Gastroenterol Hepatol. 2016;**39(Espec Congr 2)**:16-17

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

SESIÓN 3: ENFERMEDAD CELÍACA DEL ADULTO

Non-coeliac wheat sensitivity: is there still a role for gluten?

Luca Elli

Center for the Prevention and Diagnosis of Celiac Disease, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milán, Italia

The nomenclature of gluten related disorders has been recently updated.[1] The most relevant novelty introduced in the new classification proposed by Sapone et al. was the insertion, beside celiac disease (CD) and wheat allergy, of the so called non-celiac gluten sensitivity (NCGS). NCGS has been defined as a syndrome composed by intestinal and extraintestinal symptoms occurring after gluten-containing food ingestion and usually disappearing after its elimination from the diet.[2] The introduction of NCGS among gluten related disorders has been driven by the continuous increase of non-CD patients following a gluten-free diet (GFD) to improve their symptoms (often without a medical prescription).[3] Differently from CD and wheat allergy, NCGS does not present an immunomediated etiopathogenesis and does not present specific biomarkers (serological or histological) supporting its diagnosis; for this reason, a blind challenge is actually considered the gold standard for NCGS diagnosis.[4] Although gluten has been immediately considered the major environmental factor triggering gastrointestinal symptoms also in absence of a CD, different researchers hypothesised that other-than-gluten molecules could be responsible for patients' symptoms; in fact, gluten withdrawn from the diet means a complete elimination of wheat supporting the idea of a non-celiac wheat sensitivity (NCWS) instead of a real NCGS. This seems supported by Carroccio et al[5] in a recent study reviewing the clinical records of 920 patients affected by irritable bowel syndrome (IBS) who underwent an elimination diet followed by a blind wheat challenge, they demonstrated that 276 patients (30%) relapsed after wheat challenge reporting abdominal pain, altered stool consistency and bloating. Moreover, this study showed two distinct NCG(W)S patient types: the first composed by subjects with wheat sensitivity alone and the second, more frequent, with wheat sensitivity associated with multiple food hypersensitivities. In line with the Carroccio's finding, Fritscher-Ravens et al[6] investigated 36 subjects affected by IBS and reporting a relation between symptom on set and food intake. The authors demonstrated the formation of leaks into the intestinal barrier by means of *in vivo* confocal laser endomicroscopy after direct duodenal instillation of food derived molecules in the duodenum.

Other investigators completely denied a role of gluten in patients with functional gastrointestinal disorders. Biesiekierski et al[7] for first performed a trial supporting the role of gluten in development of symptoms but successively designed a trial investigating the role of Fermentable Oligo-di and Mono-saccharides, And Polyols (FODMAP) in the same type of patients; 37 subjects with suspected NCGS were previously assigned to a 2-week long diet with reduced FODMAP, and then placed on diets with different gluten contents. In all participants, reduced FODMAP intake lead to symptomatic improvement; however, gluten and placebo blind reintroduction was associated with a symptomatic relapse without statistical differences.[8]

In conclusion, although different trials using blind gluten challenge in patients affected by functional symptoms found different percentages of subjects responsive to the blind challenge strengthening the hypothesis that gluten plays a pivotal role in IBS (and its management[9,10]), current literature presents different grey zones making possible the involvement of other molecules. From this point of view, an alternative pathogenetic role could be played by FODMAP contained in different foods or by the amylase trypsin inhibitor (ATI), a proinflammatory molecule contained in wheat.[11]

References

1. Sapone A, Bai JC, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med. 2012;10:13.

2. Catassi C, Bai JC, Bonaz B, et al. Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. Nutrients. 2013;5: 3839-53.
3. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. Am J Gastroenterol. 2009;104:1587-94.
4. Catassi C, Elli L, Bonaz B, et al. Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. Nutrients. 2015;7:4966-77.
5. Carroccio A, Mansueto P, Iacono G, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. Am J Gastroenterol. 2012;107:1898-906; quiz 1907.
6. Fritscher-Ravens A, Schuppan D, Ellrichmann M, et al. Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome. Gastroenterology. 2014;147:1012-20.e4.
7. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. Am J Gastroenterol. 2011;106:508-14; quiz 515.
8. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology. 2013;145:320-8.e1-3.
9. Elli L, Tomba C, Branchi F, et al. Evidence for the Presence of Non-Celiac Gluten Sensitivity in Patients with Functional Gastrointestinal Symptoms: Results from a Multicenter Randomized Double-Blind Placebo-Controlled Gluten Challenge. Nutrients. 2016;8:84.
10. Di Sabatino A, Volta U, Salvatore C, et al. Small Amounts of Gluten in Subjects With Suspected Nonceliac Gluten Sensitivity: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial. Clin Gastroenterol Hepatol. 2015;13:1604-12.e3.
11. Junker Y, Zeissig S, Kim SJ, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med. 2012;209:2395-408.