CORRESPONDENCE

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More Than One Culprit for Nonceliac Gluten/Wheat Sensitivity

Dear Editors:

We read with interest the article by Skodje et al[1] reporting a double-blind placebo-controlled food challenge aimed at establishing whether gluten or fructan, a component of fermentable oligo-, di-, monosaccharides and polyols, evokes gastrointestinal (GI) symptoms in subjects with self-reported nonceliac gluten/wheat sensitivity. The results showed that fructan, and not gluten, could significantly trigger GI symptoms in patients with self-reported nonceliac gluten/wheat sensitivity. Although fructan can play a role in generating irritable bowel syndrome (IBS)-like symptoms, we would like to address some issues that deserve thorough consideration.

First, the study was centered on subjects with self-reported (ie, autodiagnosed), not specialist-confirmed, nonceliac gluten/wheat sensitivity. As a result, the study did not include a pre-enrollment evaluation based on symptomatic response to a gluten-free diet and worsening on gluten rechallenge quantified by a modified version of GI symptom rating scale questionnaire with extraintestinal manifestations.[2] Skodje et al[1] assessed only anxiety, depression, fatigue, tiredness, weakness, and dizziness, but not skin, muscle, joint, skeletal, and other neurologic symptoms, such as headache and numbness, which are important clinical features of patients with nonceliac gluten/wheat sensitivity.[2] Lacking this symptom score assessment in the patient recruitment process, the population studied in the present trial should be labeled as having IBS rather than nonceliac gluten/wheat sensitivity. Thus, it is not surprising that most patients experienced symptoms related to fructan consumption, as confirmed by other papers and meta-analysis.[3] Moreover, initial evidence suggests that fructan has no effect on skin, muscle, joint, and neurologic symptoms, which characterize the extraintestinal symptom profile of true nonceliac gluten/wheat sensitivity patients.[4] Studies based on double-blind placebo-controlled food challenge and patient pre-evaluation selection according to the Salerno expert criteria for nonceliac gluten/wheat sensitivity found that gluten evoked GI and extraintestinal symptoms in a subset of such patients, leaving open the possibility that other wheat proteins (eg, amylase trypsin inhibitors) may play a role in symptom generation.[4,5] In addition, as an ancillary comment, the limited number of Marsh 1 lesion detected at the duodenal biopsy in the Skodje's et al study (only 11%) may contribute to raise further questions on patient selection because published data showed Marsh 1 in about 40% of patients with nonceliac gluten/wheat sensitivity.[6]

Second, the authors reported that some of their patients tested positive for deamidated gliadin peptides IgG antibodies, a doubtful marker of celiac disease certainly not detected in patients with true nonceliac gluten/wheat sensitivity. In contrast, we would be interested to know the prevalence of anti-gliadin antibodies IgG in the population studied by Skodje et al. Several data showed that anti-gliadin antibodies IgG can be detected in 50% to 60% of patients with nonceliac gluten/wheat sensitivity and their presence (and subsequent negativization with a gluten-free diet) correlates with intestinal and extraintestinal symptoms.[7]

Third, the final comment is about autoimmunity in nonceliac gluten/wheat sensitivity versus patients with IBS. Increasing evidence indicates that yet another distinction between nonceliac gluten/wheat sensitivity and IBS concerns the prevalence of autoimmune manifestations (eg, Hashimoto's thyroiditis, autoimmune gastritis, psoriasis, and alopecia areata).[5] A positivity for antinuclear antibodies was more frequently identified in patients with nonceliac gluten/wheat sensitivity versus patients with IBS.[8] Skodje et al[1] reported only on a high prevalence of Hashimoto's thyroiditis (which was similar to other previous studies)[6,8] without mentioning antinuclear antibodies and other associated autoimmune disorders.

In conclusion, we thank Skodje et al because their study provides the opportunity to highlight some aspects that remain a matter of debate in the scientific community and that should be cautiously considered while diagnosing and managing patients with nonceliac gluten/wheat sensitivity.

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