Reumatol Clin. 2016;12(1):4–10

Reumatología Clínica

www.reumatologiaclinica.org

Special Article

Non-celiac Gluten Sensitivity and Rheumatic Diseases☆

Carlos Isasi,[a,*] Eva Tejerina,[b] Luz M. Morán[c]

[a] Servicio de Reumatología, Hospital Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain
[b] Servicio de Anatomía Patológica, Hospital Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain
[c] Servicio de Radiodiagnóstico, Hospital Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain

ARTICLE INFO

Article history:
Received 9 January 2015
Accepted 2 March 2015
Available online 11 December 2015

Keywords:
Celiac disease
Non-celiac gluten sensitivity
Fibromyalgia
Spondyloarthritis
Autoimmunity

ABSTRACT

Celiac disease is an autoimmune systemic disease having among its clinical manifestations frequent symptoms common to rheumatologic diseases such as musculoskeletal pain, asthenia, and cognitive fatigue. It is associated with other autoimmune diseases like Sjögren disease. It is a well-characterized disease with specific diagnostic tests.

Non-celiac gluten sensitivity is an emerging entity with symptoms similar to celiac disease, but without specific diagnostic tests. The concept of non-celiac gluten sensitivity and its diagnostic problems are reviewed, and the hypothesis of its association with fibromyalgia, spondyloarthritis, and autoimmune conditions is proposed. Clinical observations supporting the hypothesis are described, highlighting the benefit of treating non-celiac gluten sensitivity.

Sensibilidad al gluten no celíaca y enfermedades reumatológicas

Palabras clave:
Enfermedad celíaca
Sensibilidad al gluten no celíaca
Fibromialgia
Espondiloartritis
Autoinmunidad

RESUMEN

La enfermedad celíaca es una enfermedad autoinmune sistémica que tiene entre sus manifestaciones clínicas síntomas frecuentes en las enfermedades reumatológicas, como dolor musculoesquelético crónico, astenia y fatiga mental. Se asocia a otras enfermedades autoinmunes, como la enfermedad de Sjögren. Es una enfermedad bien caracterizada con pruebas diagnósticas específicas.

La sensibilidad al gluten no celíaca es una entidad emergente, con sintomatología similar a la de la enfermedad celíaca, pero sin pruebas diagnósticas específicas. Se revisan el concepto y los problemas diagnósticos de la sensibilidad al gluten no celíaca y se propone como hipótesis la asociación de la sensibilidad al gluten no celíaca a la fibromialgia, las espondiloartropatías y las enfermedades autoinmunes. Se describen observaciones clínicas que apoyan esta hipótesis, destacando el beneficio clínico del tratamiento de la sensibilidad al gluten.

Celiac Disease and Non-celiac Gluten Sensitivity

Celiac disease (CD) has traditionally been considered to be a pediatric gastrointestinal disease, characterized by malabsorption and failure to thrive; however, this perspective has changed substantially in recent years. It is now considered a common autoimmune disease that can present at any age, with both intestinal and extraintestinal manifestations.[1–6] Although the objective of this article is not to review CD, we think it necessary to point out certain aspects that rheumatologists should take into account: (a) CD can be present in the absence of gastrointestinal symptoms; in fact, nearly half of the CD patients diagnosed in adulthood do not have relevant gastrointestinal symptoms; (b) in addition to the classic iron-deficiency anemia, diarrhea and osteoporosis, CD is the cause of symptoms such as asthenia, mental fatigue and chronic musculoskeletal pain, which accompany many systemic diseases[7]; in fact, it has been referred to as the great imposter[8]; and (c) CD is known to be associated with other autoimmune diseases, most

☆ Please cite this article as: Isasi C, Tejerina E, Morán LM. Sensibilidad al gluten no celíaca y enfermedades reumatológicas. Reumatol Clin. 2016;12:4–10.

* Corresponding author.
E-mail address: cisasi.hpth@salud.madrid.org (C. Isasi).

Table 1
Groups at Risk for Celiac Disease.

First-degree relatives
Patients with associated diseases
Autoimmune disease
Type 1 diabetes mellitus
Autoimmune thyroiditis
Selective IgA deficiency
Inflammatory bowel disease
Sjögren's syndrome
Systemic lupus erythematous
Addison's disease
IgA nephropathy
Chronic autoimmune hepatitis
Primary biliary cirrhosis
Rheumatoid arthritis
Psoriasis, vitiligo and alopecia areata
Neurological and psychiatric disorders
Progressive encephalopathy
Cerebellar syndromes
Dementia with brain atrophy
Leukoencephalopathy
Epilepsy and calcifications
Schizophrenia
Other associations
Down syndrome
Williams syndrome
Turner syndrome
Cystic fibrosis
Hartnup disease
Cystinuria
Microscopic colitis
Cardiomyopathy
Fibromyalgia
Chronic fatigues syndrome

Taken from Diagnóstico precoz de la enfermedad celíaca. Spanish Ministry of Health and Consumer Affairs, 2008.[9]

Table 2
Symptoms of Non-celiac Gluten Sensitivity.

Intestinal	
Abdominal pain	68%
Diarrhea	33%
Nausea	
Weight loss	
Bloating, flatulence	
Cutaneous	40%
Erythema	
Eczema	
General	
Headache	35%
Bone and joint pain	11%
Muscle contractures	34%
Numbness of hands and feet	20%
Chronic tiredness	33%
Behavioral	
Attention deficit	
Depression	22%
Hyperactivity	
Oral	
Chronic ulcerative stomatitis	

Taken from Czaja-Bulsa.[11]

frequently, autoimmune thyroid disease and Sjögren's syndrome. Table 1 shows the diseases associated with CD.[9] The presence of the rheumatic diseases associated with CD is reason enough to consider performing serologic testing for CD in rheumatic patients with asthenia, anemia, chronic musculoskeletal pain or systemic diseases. In a study carried out in 211 patients with unexplained signs of joint disease, the rate of positive CD serology was much higher than that of the control population. Positivity for immunoglobulin A (IgA) endomysial antibodies (the most specific serologic test for CD) was detected in 2.3% of the patients and in only 0.28% of blood donors used as the control group.[10]

Celiac disease is considered to be an autoimmune enteropathy caused by exposure to gluten in genetically predisposed individuals. Those who are positive for human leukocyte antigen (HLA) DQ2.5 (DQA1*05-DQB1*02) or DQ8 (DQA1*0301-DQB1*0302) may have an adaptive immune response to gluten, with production of antibodies (to tissue transglutaminase [tTG] and endomysium) and infiltration of the intestinal epithelium by CD3+ lymphocytes (intraepithelial lymphocytosis), which, when severe, leads to the atrophy of the intestinal villi observed in the duodenal biopsy (Marsh type 3 lesion). The genetic susceptibility triad consisting of HLA DQ2 or DQ8, specific antibodies (to tTG and endomysium) and intestinal villous atrophy on duodenal biopsy is what characterizes and defines CD.

Non-celiac gluten sensitivity (NCGS) is an emerging entity characterized by gluten-related intestinal and extraintestinal symptoms in patients with negative CD tests who, thus, are not considered to be celiac patients.[11–14] Clinical observations of patients who responded to a gluten-free diet (GFD) in whom CD could not be confirmed date back at least to 1978. In recent years, this entity is gaining increasing prominence and is no longer regarded as a rare condition. Non-celiac gluten sensitivity is considered to be more prevalent than CD, which affects 1% of the population. Although there are no systematic epidemiological studies, due to the fact that there is no diagnostic marker that enables them to be performed, NCGS is estimated to affect around 5% of the population.

The most prevalent concept, according to a consensus reached at an expert meeting held in Oslo, is that CD and NCGS are 2 different conditions within the spectrum of gluten-related disorders, which also includes wheat allergy.[15] As there is no diagnostic test for NCGS, the diagnosis is based on the exclusion of CD (absence of anti-tTG antibodies and of intestinal villous atrophy on duodenal biopsy) and of wheat allergy in patients with gluten-related symptoms. With regard to the symptoms, CD and NCGS are indistinguishable, although NCGS is considered to have no relationship to systemic diseases. Table 2 shows the symptoms observed in 347 cases. With respect to HLA, only about half the patients with NCGS carry DQ2.5 or DQ8. In CD, the adaptive immune system predominates, responding with production of anti-endomysial and anti-tTG antibodies, which leads to an increase in intestinal permeability and to intestinal villous atrophy. Antibodies to deamidated gliadin peptide, which are nearly as specific for CD as anti-tTG antibodies, are also present. In NCGS, the innate immune system is considered to predominate. IgG antibodies against native gliadin, which have a low specificity for intestinal villous atrophy and are not useful in the diagnosis of CD, do prove to be of use in detecting NCGS, although the sensitivity is limited.

However, the dichotomous working approach of considering CD and NCGS as different entities does not depict the complexity of a disease that is probably the expression of a biological continuum. There are many examples of patients who, following strict criteria, cannot be considered celiacs, but whose profile overlaps substantially with CD. The clearest examples are the patients with gluten-sensitive enteropathy without villous atrophy. In healthy individuals, there are few intraepithelial lymphocytes and they are distributed predominantly at the base of the villus. In gluten-sensitive enteropathy, there may be no villous atrophy, only an increase in the number of intraepithelial lymphocytes all along the intestinal villus, over 25 $CD3^+$ lymphocytes per 100 enterocytes, characteristically present at the tip of the villus.[16] There are patients with CD-like symptoms, negative tests for specific antibodies and no villous atrophy, but they have HLA susceptibility and intraepithelial lymphocytosis on duodenal biopsy and respond to the GFD. It is considered that these patients have