births in Denmark between January 1,1979 and December 31, 2004, adherence to a gluten-free diet before and during pregnancy reduced the risk of having a baby with low birth weight and the risk of preterm delivery [25].

On the other hand, during a study conducted in Turkey in 2016, which included 6 patients following a gluten-free diet and 8 patients who were poorly treated, 50% of the untreated women experienced miscarriages, and 75% had preterm births. There was also an increased risk of intrauterine growth restriction, low birth weight, and stillbirth in untreated women compared to those following a gluten-free diet [24].

Suggested causes of delayed menarche, amenorrhea and premature menopause include functional hypopituitarism and abnormal functioning of the reproductive organs due to malnutrition and weight disorders. It is also suspected that circulating gluten peptides disrupt hypothalamic-pituitary regulation thereby affecting the gonads [26].

Depending on the study, the time of delay in first menstruation varied, averaging 1.5 to 2 years, while menopause occurred about 2.5 years earlier compared to control samples. In addition, it was shown that these problems mainly affected untreated women, and the gluten-free diet had a positive impact on the timing of menarche and menopause [27].

4. Musculoskeletal system

Studies have shown that already at the time of celiac disease diagnosis, many patients have reduced bone mineral density (BMD). Among the causes are calcium and vitamin D3 deficiencies. In addition, circulating inflammatory cytokines and anti-osteoprotegerin autoantibodies are also likely to underlie the impaired bone turnover [10].

Of course, individual factors such as age, gender, physical activity, medications used, menopause in women, and andropause in men also have an impact. It is estimated that osteoporosis can occur in about 4-10% of premenopausal men and women, and osteopenia in 10-50% of patients with CD [28]. Some patients also have an increased risk of bone fractures [29].

Nevertheless, routine screening for osteoporosis is not currently recommended immediately after diagnosis. Exceptions may include patients with delayed diagnosis and advanced histological changes, assessed according to the Marsh scale. The decision to diagnose should be guided by the patient's individual history and the commonly used FRAX® calculator for assessing fracture risk. [28]. Typically, the first DXA examination is performed after one year of treatment. In patients who are found to be osteopenic, supplementation of deficiencies, mainly vitamin D and calcium, is recommended. In cases of osteoporosis, bisphosphonates may be considered [20]. According to studies, thanks to a properly implemented gluten-free diet and compensation of vitamin, micro- and macronutrient deficiencies, an improvement in BMD is observed as early as 1 year after its implementation. The importance of early diagnosis of celiac disease is emphasized in children because of the intense growth and development of their bones. Hypocalcemia, low vitamin levels, low growth, elevated bone resorption markers and low BMD are common symptoms of untreated celiac disease in children [28].

5. Neuropsychiatric complications

Although the mechanisms for the development of neurological complications of celiac disease are not fully understood, immune factors, gluten toxicity and vitamin and nutrient deficiencies are thought to play a major role [30].

Neurological symptoms can be observed at various stages of the disease, and are estimated to affect about 8% of people with overt malabsorption [31]. The most commonly observed problems include headache, cerebellar ataxia, peripheral neuropathy, epilepsy and cognitive impairment [10].

Headache

More frequent headaches, especially in the form of migraines, have been observed in various age groups. Adherence to a gluten-free diet led to a significant reduction in the severity and frequency of pain in both children and adults. In some cases, the headache disappeared completely [32].

Gluten ataxia

Gluten ataxia is a “gluten-related” condition, meaning that it is associated with gluten consumption and can occur not only in celiac disease [33]. It is the most common neurological complication, affecting 20% of patients with ataxia and 40% of patients with sporadic ataxia [3]. In celiac disease, it presents with dysarthria, gait ataxia, eye movement disorders, and other visual disturbances. Improvement of symptoms is possible through a gluten-free diet [33]. Attention is drawn to the association between the occurrence of cerebellar ataxia with high titers of anti-gliadin antibodies. Depending on the study, the prevalence of these antibodies in ataxia of

unknown cause ranged from 0% to 41%. It is suggested that all patients with ataxia of unknown cause should be diagnosed for celiac disease [34].

Peripheral neuropathy

Peripheral neuropathy is the second most common neurological complication after ataxia. Distal, symmetric, predominantly sensory neuropathy is most commonly described. Motor neuropathy, autonomic neuropathy and multiplex mononeuritis have been observed less frequently [34]. The effect of a gluten-free diet on neuropathy symptoms is not fully proven, with various studies showing conflicting conclusions [33].

Epilepsy

Some studies have shown an increased risk of epilepsy in patients with celiac disease, with prevalence ranging from 3.5% to 7.2%. Putative causes of epilepsy in celiac disease include gluten toxicity, damage to the cerebral cortex and nutrient deficiencies in the body [33]. The most common type is temporal epilepsy [39]. Recent studies bring more doubt to the correlation of these diseases [35, 36].

Cognitive impairment and dementia

Mild cognitive impairment commonly referred to as “brain fog” includes memory deficits, impaired concentration and attention, episodes of confusion and disorientation [38]. Following a proper diet leads to an improvement in cognitive function after one year of implementation. This improvement correlates with the regeneration of the small intestine mucosa and the decreasing levels of tissue transglutaminase antibodies [39]. Nevertheless, in patients over 65 years of age, there is a higher likelihood of cognitive dysfunction compared to their healthy peers [40].

Depression

Among the most common psychiatric complications occurring in celiac patients are depression and anxiety disorders. Although the underlying pathomechanisms of these disorders are uncertain, many studies have shown an association between them. Other conditions, such as eating disorders, schizophrenia, attention deficit hyperactivity disorder are also mentioned, though their frequency is much lower, and the relationship between them and celiac disease is far less certain [41].

The risk of depression is associated with many factors, some of which are directly or indirectly related to celiac disease. The necessity of modifying eating habits and being more vigilant about food consumption can make patients more stressed, especially when eating outside the home. Another negative factor is financial. Some patients believe that the new diet is more expensive because gluten-free products are not as widely available as gluten-containing products. Additionally, they must ensure that the diet is varied and balanced. This situation adversely affects their emotional state and increases the risk of depression and anxiety. In addition, it makes

adherence to the diet difficult and increases the risk of deviations from the diet [42]. According to many studies, in some patients, exclusion of gluten from the diet had a protective effect against psychiatric symptoms. The whole situation described suggests the likelihood of a vicious cycle. Decreased motivation and deterioration of psychological state leads to non-adherence to the diet, and consumed gluten exacerbates symptoms of anxiety and depression which worsens the quality of life and reduces the desire for proper treatment [43].

In order to sustain a high degree of motivation and awareness, close cooperation and support from specialists in dietetics, psychology, psychiatry are necessary [44].

Summary

Celiac disease is one of the diseases that can pose a major diagnostic and treatment challenge. The wide range of extraintestinal symptoms should arouse vigilance among many medical specialists. Making a diagnosis involves a number of tests to exclude micro- and macronutrient deficiencies, which can contribute to anemia, reduced bone mineral density and gynecological and obstetric complications. In most cases, the implementation of a gluten-free diet alleviates symptoms and allows for the regeneration of the intestinal mucosa. This improves absorption processes and helps normalize lowered parameters. Among hematological diseases, iron deficiency anemia is the most commonly observed, characterized by resistance to oral iron supplementation. Other common complications from this system also include hyposplenism, which increases the risk of infections.

One of the most serious complications of celiac disease is malignancy. The most frequently observed are non-Hodgkin's lymphoma, particularly T-cell lymphoma of the intestines, and intestinal adenocarcinoma. Usually, due to the stage of the lesions, the prognosis for the patient is poor. The long-term effect of diet on the course of lymphoma is uncertain, but it has been suggested that it may improve prognosis especially early in the course of the disease.

The higher risk of low bone mineral density is due, among other factors, to deficiencies in vitamin D and calcium, and possibly immunological reactions. To exclude osteopenia and osteoporosis, a DXA scan is recommended no later than 1 year after the diagnosis of celiac disease. Here, too, a positive effect of diet on the decrease in bone mineral density has been shown.

A significant impact of celiac disease can be felt by women especially during the period of trying to get pregnant and during pregnancy. Infertility, more frequent miscarriages, low birth weight and premature birth are the most common complications they face. In some cases, menstrual disorders are also observed, such as a delay in the onset of menstruation by an average of 1.5-2

years and the occurrence of premature menopause approximately 2.5 years earlier. As in other cases, it is suggested that lack of dietary adherence increases the risk of these pathologies.

Neurological complications such as gluten ataxia, peripheral neuropathy, headaches, and cognitive function disorders occur less frequently but can also pose a significant problem for the patient.

A diagnosis marks the beginning of major changes for the patient. They involve a number of difficulties, not only financial, but also social and psychological. It is directly associated with an increased risk of depressive disorders and medication. In addition, it leads to a decrease in motivation to adhere to the diet, as well.

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