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Celiac Disease - A New Old Disease: Do We Really Think Enough of Celiac Disease, and Malignant Complication?

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1. Abstract

Celiac disease is an autoimmune disease characterized by injuries of the small intestine and malabsorption of nutrients in gluten sensitive individuals. It is one of the most common gastrointestinal and systemic diseases with the prevalence of 0.5-1%, Different clinical presentation delays diagnose sometimes after several years of having symptoms. The main features of enteropathy are the presence of the human leukocyte antigen haplotype (HLA) DQ2 or DQ8 and antibodies typical of celiac disease. Even after many years of various researches, celiac disease is a challenging condition due to constant new knowledge about pathophysiology, diagnosis, treatment and possible new therapeutic procedures. History of these rare diseases was the identification of tissue transglutaminase as an autoantigen, which confirmed the autoimmune nature of the disorder. The genetic background informed about the determinant of disease development that occurs due to the contribution of environmental factor. The only way of treatment for celiac disease is available with strictly gluten-free diet that lead to improved quality of life, relive symptoms and prevent complications (especially malignancy). In this review article, a patient with a late diagnosis of celiac disease complicated with already developed lymphoma of the small intestine is presented.

2. Introduction

Coeliac disease is an autoimmune disease characterized by injuries of the small intestine and malabsorption of nutrients in gluten sensitive individuals. Prevalence in the general population ranges from 0.5%-1%. The development of the coeliac enteropathy depends on a complex immune response to gluten proteins. Different clinical presentation delays diagnose sometimes after several years of having symptoms. The disease is associated with a risk of complications, such as osteoporosis and intestinal lymphoma. Diagnosis of coeliac disease requires a positive serology (IgA anti-transglutaminase 2 and anti-endomysial antibodies) and villous atrophy on small-intestinal biopsy. In the case of an allergic form to gluten, it is necessary to adhere to a gluten-free diet [1]. However, they are conducting numerous studies in search of a pharmacological solution, primarily in blocking the effect of anti-gliadin antibodies.

2.1. Epidemiology and Prevalence

The prevalence of celiac disease as one of the autoimmune diseases is thought to be 0.5% to 1% of the general population (with the exception of Africa and Japan which show extremely low gluten consumption). The highest prevalence is in the Scandinavian countries such as Finland and Sweden, where the prevalence is as high as 2-3%, while Germany is the country with the lowest prevalence of 0.2%. Various studies have shown that most cases remain undetected in the absence of serological examination due to heterogeneous symptoms and / or poor awareness of this disease. Between 1975 and 2000, the incidence of celiac disease increased fivefold. Patients with Down syndrome and type 1 diabetes have a 10% -15% higher chance of developing celiac disease [2].

2.2. Clinical Presentation

In an average of 2,000 patients enrolled with a general practitioner, every 10-20 patients should have celiac disease but most of them are unrecognized. There are seven undiagnosed patients per

diagnosed person. The time interval for recognizing this reversible disease is ten years and only 5% of patients are included in the work with the expert team. In the pediatric population, it is considered that there are the most undiagnosed children who have celiac disease because they have many gastrointestinal symptoms, but not specific enough for a correct diagnosis. A large number of children in the world are misdiagnosed without knowing that they are suffering from this treacherous disease. People with unrecognized celiac disease have a 4-fold higher risk of death. Female population in this disease dominates over the male population with a 3: 1 ratio. It has been shown that Caucasians are much more likely to get sick than blacks. Recent research shows a declining consumption of rice per capita and a parallel increase in the consumption of wheat-based products. Due to these dietary trends, an increasing incidence of celiac disease in eastern countries can be expected in the near future [3] (Table 1).

There are classical and non-classical gastrointestinal symptoms, extraintestinal manifestations, and subclinical cases. Celiac disease is a disease with a "thousand faces" and is associated with several autoimmune diseases such as: type 1 diabetes and autoimmune thyroid disease, Addison's Disease, Autoimmune Chronic Active Hepatitis, Myasthenia Gravis, Pernicious Anemia, Raynaud's Phenomenon, Scleroderma, Sjogren's Syndrome, Systemic Lupus Erythematosus.

Table 1: Thousand faces disease.

Gastrointestinal symptoms	Non-intestinal symptoms	Neurological symptoms
Chronic diarrhea	Anemia	Polyneuropathy
Abdominal pain	Elevated AST and ALT	Autonomic nervous system disturbances
Abdominal distention	Dermatitis herpetiformis	Brain white matter lesions
Vomiting	Enamel hypoplasia	Cerebellar ataxia
Constipation	Recurrent aphthous stomatitis	Headache
	Developmental delay	Myoclonus
	Short stature	
	Delayed puberty	
	Reccurent miscarriage infertility	

2.3. New Diagnostics Guidelines

New Guidelines for the Diagnosis of Paediatric Coeliac Disease by European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), from 2020 suggested testing for children with gastrointestinal (chronic or intermittent diarrhea/constipation/abdominal pain, distended abdomen, recurrent nausea and/or vomiting), extraintestinal symptoms (weight loss/failure-to-thrive, delayed puberty, amenorrhea, irritability, chronic fatigue, neuropathy, arthritis/arthralgia, chronic iron-deficiency anaemia, decreased bone mineralization (osteopenia/osteoporosis), repetitive fractures, recurrent aphthous stomatitis, dermatitis herpetiformis–type rash, dental enamel defects, abnormal liver biochemistry), specific conditions (first-degree relatives with CD, autoimmune conditions: T1DM, thyroid disease, liver disease, Down syndrome, Turner syndrome , Williams-Beuren syndrome , IgA deficiency) [10].

Intake of gluten into the digestive system of patients causes damage - initially inflammation, and then atrophy of the intestinal mucosa, which therefore cannot normally absorb nutrients. In identical twins, there is a high percentage of concordance (75%), while in those identical and first relatives, the disease occurs in a much smaller percentage (10-15%) [4].

2.4. Pathophysiology and Genetics

In addition, the disease is known to be strongly associated with alleles of human leukocyte class II antigen. Human leukocyte antigen (HLA) of the major histocompatibility complex (MHC) [4]. More than 95% of celiac patients carry the HLA DQ2 or DQ8 haplotype. Although 30% of Caucasians are DQ2 and / or DQ8-positive, celiac disease will develop in only 3% of carriers of the at-risk genotype, much of the genetic susceptibility is still present in genes outside the HLA system [4]. Genes have relatively little individual influence on the development of celiac disease and are only partially common to individual patients, suggesting genetic genetic heterogeneity of the disease [4].

2.5. Pathology

Pathological changes are found exclusively in the mucosa, mainly in the upper parts of the small intestine, the duodenum and the initial part of the jejunum [5]. In rare cases, changes can be found in both the ileum and the colon, which is proportional to the severity of the clinical presentation [5]. Affected intestinal villi are atrophic, infiltrated by numerous intraepithelial lymphocytes (IELs), eosinophils, neutrophils, and plasma cells, enterocytes show some degree of damage, and there is crypt hyperplasia. Pathohistologically, we can classify changes into several categories according to the modified Marsh-Oberhuber classification, one of the most commonly used among pathologists (Table 2).

Table 2 - explanation:

Type 0 - there is no villi atrophy or crypt hyperplasia, and the number of intraepithelial lymphocytes (IEL) is small, so it is very likely not

a diagnosis of celiac disease. In type 1 the mucosal architecture is normal, but the number of intraepithelial lymphocytes is increased which may suggest to us that it could be celiac disease. This presentation can also be seen in patients on a gluten-free diet. Type 2 is characterized by crypt hyperplasia, and type 3, which we divide into a, b and c subcategories, also contains villi atrophy. Type 4 is also mentioned in the literature, which is characterized by villi atrophy, but with a normal number of intraepithelial lymphocytes and a normal crypt height. An increased number of IELs should raise the suspicion of celiac disease without changes in the villi and crypts, although an increased number of IELs can be found in Crohn's disease, parasitic infections or autoimmune diseases [6].

Table 2: Marsh-Oberhuber classification

Marsh type	Intraepithelial lymphocyte count (IEL)	Crypt Hyperplasia	Villi	Positiv celiakia
0	<30	Normal	Normal	No
1	>30	Normal	Normal	No
2	>30	Increased	Normal	Yes
3a	>30	Increased	Mild atrophy	Yes
3b	>30	Increased	Marked atrophy	Yes
3c	>30	Increased	Complete atrophy	Yes
4	normal	Normal	Complete atrophy	Yes

2.6. Diagnostics Protocol

Celiac disease can be diagnosed in people of younger age all the way to old age with a whole range of atypical symptoms and signs. These are patients with mild and long-term ailments such as chronic fatigue, anemia, bloating or elevated transaminases [7]. It is important to make a correct diagnosis due to the risk of developing malignancy in untreated disease, the potential presence of nutritional deficiencies, the risk of giving birth to low birth weight children, and the accompanying occurrence of other autoimmune diseases [7]. The classic symptoms in childhood occur after cessation of breastfeeding and the introduction of cereals into the diet. The infant progresses less in weight, is pale, disinterested, dissatisfied, loses appetite, and loses muscle itself. Generalized hypotension and abdominal distension accompanied by frequent fatty stools occur. Constipation and rectal prolapse sometimes occur. At that age, the symptoms are clear and typical, while after the second year they are less recognizable or atypical. Preschool and school-age children are primarily prone to sideropenic anemia, rickets, short stature, or delayed puberty, while adults have very different symptoms and signs of the disease [7].

The basic rules for diagnosing celiac disease are:

1. The diagnostic procedure should be performed while the person is consuming gluten, ie, a gluten-free diet, the results of diagnostic tests may be false negative

2. The first diagnostic procedure is the determination of total immunoglobulin A (IgA) in the blood to avoid "false negative" findings by testing antibodies to tissue transglutaminase (IgA tTG) in patients with serum IgA deficiency.IgA anti-endomysial antibodies are found in 90% coeliac patients. Since coeliac disease is commonly associated with IgA deficiency, care must be exercised in diagnosing these patients since clearly they do not express IgA antibodies. In that case, IgG anti-endomysial antibodies are positive. Presence of the human leukocyte antigen haplotype (HLA) DQ2 or DQ8 and antibodies typical of celiac disease (antibodies to tissue transglutaminase (anti-tTG), endomysial antibodies (EMA) and antibodies to deamidated gliadin peptide (DGP)). The mentioned antibodies can be immunoglobulin IgA and IgG classes, but only those of the IgA class are considered are highly sensitive and specific for celiac disease. Antibodies of the IgG class have a high percentage of false positive findings, so their use should be limited only to people with selective IgA deficiency [11,12]

3. In case of clear suspicion in case of a negative finding, it is necessary to repeat the negative serological or path histological finding and check whether the person takes gluten in the diet backwards at least 6-8 weeks before the findings.

4. Gene test - determination of DQ2 and DQ8 heterodynes, used as an exclusive test because 30-40% of people have DQ2 and DQ8 positive heterodimer. With a positive finding, the genetic basis for the development of the disease is confirmed, but not a definite diagnose .Level of endomysial and antigliadin antibodies of the new generation, help as to monitoring whether an individual adheres to a diet protocol

5. In endoscopic sampling, it is important to take 4-6 samples for path histological analysis at least four from the deep duodenum and one from the bulbous duodenum [8,11,12].

2.7. Complications of Late Diagnosis

The late diagnosis of celiac disease (after the age of 50) and / or non-adherence to a strict gluten-free diet can lead to higher mortality compared to the general population. Although rare (about 1% of patients diagnosed with celiac disease), complications include hyposplenism, intestinal lymphoma, small bowel adenocarcinoma, and ulcerative jejunoileitis. Complications should be suspected in all patients who, despite adherence to a diet, complain of unexplained persistence or recurrence of symptoms (i.e. diarrhoea, abdominal pain, weight loss). These complications are more common when diagnosed in elderly patients and / or in those who are homozygous for DQ2 who do not follow a strict gluten-free diet [9].

3. Case Report

A 47-year old patient was admitted to the Department of Gastroenterology through the Emergency Service, with different symptoms: cramping pains in the upper abdomen, under both ribs of the arch, with a feeling of fullness, bloating with nausea, weakened appetite, which has caused him to lose a lot of weight. He took rabeprasol 40mg. Abdominal MSCT was done and showed concentrically thickened jejunum wall curvature up to 20 mm thick on a section up to 6 cm long with multiplied and enlarged mesenteric elephant cells measuring up to 20 mm and turbidity of adjacent mesenteric adipose tissue. In that moment here was no indication for urgent surgical treatment.

We made partial double balloon enteroscopy using NaviAid Balloon Guided Endoscopy and search of about 100 cm into the jejunum. We had great resistance to the passage of the endoscope into the lower parts of the small intestine, so we stopped the examination to avoid complications. Mucosa was without lustre, uneven, thinned, with numerous changes in terms of chronic healing of the mucosa, furrows, and hyperaemia. Numerous biopsies were taken for pathologist analysis (70 CD3 positive intraepithelial lymphocytes per 100 entrecotes - Marsh-Oberhuber tip 3b.

Patient starts with gluten-free diet, and waits for nuclear magnetic enterography.

After a month, due to severe and sudden abdominal pain, he underwent surgery. The distal part of the jejunum was resected with a length of 33 cm. Path histological finding was non-Hodgkin's lymphoma. He was treated according to the R-CHOP and 2 R protocol (rituximab, solu-medrol, synopen, calcihept, H2 blocator, paracetamol, endoxan, vincristine, dexorubicin), and gluten free diet.

4. Conclusion

Celiac disease as a chronic autoimmune disease is considered to be an insufficiently recognized public health problem precisely because of its diverse clinical presentation and the vicissitudes of the disease itself. This gluten enteropathy creates a great challenge for sufferers because gluten is present in a large number of foods nowadays. It is very important to pay attention to a gluten-free diet and plan meals throughout the day, which can further create stress in patients. The diagnosis itself is difficult to come by, and patients must undergo numerous tests before a proper diagnosis is made. Patients should also be warned about the consequences of not following a strict gluten-free diet and possible complications. Screening for celiac disease should be considered at an early age, perhaps in kindergartens, elementary school, using non-invasive rapid finger-prick blood tests, in order to avoid greater damage to the organism in time. The future of treatment may lie in the detection of a molecule that will act as an inhibitor of tissue transglutaminase.

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