

Celiac Disease: What Do We Know in 2017?

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Keywords

Celiac disease · Pathophysiology · Diarrhea · Intestinal infection

Abstract

Celiac disease is one of the most prevalent digestive conditions. Diagnosis requires that strict criteria are used so that a life-long gluten-free diet may be correctly prescribed. Although genetic susceptibility has been known for a long time, there have been elusive environmental factors that lead to the occurrence of clinical disease. Many studies have addressed the identification of environmental modifiers, and different lines of research have been tried with variable success and even contradictory results. Infections and age of gluten introduction into the diet in the first few months of life have been evaluated, but a firm relationship could not be established. A recent paper addresses a fascinating hypothesis that could explain how some infectious agents might modulate the immune system and modify response to dietary antigens. Subsequently, animal models with genetic susceptibility were tested, and, indeed, there was abnormal response to gluten. These observations still do not provide final answers about the pathophysiology of celiac disease but certainly lead to progress in the knowledge of gluten sensitization and the role of some environmental factors.

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Doença Celíaca: O Que Sabemos em 2017

Palavras Chave

Doença celíaca · Fisiopatologia · Diarreia · Infecção intestinal

Resumo

A Doença Celíaca é uma das doenças digestivas mais prevalentes. O seu diagnóstico exige critério rigoroso para se justificar a prescrição de dieta restritiva a título definitivo. Apesar de ser conhecida a predisposição genética, há fatores ambientais que levam ao desencadear da doença clínica. Vários estudos se têm dedicado a investigar os modificadores ambientais, prosseguindo várias linhas possíveis, com resultados variáveis. Hipóteses de infecções, idade ou sequência de introdução de alimentos durante os primeiros meses de vida foram investigados e não conduziram a resultados claros. Um artigo recente abre uma fascinante hipótese que poderia explicar como certos agentes infecciosos poderão levar à modulação do sistema imunitário e à modificação da sua resposta perante antigénios alimentares. Os dados observados foram testados em modelos de susceptibilidade de doença celíaca e confirmaram aumento de resposta imune ao glúten. Estes resultados não dão ainda respostas definitivas

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sobre a fisiopatologia ou alternativas terapêuticas da doença celíaca mas permitem progredir claramente na compreensão da sensibilização ao glúten e o papel de alguns factores ambientais.

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Introduction

Celiac disease (CD) has been a topic of intense research since Dicke et al. [1] identified the relationship with wheat consumption during World War II. We now know that strict diagnostic criteria (clinical, immunological, and usually histological) must be applied, and a life-long gluten-free diet must be prescribed [2].

CD derives from an inflammatory T helper 1 (Th1) immune response against dietary gluten present in wheat and other cereals. Genetic factors have a crucial role in the susceptibility to developing CD, but there is a striking discrepancy between the population that bears the HLA-DQ2 or HLA-DQ8 expression and the subjects affected by gluten intolerance and villous atrophy. Several studies have shown marked temporal variations within the same population [3]. These and other observations clearly show that additional environmental factors play a relevant role in the development of CD in subjects with a favorable genetic background. An attractive option to explain the increment in risk would be the early introduction of gluten into the weaning diet in infants or the duration of breast milk feeding. It was hypothesized that breast milk at the time of introduction of gluten might have a protective effect on the risk of development of CD. An International Consortium was created to test this hypothesis (PreventCD; www.preventcd.com). Newborn babies with a high genetic risk of developing CD were identified from family history and HLA typing after birth. They were breastfed and allocated to 2 groups: one was exposed to gluten at 4–6 months while still being breastfed; the other received placebo and only had contact with gluten at 6 months. In this study, almost 950 children were followed until 3 years of age; 5.9% of the “early-gluten” group developed CD compared to 4.5% of the “late-gluten” group. There was no statistical difference [4]. In the same issue of the journal, another study was published from Italy by Lionetti et al. [5]. In this study, 832 newborns having first-degree relatives with CD were randomly allocated to receive gluten at 6 or 12 months of age. Again, results showed that the age of gluten introduction, although affecting the age of onset of

the disease as expected, would not prevent the occurrence of CD altogether.

Following these consistent results, it is then apparent that the age of exposure to gluten in the diet of infants cannot prevent the onset of CD. A systematic review concluded that feeding practices could not account for the variability in the occurrence of CD [6]. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) updated the recommendations on the weaning practiced in infant nutrition regarding the age of gluten introduction [7].

These various studies show that although there are environmental factors affecting the risk to develop CD, we still do not know what they are and how to protect at-risk infants from developing it. Another line of research has been the possible cross-reactivity of the immune system against infectious agents and increased susceptibility to repeated early infections [8, 9]. However, conflicting results have limited the clear assumption of the role of co-factors precipitating CD in genetically susceptible children.

A recent publication added new information to this intriguing quest [10]. In this fascinating work, Bouziat et al. [10] started from the observation that similar levels of wheat consumption and genetic risk coexist with striking differences in CD prevalence, as reported in the adjacent regions of Finnish Karelia and Russian Karelia [11]. Based on these data, the authors speculate that infectious agents may modulate the Th1 response even in the absence of overt infectious disease and explore the possible mechanisms to explain such a causal relationship. Two human reovirus isolates were used to infect the intestine in animal models. After infection, both viruses were cleared without inducing intestinal damage. Both viruses induced similar Th1 responses in Peyer’s patches, revealing an equal capacity to induce immunity. Later, the tested models were exposed to dietary antigens, and a clear difference emerged in the immune activity in the lamina propria and mesenteric lymph nodes between the 2 groups with different virus strains. Using subsequent experiments, the authors noted that after infection with one of the tested virus strains, there was reduction of tolerogenic response, and, instead, Th1 immunity to dietary antigens was induced. Therefore, despite similar induction of Th1 immune response in Peyer’s patches, different viruses may induce distinct immunopathological properties. The authors went on further testing transgenic mice expressing the usual HLA genes of CD-associated risk and indeed verified that there was a modification in the antigen-presenting

cells leading to loss of tolerance to gluten after infection with the strain of virus that induced immune changes. Antigliadin antibodies and a Th1-delayed hypersensitivity reaction could be detected in this group.

This paper does not provide all the answers related to the pathogenesis of CD and does not lead directly to the prevention of the disease but adds evidence and identifies some environmental agents, like non-pathogenic viruses, that may modulate some steps of the immune system, thereby shifting tolerance to dietary antigens to hypersensitivity. Further work will be needed to assess other agents. Again, the microbiome provides new answers to old questions, and a complex inter-relationship is being discovered in relation to diet and inflammatory and metabolic processes [12].

These remarkable studies provide very interesting and promising information that will help further research on the pathogenesis and perhaps prevention of CD and other autoimmune diseases, but for the time being, we must still rely on the accurate diagnosis of CD, using the usual clinical, immunological, and histological information. Knowing that CD is a long-lasting intolerance to gluten that requires a life-long elimination diet, it is important that accurate diagnostic criteria are strictly followed. This is relevant to avoid subjecting patients to modifications of the diet that may bring some constraints and costs but also to rule out another possible diagnosis that may need a different approach.

ESPGHAN has devoted great interest to CD and provided the first diagnostic protocol in 1969, with the so-called Interlaken criteria [13]. Further advances in diagnostic techniques and antibody testing led to periodic revisions of those criteria in order to be accurate but also to spare patients from multiple biopsies or damaging exposure to gluten challenges. Recently, a working group within ESPGHAN has proposed a new diagnostic algorithm that is more complex than the previous one but takes into account the clinical features and the use of im-

munological and genetic information [2]. It is now accepted that a small group of patients with typical features, which *also* have a high (>10× normal) titer of anti-endomysium antibodies *and* positive HLA antigens (DQ2–DQ8), may be diagnosed without a biopsy, if diagnosis is validated by an experienced pediatric gastroenterologist. All other cases should undergo upper digestive endoscopy and biopsy. Processing of the biopsy samples and reporting is also important to make a correct diagnosis.

If clinical and histological features confirm CD, then no further diagnostic tests are needed and a permanent gluten-free diet should be prescribed. Patients should be monitored periodically and routinely tested for anti-transglutaminase antibodies to assess the compliance with the diet. Patients should also be monitored for the emergence of thyroiditis and diabetes, as these entities have an increased prevalence in CD [14].

Patients with CD and their parents should be carefully informed that CD is an autoimmune and food-related disease but not a food allergy. As ingestion of gluten may occur without obvious symptoms, patients and their relatives may be tempted to promote increasing the intake of gluten on the assumption that the intolerance has gone! Doctors should be very clear to patients that, in CD, there may be immunological and metabolic consequences (osteoporosis, iron deficiency, cerebral calcifications, behavior disturbances and even malignancy) related to the continued ingestion of gluten regardless of apparent signs or symptoms. For all these reasons, we must promote accurate diagnosis of and correct information to patients.

Disclosure Statement

The author has no conflicts of interest to declare.

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