Turk J Gastroenterol *2014; 25: 456-7*

Celiac or non-celiac gluten sensitivity. The new debate

To the Editor,

I read the case series written by Borghini et al. (1) published in the last issue of the Turkish Journal of Gastroenterology with interest. This is an article pointing out that care should be exercised when evaluating non-celiac gluten sensitivity (NCGS), which has recently become popular. In their paper, three cases who had gluten-associated symptoms but did not meet the diagnostic criteria of celiac disease (CD) are presented. In these cases, NCGS was considered first, but after CD serology was found to be positive in duodenal biopsy tissue cultures, they made the accurate diagnosis which was CD.

The prevalence of CD is approximately 1%, with most of the undiagnosed cases being dormant, atypical, or latent patients. Recognition of these patients is important for the prevention of morbidity and mortality. The diagnostic criteria of CD have been well defined (2). The diagnosis is made with villous atrophy in the duodenal biopsy and anti-EMA, anti-tTG, or anti-DAGP positivity supporting the diagnosis. The sensitivity and specificity of serological tests are low in cases with mild duodenal pathology. In the histological diagnosis, villous atrophy is the gold standard. However, Marsh type 1 intraepithelial lymphocyte increase is also important and is even considered pathognomonic of CD by some pathologists. CD develops in those who are HLA DQ2 or DQ8 haplotype-positive. One of the important clinical findings of the disease is iron deficiency anemia, which does not respond to oral iron supplementation. All three cases presented had HLA DQ-2-positive, Marsh type 1 duodenal pathology. In addition, case 2 had iron deficiency anemia, and cases 2 and 3 had suspicious borderline serological results. These findings are similar to those encountered frequently in daily clinical practice in patients with borderline symptoms. However, as a clinician, it is my belief that in the patients presented in the article and similar ones, CD should be primarily considered. In support of our opinion, the diagnosis of CD was established with serological tests on duodenal biopsy tissue cultures. This method, proposed by Borghini et al. (1), seems to be one that will render the diagnosis easier in borderline cases. The authors reported that this method is a cheap test that can be used in all kinds of laboratory environments (3). However, this should be confirmed in larger patient series.

Non-celiac gluten sensitivity is a diagnosis of exclusion, being diagnosed when CD and wheat allergy which is another condition associated with gluten, are demonstrated to be absent. So far, no specific marker has been found for NCGS. It was only reported that it may yield AGA IgG positivity (56%) (4), and the HLA DQ2 and DQ8 haplotypes may be positive in 50% of NCGS patients (5). But, upon reading the article of Borghini et al., one can not help but wonder whether these cases actually had CD. In view of this information, I think that the cases presented in these articles deserve to be evaluated again.

In conclusion, investigation of CD serology in duodenal biopsy tissue culture seems to be a satisfactory alternative in establishing the diagnosis in patients in whom differentiation of CD from NCGS is a challenge. However, it should be proven in larger patient series. Until then, I think that in patients with gluten-associated symptoms, which make it difficult to distinguish from NCGS, it is more reasonable to give priority to CD.

Conflict of Interest: No conflict of interest was declared by the authors.

Orhan Sezgin

Department of Gastroenterology, Mersin University Faculty of Medicine, Mersin, Turkey

REFERENCES

1. Borghini R, Donato G, Di Tola M, Isonne C, Picarelli A. Mutatis mutandis: are we diagnosing too many people with non-celiac gluten sensitivity? Multiple case report. Turk J Gastroenterol 2014: 25: 319-23. **[CrossRef]**
2. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical

guidelines: Diagnosis and management of celiac disease. Am J Gastroenterol 2013; 108: 656-76. **[CrossRef]**
3. Picarelli A, Di Tola M, Marino M, et al. Usefulness of the organ culture system when villous height/crypt depth ratio, intraepithelial lymphocyte count, or serum antibody tests are not diagnostic for celiac disease. Transl Res 2013; 161: 172-80. **[CrossRef]**
4. Volta U, Tovoli F, Cicola R, et al. Serological tests in gluten sensitivity (nonceliac gluten intolerans). J Clin Gastroenterol 2012; 46: 680-5. **[CrossRef]**
5. Bizzaro N, Tozzoli R, Villalta D, Fabris M, Tonutti E. Cutting-edge issues in celiac disease and in glluten intolerans. Clin Rev Allergy Immunol 2012; 42: 279-87. **[CrossRef]**

Address for Correspondence: Orhan Sezgin, Department of Gastroenterology, Mersin University Faculty of Medicine, Mersin, Turkey
E-mail: drorhansezgin@gmail.com
Received: 30.7.2014 **Accepted:** 3.8.2014

Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2014.0022

Author's Reply

To the Editor,

We sincerely appreciate your considerations regarding the controversial and sensitive topics we have presented. As we mentioned in our work, gluten-related disorders are increasingly in the spotlight and nowadays there are still no precise diagnostic criteria for non-celiac gluten sensitivity (NCGS), as well as for "border-line" cases of celiac disease (CD). Current literature shows that the newcomer NCGS has a prevalence even higher compared to CD (6% vs 1%, respectively), justifying a greater propensity to diagnosis of NCGS in unclear cases (1).

We presented three genetically susceptible patients testing positive for DQ2, with clear gluten-related signs and/or symptoms. Serology showed negative or borderline results, thus proving incapable of making a difference in diagnosis. In this respect, it should be recalled that slight alterations of CD serum antibodies could be even due to several other pathological conditions unrelated to CD (2-4), implying further consideration.

Histology showing villous atrophy is still considered the gold standard for CD diagnosis. Despite some pathologists inappropriately consider infiltrative lesions suggestive for CD also when not supported by clinical data and/or serological tests, it has been demonstrated that duodenal Marsh-Oberhuber Type I lesions is a morphologic feature associated with a broad differential diagnosis: increased lymphocyte numbers in the epithelium of architecturally preserved proximal small intestinal biopsies can be observed in NCGS, non-gluten food hypersensitivity, infections (e.g., viral enteritis, Giardia, Helicobacter pylori), bacterial overgrowth, drugs (e.g., NSAIDs), immune dysregulation (e.g., Hashimoto thyroiditis, autoimmune enteropathy), immune deficiency, infammatory bowel disease, lymphocytic and collagenous colitis (5,6). For this reason, in our opinion, the final CD diagnosis was not at all obvious. On the other hand, we did not want to make just a "trendy" and hasty diagnosis of NCGS, often conditioned by misleading personal convictions of both patients and clinicians.

Since long time, organ culture system has been showing its usefulness in tipping the balance against or in favor of CD in many cases, even in multicentre studies (7,8): anti-endomysial (EMA) and anti-tissue transglutaminase antibodies (anti-tTG) detectable in culture supernatants of duodenal biopsy are able to give a qualitative and quantitative response, respectively. It is certainly an effective and rapid scientific method, able to make a difference in cases of doubtful diagnosis of CD.

With regard to costs, this method offers the chance to be developed only in cases of necessity, with intestinal biopsy taken, cultured, frozen and eventually processed only in case of persistent diagnostic dilemma. This implies benefits for the patient and for the National Health Service, preventing a second invasive and expensive endoscopic examination.

As suggested, further studies on a large scale on this topic could be very useful, but current scientific evidence can already provide valuable guidance and useful answers in our clinical practice.

Raffaele Borghini, Antonio Picarelli
Department of Internal Medicine and Medical Specialties, Sapienza University - Policlinico Umberto I, Rome, Italy

REFERENCES

1. Picarelli A, Borghini R, Isonne C, Di Tola M. Reactivity to dietary gluten: new insights into differential diagnosis among gluten-related gastrointestinal disorders. Pol Arch Med Wewn 2013; 123: 708-12.
2. Di Tola M, Barillà F, Trappolini M, Palumbo HF, Gaudio C, Picarelli A. Antitissue transglutaminase antibodies in acute coronary syndrome: an alert signal of myocardial tissue lesion? J Intern Med 2008; 263: 43-51. **[CrossRef]**
3. Di Tola M, Sabbatella L, Anania MC, et al. Anti-tissue transglutaminase antibodies in inflammatory bowel disease: new evidence. Clin Chem Lab Med 2004; 42: 1092-7.
4. Picarelli A, Di Tola M, Sabbatella L, et al. Anti-tissue transglutaminase antibodies in arthritic patients: a disease-specific finding? Clin Chem 2003; 49: 2091-4. **[CrossRef]**
5. Villanacci V, Ceppa P, Tavani E, et al. Coeliac disease: The histology report. Dig Liver Dis 2011; 43 (Suppl 4): S385-95. **[CrossRef]**
6. Brown I, Mino-Kenudson M, Deshpande V, Lauwers GY. Intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa: an increasing diagnostic problem with a wide differential diagnosis. Arch Pathol Lab Med 2006; 130: 1020-5.
7. Picarelli A, Di Tola M, Marino M, et al. Usefulness of the organ culture system when villous height/crypt depth ratio, intraepithelial lymphocyte count, or serum antibody tests are not diagnostic for celiac disease. Transl Res 2013; 161: 172-80. **[CrossRef]**
8. Picarelli A, Di Tola M, Sabbatella L, et al. Usefulness of the organ culture system in the in vitro diagnosis of coeliac disease: a multicentre study. Scand J Gastroenterol 2006; 41: 186-90. **[CrossRef]**

Address for Correspondence: Antonio Picarelli, Department of Internal Medicine and Medical Specialties, Sapienza University - Policlinico Umberto I, Rome, Italy
E-mail: antonio.picarelli@uniroma1.it