CORRESPONDENCE

Readers may submit letters to the editor concerning articles that appeared in *Gastroenterology* within one month of publication. Detailed guidelines regarding the content are included in the Instructions to Authors.

Is Autoimmunity More Predominant in Nonceliac Wheat Sensitivity Than Celiac Disease?

Dear Editor:

We read with great interest the recent paper published by Carroccio et al reporting on the prevalence of autoimmunity (as identified by positivity of antinuclear antibodies [ANA] and associated autoimmune disorders) in nonceliac wheat sensitivity (NCWS) versus celiac disease (CD) and irritable bowel syndrome (IBS).[1] More in detail, the results of the study, based on a retrospective and prospective arm, showed that the prevalence of ANA in NCWS was significantly higher than in CD and IBS (46% in NCWS vs 24% in CD and 2% in IBS, retrospectively; and 28% in NCWS vs 7.5% in CD and 6% in IBS, prospectively). Moreover, in both retrospective and prospective analysis, autoimmune disorders (mainly autoimmune thyroiditis) were found in a slightly higher proportion in NCWS (29% vs 24%) than CD (21% vs 20%). Both NCWS and CD showed a significantly higher prevalence of autoimmune disorders than IBS. ANA were significantly related to HLA-DQ2 and -DQ8 in NCWS (both retrospectively and prospectively), whereas these autoantibodies were associated significantly with autoimmune disorders only in the prospective arm.

Clearly, the results from Carroccio et al capture the interest of the scientific community as NCWS, more than an established autoimmune disorder, such as CD, exhibits a surprisingly high autoimmune profile. Indeed, CD is a well-established autoimmune condition characterized by frequent occurrence of different types of autoantibodies and associated autoimmune disorders.[2] These autoimmune features have not been demonstrated previously in NCWS and whether these patients are actually prone to develop autoimmune dysfunction remains an open issue.[3,4] In this regard, recent data from our group showed that only 14% of 486 patients with NCWS had an associated autoimmune disorder including thyroiditis, psoriasis, Graves disease, type 1 diabetes mellitus, and atrophic gastritis.[5] In contrast, the same autoimmune manifestations were detected in CD patients, but with a markedly higher prevalence (ie, about 30% of 770 CD patients) than that reported in NCWS.[6] These findings are in line with previously published data.[7]

A further interesting aspect that emerged from the study of Carroccio et al[1] is the very high prevalence of ANA in their cohort of NCWS versus CD and IBS patients. In our experience, however, the prevalence of ANA was found to be higher in CD than NCWS and IBS (49% vs 37% vs 6%), which reflects a predominant autoimmune profile in CD rather than in the 2 other conditions. However, the evidence that patients with NCWS display a higher expression of ANA compared with IBS is in line with the results presented by Carroccio et al.[1]

In conclusion, consistent evidence supports a major role of adaptive immunity in CD more than NCWS, and this peculiarity is reflected by a predominant occurrence of autoimmune disorders and autoantibodies (eg, ANA).[8] However, the challenging data shown by Carroccio et al provide the basis to understand whether NCWS, like CD, exhibits a wide spectrum of autoimmune manifestations mediated by adaptive mechanisms. Further studies are eagerly awaited to shed light on the intriguing relationship between autoimmunity and NCWS.

UMBERTO VOLTA
GIACOMO CAIO
ROBERTO DE GIORGIO
Department of Medical and Surgical Sciences
University of Bologna
Bologna, Italy

References

1. Carroccio A, et al. Gastroenterology 2015;149:596–603.
2. Sategna-Guidetti C, et al. Gut 2001;49:502–505.
3. Volta U, et al. J Clin Gastroenterol 2012;46:680–685.
4. Fasano A, et al. Gastroenterology 2015;148:1195–1204.
5. Volta U, et al. BMC Med 2014;12:85.
6. Volta U, et al. BMC Gastroenterol 2014;14:194.
7. Kocsis D, et al. Eur J Intern Med 2013;24:461–467.
8. Sollid LM, et al. Nat Rev Immunol 2013;13:294–302.

Conflicts of interest
The authors disclose no conflicts.

Most current article

http://dx.doi.org/10.1053/j.gastro.2015.08.058

Reply. We thank Volta et al for their interest in our work[1] and for their comments and data on the frequency of autoimmune diseases and serum autoantibodies in patients suffering from nonceliac wheat sensitivity (NCWS). These authoritative colleagues have emphasized that celiac disease is a well-established autoimmune condition, and we agree that NCWS is still an undefined syndrome with uncertain pathogenesis.

However, the data they reported actually further strengthen our data on a link between NCWS and autoimmunity and contribute to suggesting a strong role for innate and adaptive immunity in the pathogenesis of NCWS. The authors reported that, in their experience, 37% of NCWS patients were positive for antinuclear antibodies, a percentage clearly higher than in patients with irritable bowel syndrome and in the middle of the frequencies we observed in our

retrospective (46%) and prospective (28%) cohorts. We think the lower frequency of serum for antinuclear antibody positivity we found compared with the data from Volta et al is much less relevant among our findings. We studied only a small group of celiac disease patients as a control group, and our study was not designed to evaluate this aspect of celiac disease.

Regarding the frequency of autoimmune disorders associated with NCWS, we underline that ours is the first single-center study designed to provide data on this point. The discrepancy between the frequency we observed (24% vs 29%) and that reported in the Italian multicenter study (14%)[2] could be owing to the heterogeneity of the patients included in that study. In a brilliant editorial Lebwohl and Leffler have written, "in critical moments, men sometimes see exactly what they wish to see,"[3] and it is evident that at the moment there is no agreement in the scientific community not only about NCWS pathogenesis, but even on its real existence. Although relevant in many ways, the Italian multicenter study probably suffered from the "negative preconception" of those centers skeptical about NCWS, a preconception that was amplified by the confuse diagnostic criteria and the lack of a double-blind challenge as diagnostic method.

In contrast, it is certain that NCWS should be considered a heterogeneous condition as we first suggested some years ago,[4] in which different kinds of patients with different pathogenesis of their wheat-related symptoms are still lumped together. Since the beginning of our interest in NCWS, we have focused on the patients who had an "immunologic characteristic": food allergy in infancy, associated atopic disease, eosinophil or lymphocyte infiltration in the intestinal mucosa, and so on.[5] Consequently, in the Rorschach test of sorts[3] we view a strong immunologic basis for NCWS pathogenesis, but in the discussion section we warned readers about this possible bias of a highly selected study population.

In conclusion, we feel that the "NCWS field" still remains a "fertile crescent" for research[6] and in this respect, understanding the immunological path is the most promising, as suggested by our recent data,[1] especially considering the possible role of amylase/trypsin inhibitors as activators of innate immunity.[7,8]

ANTONIO CARROCCIO
DiBiMIS University of Palermo
Palermo *and*
Internal Medicine
Giovanni Paolo II Hospital
Sciacca (ASP Agrigento), Italy

ALBERTO D'ALCAMO
PASQUALE MANSUETO
DiBiMIS University of Palermo
Palermo, Italy

References

1. Carroccio A, et al. Gastroenterology 2015;149:596.
2. Volta U, et al. BMC Med 2014;12:85.
3. Lebwohl B, et al. Clin Gastroenterol Hepatol 2015;13:1613.
4. Carroccio A, et al. Am J Gastroenterol 2012;107:1898.
5. Carroccio A, et al. Am J Gastroenterol 2013;108:1845.
6. Ball AJ, et al. Am J Gastroenterol 2010;105:222.
7. Fasano A, et al. Gastroenterology 2015;148:1195.
8. Schuppan D, et al. Best Pract Res Clin Gastr 2015;29:469.

Conflicts of interest
The authors disclose no conflicts.

Most current article

http://dx.doi.org/10.1053/j.gastro.2015.11.034

High False-Negative Rate for Nonalcoholic Steatohepatitis in Extreme Obesity

Dear Editor:

The article by Lassailly et al[1] reported on 1540 patients who had undergone a bariatric surgery procedure that included 1489 cases in whom intraoperative liver biopsies were obtained. Surprisingly, histologic nonalcoholic steatohepatitis (NASH) was diagnosed in only 115 of the 1489 cases (7.7%). In the Discussion, this unusually low rate of disease is given only sparse attention. In addressing limitations of the study the authors state that, "the prevalence of NASH was lower than in other studies, but this could be explained by the absence of any selection of enrolled patients among surgical candidates." This is not an adequate explanation for results that are significantly discrepant from other published studies of liver biopsy data from patients with extreme obesity undergoing bariatric surgery procedures. A review[2] of such studies found the prevalence of nonalcoholic fatty liver disease (NAFLD) and NASH averaged 90% and 37%, respectively, consistent with our own recent data.[3] Rather than an absence of selection criteria as an underlying cause, the results presented are more likely highly biased owing to a lack of representative sampling from an extremely high false-negative detection rate, that is, many individuals from a cohort with extreme obesity expected to manifest NASH were excluded. We believe that sampling error from the use of needle biopsies versus the much larger size of wedge biopsies commonly used in other studies contributes to the disparity in the NASH prevalence reported. Wedge biopsies have consistently been shown to be superior to needle biopsies for assessment of liver histology primarily because substantially more tissue is obtained for evaluation.[4,5]

In addition, the lack of correction for multiple comparisons is highly problematic and further weakens the