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Non-celiac gluten sensitivity: A work-in-progress entity in the spectrum of wheat-related disorders

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A B S T R A C T

Non-celiac gluten sensitivity is an undefined syndrome with gastrointestinal and extra-intestinal manifestations triggered by gluten in patients without celiac disease and wheat allergy. The pathogenesis involves immune-mediated mechanisms requiring further research. Symptoms disappear in a few hours or days after gluten withdrawal and recur rapidly after gluten ingestion. Besides gluten, other wheat proteins as well as fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) may contribute to this syndrome. This syndrome occurs mainly in young women, being rare in children. Its prevalence ranges from 0.6% to 6%, based on

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primary or tertiary care center estimates. No biomarker is available, but half of patients tests positive for IgG anti-gliadin antibodies, which disappear quickly after gluten-free diet together with symptoms. Also, genetic markers are still undefined. Although currently limited to a research setting, double-blind, placebo-controlled, cross-over trial strategy is recommended to confirm the diagnosis. Treatment is based on dietary restriction with special care to nutrient intake.

Introduction

Until a few years ago gluten and wheat proteins were considered responsible for the occurrence of two well-defined clinical entities, i.e. celiac disease (CD) and wheat allergy (WA) [1,2]. The evidence of gluten sensitive patients, i.e. symptoms evoked by gluten/wheat in patients without CD or WA, was brought up for the first time at the beginning of the '80s by Geoffrey Holmes' group in the UK [3]. That remarkable report highlighting the existence of gluten sensitivity fell into shadow as most clinicians were dissatisfied by the lack of established diagnostic criteria to identify those patients. Likewise functional bowel disorders, most subjects with a suspicion of gluten sensitivity were thought to be imaginary (i.e. 'psychiatric') patients belonging to a sort of 'no man's land' of gluten related disorders [4]. Nonetheless, with the increasing number of patients complaining of symptoms following gluten ingestion, the awareness of a new gluten-related syndrome (currently referred to as non-celiac gluten sensitivity, NCGS) has grown with a progressive pace over the years [5–9].

Why NCGS has markedly increased over time? The answer(s) to this question is / are still unclear, although a number of factors should be considered. First, the novel variants of wheat that are known to contain high amount of toxic gluten peptides potentially harmful to the integrity of the enteric mucosa; secondly, the mechanization of farming and the growing industrial use of pesticides; thirdly, the overall reduced time of dough fermentation resulting in a higher content of toxic gluten fractions in bakery products [10]. Finally, the media hype and the growing awareness of clinicians towards this condition contributed to the increasing rate of NCGS diagnosis, not always supported by evidence [11].

Currently, NCGS should be regarded as a new entity although with a possible overlap with other conditions, i.e. mainly functional bowel disorders (irritable bowel syndrome, IBS) and a variety of food hypersensitivities [12]. In this respect, dietary components other than gluten, such as wheat proteins (i.e. amylase- and trypsin-inhibitors – ATIs) and fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) could have a role in symptom generation of NCGS [13,14]. However, the relative contribution exerted by single dietary factors in NCGS-related symptoms is still unclear as cereals contain both ATIs and FODMAPs admixed with gluten. NCGS should be suspected in patients displaying intestinal symptoms (often dismissed as 'IBS patients') and extraintestinal manifestations, which occur soon after gluten ingestion [15,16]. A diagnostic pre-requisite for establishing NCGS in a symptomatic patient is that both CD and WA have been ruled out. Due to the lack of biomarkers, the diagnosis of NCGS remains strictly related to clinical criteria [17,18]. The improvement of symptoms after gluten exclusion is regarded as one of the major diagnostic criteria for NCGS, although the possibility of a 'placebo effect' (associated to a dietary exclusion of certain foods) should not be discarded [19]. Thus, a cautionary approach in recommending a gluten free diet (GFD) should be adopted in symptomatic patients lacking a clear diagnosis of NCGS [20].

This chapter has been designed to provide a practical guidance in the various aspects related to NCGS, i.e. basic immunological mechanisms and pathogenesis, epidemiology and clinical picture, diagnostic criteria, treatment (including a possible approach by enzyme therapy) and future tasks, in order to provide specialists and general practitioners with a most updated review on this emerging topic.