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CELIAC DISEASE OVERVIEW

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Abstract:

Introduction: *Celiac disease is considered an autoimmune disease that happens in genetically predisposed individuals who get an immune reaction to gluten. The disease mainly influences the small intestine; but the clinical presentation are wide, with both intestinal and extra-intestinal symptoms. Celiac disease is noteworthy as broad clinical spectrum of presentations, large age range at which beginning can happen, and the elevated morbidity and mortality that has been shown in many studies. The disease also adds a model of an immune -based disease with both strong genetic and environmental risk factors.*

Aim of work: *In this review, we will discuss regarding celiac disease.*

Methodology: *We did a systematic search for celiac disease using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *In spite of the increase in the prevalence of celiac disease and enhanced recognition and numbers of diagnosis, many avenues of investigation are necessary to understand the pathogenesis and enhanced the management of patients with this condition. Enhancements in the pathophysiology of celiac disease may let preventive techniques in individuals at high risk for disease development. The development of non-dietary therapies may relieve symptoms in patients with celiac disease and inadvertent gluten exposure, and an effective alternative of the gluten-free diet could greatly enhance the quality of life of those many patients who find adhering to the diet very difficult. advances for the detection of gluten in food and to examine for recent gluten exposure may enhance the design of future clinical trials and may be of critical value in patients daily activities.*

Key words: *celiac disease, pathophysiology, risk factors, epidemiology, management.*

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INTRODUCTION:

Celiac disease is considered an autoimmune disease that happens in genetically predisposed individuals who get an immune reaction to gluten. The disease mainly influences the small intestine; but the clinical presentation are wide, with both intestinal and extra-intestinal symptoms. Celiac disease is noteworthy as broad clinical spectrum of presentations, large age range at which beginning can happen, and the elevated morbidity and mortality that has been shown in many studies. The disease also adds a model of an immune -based disease with both strong genetic and environmental risk factors.

In this review, we will discuss the most recent evidence regarding celiac disease.

METHODOLOGY:

We did a systematic search for celiac disease using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: celiac disease, pathophysiology, risk factors, epidemiology, management.

PATHOGENESIS:

Gluten

The main environmental factor accountable for the development of celiac disease is gluten. Gluten is the term for the prolamin storage proteins of the cereal grains wheat, rye, and barley. Gluten is favored in breadmaking for its elasticity; but, it is rich in glutamines and prolines and, is partly digested by gastric, pancreatic, and brush border peptidases, leaving great part of peptides up to 33 aminoacids long. [1] These peptides get into the lamina propria of the small intestine via transcellular or paracellular pathways–6 where, in affected individuals, an adaptive immune reaction occurs that is dependent on deamidation of gliadin molecules by the enzyme tissue transglutaminase (TTG), the predominant autoantigen of celiacdisease. [2] Deamidation rises the immunogenicity of gliadin, helping binding to the HLA-DQ2 or HLA-DQ8 molecules on antigen presenting cells.8 Gliadin peptides are then presented to gliadin-reactive CD4+ T cells. [3] During this process, antibodies against TTG, gliadin, and actin are made through uncertain mechanisms. These antibodies may add to extra-intestinal manifestations of celiac disease, like dermatitis herpetiformis and gluten ataxia. [4]

Both the lamina propria (adaptive) and intraepithelial (innate) immune responses might to be essential for the formation of the complete celiacpathological lesion, however the mechanism on how these two processes interact is not clear. People with celiac disease will have an intense immune response to some however, of noteworthy, not all non-gluten proteins in wheat. [5] The importance of these non-gluten wheat proteins in the pathogenesis of celiac disease is not obvious, though one class of these proteins, the amylase trypsin inhibitors, may have a major role in the epithelial cell damage, leading to the innate response and in non-celiac gluten sensitivity, another wheat-related problem. [6]

Genetic factors

The significance of a genetic component for the development of celiac disease is obvious, this is based on the familial occurrence and the high concordance in identical twins. [7] Almost all patients with celiac disease possess specific variants of the HLA class II genes *HLA-DQA*1 and *HLA-DQB*1 that, encode the two chains (α and β) of the coeliac-associated heterodimer proteins DQ2 and DQ8 that are expressed

on the surface of antigen presenting cells. More than ninety percent of patients with celiac disease are have DQ2 positive and most of the others are DQ8 positive. Geographical inconsistency in the prevalence of DQ2 and DQ8 in patients with celiac disease has been founded. [8] Some individuals with celiac disease do not have the full component of alleles that compose the haplotype HLADQ2 and are, therefore, DQ2 negative, but are considered half DQ2 positive.20 This finding shows the importance for the doctors that the reports of whether a patient is HLA-DQ2 positive or HLA-DQ8 positive should include not only whether the haplotypes are present, but also whether the allelic components are present.

Environmental factors

The essential HLA genes and gluten ingestion are not uncommon; but celiac disease are diagnosed only in less than one percent of the general population, proposing that other environmental factors besides gluten are involved.

Breastfeeding and infant feeding practices

The Swedish epidemic of celiac disease between 1984 and 1996 was considered to be due to the changes in infant feeding practices. [9] But, studies have not detected an effect of breastfeeding on the risk of celiac disease. Observational and large prospective studies of gluten introduction in kids who were at high risk of celiac disease because of familial history and compatible HLA haplotype did not find that the timing of gluten introduction had a marked

effect on risk of celiac disease. though delaying gluten introduction beyond twelve months of age could lead to a lower risk of celiac disease in the short term.

Other risk factors

The season of birth and elective caesarean section are risk factors for progression of the disease, though studies of elective caesarean sections have concluded controversial findings. Gastrointestinal infections, rotavirus in pediatric population and campylobacter infection in adults, have been found as risk factors, with rotavirus vaccination seeming to add a protective effect. An increased total number of infections and respiratory infections seem to rise the risk of developing celiac disease later in childhood. [10]

Role of the microbiome

The complicated interaction between genes, diet, and the microbiome may be essential to the progression of celiac disease and to the creation of possible preventive or therapeutic methods. A study [11] on mice expressing HLA-DQ8 concluded that the intestinal microbiota can improve or attentuate gluten-induced immunopathology, dependent on the specific microbial milieu. Studies have concluded that patients with celiac disease have changes to their intestinal microbiome that are not completely normalized after introduction of a gluten-free diet. Fecal concentrations of *Bifidobacterium bifidum* were shown to be markedly higher in untreated patients with celiac disease than in healthy adults, [12] and children with celiac disease had a higher incidence of duodenal Gram-negative and, potentially, pro-inflammatory bacteria at diagnosis than did children in a control group. [13]

Epidemiology

It is estimated that celiac disease affects about one percent of the population. Globally, there are differences in prevalence that are not understood by the known genetic and environmental risk factors. Examples include Europe, Germany has a lower prevalence of celiac disease than other countries, with the greatest prevalence being in Sweden and Finland. Within the USA, the prevalence in African Americans is low compared with those of white ethnic background; [14] similar in Brazil, Brazilians of African descent have low rates of celiacdisease. [15]

Though the prevalence of celiac disease has raised, the rate of diagnosis has raised more gradually. Analysis of the National Health and Nutrition Examination Survey, a national survey that includes about five thousand individuals annually and is considered representative of the US population, revealed that more than eighty percent of people with celiac disease were undiagnosed.

Clinical manifestations

In the past ten years, there have been many attempts made to bring consensus to the terminology of the clinical stages of celiac disease. [16] The most common presentation of celiac disease has moved from the historically classic symptoms of malabsorption in childhood to non-classic symptoms, which are present in childhood or adulthood. Classical symptoms consist of chronic diarrhea, weight loss, and failure to thrive, [17] which are very unusual.

The more common, non-classical symptoms consist of iron deficiency, bloating, constipation, chronic fatigue, headache, abdominal pain, and osteoporosis. A 2010 study [18] found a significantly reduced quality of life in patients living with undiagnosed celiac disease in comparison to those who had been diagnosed and managed. Increased awareness is required in both primary and secondary care to recognize the shift of the common presenting features and the non-specific manifestations of celiac disease. Moreover, patients can present with these diverse features to many different sub-specialties of medicine.

Diagnosis

A mixture of celiac disease serology testing and duodenal biopsy sampling is needed for the diagnosis of celiac disease in adults. The current guidelines suggest testing high-risk adults with celiac serology. Measurement of the concentration of IgA-TTG antibodies should be done as a first-line screening test because of its high sensitivity and negative predictive value, and because it is less expensive than measurement of endomysial antibodies (EMA).

Controversies in testing for celiac disease

There is disagreement as to whom to test for celiac disease. A key tenet of this issue is the ethical difference between population screening and case-finding. If a patient seeks medical advise then the doctor is attempting to diagnose an underlying condition; for example, patients with celiac disease can present with symptoms of irritable bowel syndrome or with osteoporosis.

Treatment

The standard treatment of celiac disease continues to be adherence to a gluten-free diet. Enhancement and resolution of symptoms classically happens within

days or weeks, and frequently occur before normalization of serological markers and of duodenal villous atrophy. In spite of its effectiveness in maintaing normalization of these parameters in most patients, the gluten-free diet has many challenges. Gluten-free substitute foods are markedly more expensive than their gluten containing counterparts. Patients with low incomes may be at specifically high risk of nonadherence to this diet. The quality of information about the gluten-free status of food ingredients is variable in online resources, which can lead to confusion among patients. Possible gluten exposure when travelling or eating in restaurants can be a hazard and a source of anxiety. Social pressures, particularly in adolescence, can also be an impediment to strict adherence. Uncertainty regarding the presence of gluten in trace amounts in medications and supplements is another concern. As a result of the vigilance needed to adhere to this diet, the burden of treatment of celiac disease is high. The self-rated burden of management in celiac disease in adults is greater than that rated by patients with chronic conditions such as hypertension, and is similar to the management burden of diabetes. [19]

Patients with recently diagnosed celiac disease should be referred to an expert dietitian, due to the gluten-free diet needs knowledge not only of hidden sources of gluten, however also of healthy gluten-free substitute grains that provide adequate fiber and nutrients. At diagnosis, patients should be checked for micronutrient deficiencies, including iron, folic acid, vitamin B12, and vitamin D. Pneumococcal vaccination can be considered, because of the association between celiac disease and increased risk of community-acquired pneumonia.

Non-dietary therapies

Several patients with celiac disease are not pleased with the gluten-free diet and are interested in unconventional, nondietary therapies. Together with the knowledge of the pathophysiological mechanism of celiac disease, this finding has resulted in an interest in developing medications either as an addition to the gluten-free diet or as a substitute. [20] Medications in different stages of development and testing use mechanisms such as inactivation of the toxic peptides in the bowel lumen, prevention of passage of gliadin into the mucosa, induction of immune tolerance, and inactivation of the immune process in the lamina propria.

Larazotide acetate, an oral peptide that change tight junctions and prevents passage of gliadin peptides through the epithelial barrier, was superior to placebo in alleviating symptoms in patients on a gluten-free diet compared with the diet plus placebo in a 12-week study. Latiglutenase, an enzyme preparation that prevents the pathological damage caused by gluten in patients with celiac disease, was studied in a large clinical trial of patients with celiac disease with symptoms and evidence of pathological damage (consistent with ongoing gluten ingestion in spite of attempts at adhering to the gluten-free diet). Latiglutenase did no better than placebo in alleviating symptoms or villous atrophy, which was thought to be due to a trial effect in which patients in the placebo group became more compliant to the diet and reduced their gluten consumption. More trials of both drugs should be done.

Non-responsive and refractory celiacdisease

More than twenty percent of patients with celiac disease have constant or recurrent symptoms in spite of a gluten-free diet. These conditions are caused by heterogeneous conditions. A necessary first step in evaluating these patients is to confirm the accuracy of the initial diagnosis of celiac disease. If a patient did not originally have a duodenal biopsy showing villous atrophy while on a glutencontaining diet, or if the patient had a negative celiac disease result from serological testing despite the presence of villous atrophy, an alternative diagnosis is possible. In this context, revisiting the diagnosis of celiac disease with HLA testing and a gluten challenge may be applicable.

When the diagnosis of celiac disease is confirmed, the most common cause of persistent symptoms is inadvertent gluten exposure, and this can be ascertained with careful assessment by a knowledgeable dietitian. Other causes of persistent symptoms include irritable bowel syndrome, microscopic colitis, lactose or fructose intolerance, pancreatic insufficiency, and small intestinal bacterial overgrowth.

Malignancy and mortality risk

Adding to enteropathy-associated T-cell lymphoma, celiac disease is linked with an increase in other types of non-Hodgkin lymphoma.132,133 In a population-based study, the risk of increased malignancy was higher for adenocarcinoma of the esophagus, small intestine, colon, liver, and pancreas, though only estimates for the small intestine and liver continued to be remarkable after excluding the first year after celiac disease diagnosis.

The risks of breast and lung carcinoma are decreased in patients with celiac disease, however this may be due to smoking is less common in patients with

celiacdisease. In view of these differential associations of celiac disease with malignancy risk according to organ type, pooling overall malignancy as an outcome yielded a null association with celiac disease in a 2012 meta-analysis. An association between celiac disease and increased mortality is well documented, with several studies showing an increased risk of mortality that is reduced with time after diagnosis of celiac disease. A population based study in Sweden investigating cause-specific mortality discovered that patients with celiac disease were at increased risk of death due to cardiovascular disease, pulmonary disease, and cancer. The mortality risk associated with undiagnosed celiac disease continues to be uncertain. Though a study found a large arise in mortality among people with undiagnosed celiac disease who gave serum to the Warren Air Force Base (Cheyenne, WY) in the USA 63 other analyses of stored serum found no increase in mortality. These controversial findings could be due to differing definitions of celiac disease or heterogeneous settings and time periods, in which the clinical threshold that would prompt a diagnosis could be varied. Although the data are weak, it is reasonable to conclude that celiac disease, particularly symptomatic yet untreated celiac disease, is linked with a modestly increased risk of mortality

CONCLUSIONS:

In spite of the increase in the prevalence of celiac disease and enhanced recognition and numbers of diagnosis, many avenues of investigation are necessary to understand the pathogenesis and enhanced the management of patients with this condition. Enhancements in the pathophysiology of celiac disease may let preventive techniques in individuals at high risk for disease development. The development of non-dietary therapies may relieve symptoms in patients with celiac disease and inadvertent gluten exposure, and an effective alternative of the gluten-free diet could greatly enhance the quality of life of those many patients who find adhering to the diet very difficult. advances for the detection of gluten in food and to examine for recent gluten exposure may enhance the design of future clinical trials and may be of critical value in patients daily activities.

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