or ongoing biliary obstruction. We are grateful to Drs Tse and Yuan for the publication of their Cochrane Review, as this is an area that warrants ongoing analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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[1]Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, Washington, USA; [2]Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA. Correspondence: Jessica M. Fisher, MD, Division of Gastroenterology, Department of Medicine, University of Washington, 1959 NE Pacific, Street Box 356424, Seattle, 98195 Washington, USA. E-mail: jfisher@medicine.washington.edu

Lymphocytic Enteropathy, HLA-DQ2/DQ8 Genotype and Wheat-Dependent Symptoms: Non-Celiac Wheat Sensitivity or Marsh I Celiac Disease?

Javier Molina-Infante, MD[1], Santos Santolaria, MD, PhD[2], Fernando Fernandez-Bañares, MD, PhD[3], Miguel Montoro, MD, PhD[2] and Maria Esteve, MD, PhD[3] on behalf of the Work Group on Upper GI Diseases of the Spanish Gastroenterological Association

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To the Editor: We read with interest the manuscript by Carroccio *et al.* (1), in which the authors try to delimit the diagnostic criteria of a novel entity, the non-celiac wheat sensitivity (NCWS), in patients mislabelled as suffering from irritable bowel syndrome (IBS). This disorder is split into two subtypes: wheat sensitivity (WS), clearly overlapping with celiac disease (CD), and multiple food sensitivity. The most noteworthy finding is the detection of duodenal and colonic eosinophilic inflammation in patients with wheat-dependent symptoms not fulfilling diagnostic criteria for CD. However, the definition for CD in this study might be controversial.

The authors excluded CD upon negative serum antibodies and the absence of villous atrophy in histology. In all, 94% of NCWS patients presented with lymphocytic enteritis (LE; >25 CD3+ intraepithelial lymphocites/100 epithelial cells), which represents Marsh I grade in the Marsh-Oberhuber classification (2). Interestingly, 75% in the WS group had HLA haplotypes and 30% had positive anti-endomysium antibodies culture in biopsies. As recent evidence and consensus guidelines (3,4) have stressed that CD is likely in Marsh I patients with either typical immunohistochemical changes or mucosal deposit of specific antibodies, it is conceivable that this 30% of patients in the WS group should have been classified as CD. A definitive diagnosis for the remaining seronegative LE patients with HLA haplotypes is uncertain. Clinicohistological re-evaluation on gluten-free diet (GFD) could have been helpful, but the retrospective design of the study limits drawing any conclusion. In agreement with other authors (5), we believe that CD can be absolutely precluded without HLA-DQ2/HLA-DQ8 haplotypes or with HLA heterodimers and normal duodenal biopsy (Marsh 0).

Notwithstanding LE has been considered an asymptomatic mild enteropathy within CD, this concept has evolved seeing as LE may induce similar symptoms and complications than in those with villous atrophy (6) and clinicopathological remission can be achieved on GFD (3,6). Thus, a proper definition of CD, including minor subtypes, is crucial to avoid mislabelling patients previously misdiagnosed for having IBS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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[1]Department of Gastroenterology, Hospital San Pedro de Alcantara, Caceres, Spain; [2]Hospital San Jorge, Huesca, Spain; [3]Hospital Mutua Terrassa, Barcelona, Spain. Correspondence: Javier Molina-Infante, MD, Department of Gastroenterology, Hospital San Pedro de Alcantara, Caceres 10003, Spain. E-mail: xavi_molina@hotmail.com

Response to Molina-Infante *et al.*

Antonio Carroccio, MD[1] and Pasquale Mansueto, MD[2]

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To the Editor: We thank the Work Group of the Spanish Gastroenterology Association for their interest and the comments about our work (1). We fully agree with their opinion that a subgroup of patients who fulfill the current criteria for gluten sensitivity (GS) could actually suffer from celiac disease (CD). The presence of villous atrophy and positive CD-specific serum antibodies cannot be considered

mandatory for CD diagnosis; furthermore, it is known that less severe intestinal histology damage is more frequently associated with a negative serology. Despite the negativity of the CD-specific serum antibodies and the absence of villous atrophy, we demonstrated that symptomatic patients who produced anti-endomisyum antibodies (EmA) in the duodenal mucosa culture can subsequently develop villous atrophy when remaining on a gluten-containing diet (2,3) and identical findings have been reported for serum EmA-positive patients with an initial evaluation of normal duodenal histology (4), as well as for patients without villous atrophy but immunohistochemical evidence of anti-transglutaminase deposits in the duodenal mucosa (5).

Our study recently published in *American Journal of Gastroenterology* reflects our clinical practice; we regularly performed HLA determination and duodenal sample culture to search for EmAs in the culture medium, in all patients with elevated clinical suspicion of CD diagnosis (family members of CD patients, coexistence of autoimmune diseases, self-reported "sure" relationship between gluten ingestion and symptoms onset, etc.), despite an initial evaluation that showed negative CD serum antibodies. In this way, however, our study found that only 22 of 276 patients (8%) showed positive EmAs in the culture medium of the duodenal biopsies, which we consider the strongest clue of CD in this very difficult diagnostic category.

On the other hand, a "simple" duodenal lymphocytosis (Marsh 1 histology), in the absence of positivity of serum CD-specific antibodies, cannot be considered diagnostic for CD. All "CD experts" view a Marsh 1 histology with caution. A prospective study (6) revealed that only 16% of the patients, who underwent duodenal biopsy for suspected CD and showed lymphocytic duodenosis, actually suffered from CD; lymphocytic duodenosis was most commonly associated with drugs (21%) and infection (19%).

In conclusion, we would underline that the main histology characteristic of the patients we studied was the eosinophil infiltrate in the duodenal and colon mucosa: this could be the GS "marker" in most of the patients. However, the evidence that GS includes patients with very different clinical, serologic, and histology characteristics—probably different subgroups with different disease pathogenesis—is actually the basis of our ongoing studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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[1]Internal Medicine, Giovanni Paolo II Hospital of Sciacca, University of Palermo, Palermo, Italy; [2]Internal Medicine, University Hospital of Palermo, Palermo, Italy. Correspondence: Antonio Carroccio, MD, Medicina Interna, Hospital of Sciacca, via Pompei, Sciacca (AG), Palermo, Italy. E-mail: acarroccio@hotmail.com

Tissue Biomarkers Distinguishing EoE From GERD: Concerns About the Control Group

Javier Molina-Infante, MD[1] and David A. Katzka, MD[2]

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To the Editor: We read with interest the manuscript by Dellon *et al.* (1), which investigates the accuracy of major basic protein (MBP) and eotaxin-3 in esophageal biopsies to differentiate eosinophilic esophagitis (EoE) from gastroesophageal reflux disease (GERD). Significantly higher levels of MBP and eotaxin-3 were observed in EoE compared with GERD, suggesting they could be a potential biomarker for EoE. Interestingly, another recent study on the topic discloses the opposite conclusion (2), as levels of eosinophil-derived neurotoxin and MBP were found to be similar in EoE and GERD patients, when patients were matched for esophageal eosinophilia (EE). This study suggested that it is the level of eosinophilia that predicts the density of eosinophil-derived products and not the underlying etiology of tissue eosinophilia.

The studies so far reporting histological parameters or eotaxin-3 levels distinguishing GERD from EoE are summarized in **Table 1**. In all of them, including the study by Dellon *et al.* (1), the diagnosis of GERD was established *a priori* on the basis of low-grade eosinophilic inflammation, resulting in EoE patients having significantly higher levels of intraepithelial eosinophils than GERD patients (**Table 1**). Furthermore, GERD patients in these studies rarely presented with dysphagia or food impaction, and endoscopic findings of EoE were seldom reported. As such, these studies might be addressing differences between patients with low-grade and high-grade eosinophilic inflammation. Two recent studies (2,3) could not replicate these distinguishing features in patients with symptomatic EE when a non-EoE diagnosis was only given after checking response to therapy.

Although this concept of differentiating EoE and GERD upon density of eosinophilia and its products has prevailed for many years, re-anaylsis of this concept rapidly evolved in the last 5 years. A rigid distinction between both diseases cannot be made, seeing as neither eosinophil density, histological, nor immunohistochemical features (2,3), response to proton-pump inhibitors (PPI) therapy or negative pH monitoring (3,4) are reliable predictors of EoE. A novel phenotype (PPI-responsive EE), indistinguishable from EoE "off-PPI therapy," has been described in recent updated guidelines (5), underscoring the difficulty of definitively