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Conflicts of interest

The authors disclose the following: G.K. and D.H. belong to a group of patent holders for a portable bedside device for CFF analysis. The remaining author discloses no conflicts.

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Nonceliac Wheat Sensitivity in the Context of Multiple Food Hypersensitivity: New Data From Confocal Endomicroscopy



Dear Editor:

We enjoyed reading the article by Fritscher-Ravens et al who showed, by confocal endomicroscopy, that candidate food antigens caused immediate duodenal mucosa damage in irritable bowel syndrome (IBS) patients with a prolonged clinical history of symptoms after meals.¹ Their in vivo data add evidence to the relationship between IBS and food allergy and seem to reinforce our hypothesis that a percentage of “nonceliac wheat sensitive” (NCWS)—patients with an IBS-like clinical presentation could suffer from non-immunoglobulin E-mediated wheat allergy.²

However, we would suggest that the very high percentage of positive confocal laser endomicroscopy patients (CLE)—22 out of 36—found in the study of Fritscher-Ravens et al could depend on their inclusion criteria (refractory daily symptoms >1 year, daily shortly after meal symptoms); in our experience, the frequency of food hypersensitivity diagnosed by double-blind, placebo-controlled (DBPC) food challenges in IBS is slightly <30% (276 patients out of 920).³

Apart from the epidemiologic data, which were not the objectives of this pilot study, we would like to underline some aspects of the study and make some suggestions for future research.

It is interesting that a total of 32 reactions were analyzed, with different food antigens, in 22 CLE-positive patients and that the second most frequently offending food, after wheat, was cow’s milk. This is in keeping with our data about the high frequency of multiple food hypersensitivities in patients with NCWS. We showed that 206 of 276 NCWS subjects also became symptomatic after DBPC cow’s milk proteins challenge.³ These observations should induce the physicians who suspect a relationship between NCWS or food hypersensitivity and IBS to suggest an elimination diet with the exclusion of more food rather than just

wheat, and that the reintroduction should be performed singly and with great caution, as described.³ In fact, a lack of response to a wheat-free diet could depend on hypersensitivity to other food antigens which are still included in the patients’ diet.

We found also of great interest that CLE showed significantly higher intraepithelial lymphocyte (IEL) count in CLE-positive than CLE-negative patients and in controls. Furthermore, histology showed that the mean values of IEL in CLE-positive patients were 26.4 ± 2.7 per 100 cells. Overall, this could indicate a state of mucosal inflammation owing to food hypersensitivity. A previous NCWS study which excluded patients with >25 IEL per 100 EC in the duodenal mucosa, very probably missed the group of NCWS patients who had an immunologic pathogenesis at the basis of their troubles.⁴ However, in our opinion, NCWS is a heterogeneous condition,² which includes different subgroups of patients and the “allergic hypothesis” does not exclude that, in other NCWS patients, wheat amylase trypsin inhibitors⁵ or fermentable sugars⁴ could be the main pathogenetic triggers.

Finally, we think that the authors showed that CLE is an excellent instrument to demonstrate food-related reactions in IBS and to separate a subgroup of the NCWS—those with non-immunoglobulin E-mediated wheat hypersensitivity—from the confuse melting pot that NCWS still is. However, awaiting a wider diffusion of this endoscopic means, and taking into account that the economic resources are decreasing in developed countries, it would be very important to correlate the CLE finding with simpler, noninvasive biomarkers. In this respect, it would be interesting to know whether CLE findings correlate with the eosinophil cationic protein concentrations in the stools or with the flow cytometric allergen stimulation assay results, biomarkers that showed a good concordance with the DBPC challenge results in IBS patients.^{6,7}

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Reply. We thank Carroccio et al for their comments on our study¹ and their thoughts about nonceliac wheat sensitivity. Recently, there has been increased interest in food intolerances (defined as a lack of enzymes to digest the incriminated food) and sensitivities (involving an immune reaction to the food) that may trigger symptoms in patients with irritable bowel syndrome (IBS).¹ Although intolerances to lactose or FODMAPs (fermentable oligo- and disaccharides, monosaccharides and polyols) are dose dependent and can be defined and treated relatively easily, identification of food sensitivities is more difficult, especially in case of food allergy.² Moreover, contrary to Carroccio et al's suggestion, FODMAPs have never been shown to cause intestinal inflammation, including intraepithelial lymphocytosis. In contrast, they are considered healthy for gut homeostasis. Thus, apart from celiac disease which can be categorized as type IV hypersensitivity to gluten peptides,³ allergic food reactions are either immunoglobulin E (IgE) mediated via degranulation of mast cells, basophils, and eosinophils, a substantial proportion of food allergies are not characterized by marked IgE production and are thus difficult to diagnose.⁴ These "atypical" food reactions are commonly induced by cow's milk, wheat, egg, and soya,⁵ and individuals are frequently sensitive to >1 food. Reaction to food in these cases seems to be immediate in the majority of patients, as found in our study. It is therefore likely that most of our 22 of 36 confocal laser endomicroscopy (CLE)-positive patients had this kind of allergic reaction to the tested foods. However, as alluded to by Carroccio et al, some of our patients might have had an immediate reaction to amylase trypsin inhibitors of wheat (ATIs), which, apart and different from allergic reactions, can also elicit an innate immune response in dendritic cells and macrophages of the gut via direct activation of Toll-like receptor 4,⁶ an event that is also quick, but slower than a classical allergic reaction. Interestingly, these ATIs can both exacerbate adaptive (type IV) and allergic (type I) immune reactions (Zevallos et al, unpublished data). It is thus possible that both classical food allergens and ATIs contributed to the observed food sensitivities.

The novelty of our pilot study is the real-time visualization via CLE of immediate dynamic structural and functional changes in the duodenal epithelium when exposed to food antigens in a subgroup of IBS patients with suspected food sensitivities. Our secondary aim and translational proof of principle was the identification of those patients in whom exclusion of candidate foods might improve symptoms.

The excellent success rate of the exclusion diet based on CLE findings provides proof that (1) a subgroup of IBS

patients (likely the ~30% of subjects mentioned by Carroccio et al) can be classified as food sensitive and thus be treated appropriately with an exclusion diet; and (2) these food sensitivities are possibly nonclassical cases of food allergies and/or possibly innate reactions to common nutritional components like wheat ATIs. Thus, CLE now permits testing select IBS patients for individual food antigens and further elucidation of the immune reactions involved.

As Carroccio et al correctly stated, this methodology is currently available only to a few centers. However, we disagree that this kind of testing for suspected but undiagnosed food sensitivities is not cost effective, given the high costs of unnecessary/noncontributory studies and absence from work, apart from unnecessary suffering of undiagnosed patients.

As to diagnostic protein markers, we recently reported eosinophilic cationic protein (ECP) and tryptase levels in duodenal lavage fluid collected at CLE as a measure of eosinophil and mast cell activation.⁷ In 13 of 14 CLE-positive patients, only ECP but not tryptase trended to be higher than in healthy controls (n = 10). These data suggest that allergic responses occurred in the majority of these patients who were all (serum) IgE negative. Because this response seems to be transient and variable, a much larger study is required.

We agree that a robust and easy to assess (serum) biomarker is highly desirable to replace CLE after defined food challenge, or even the current gold standard of double-blind placebo-controlled food challenges (DBPC), which are cumbersome, labor intensive, and usually not reimbursed. Here, CLE can quickly confirm hypersensitivity reactions to food antigens and serve as a novel gold standard to develop noninvasive biomarkers.

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Conflicts of interest

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