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Non-celiac wheat sensitivity: Differential diagnosis, triggers and implications

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A B S T R A C T

Non allergy-non-celiac wheat sensitivity (NCWS) has become a common and often overrated diagnosis. Skepticism mainly relates to patients with prominent intestinal symptoms in the absence of general or intestinal signs of inflammation. There is consensus that the major wheat sensitivities, celiac disease and wheat allergy, have to be ruled out which may be difficult for wheat allergy. The non-inflammatory intolerances to carbohydrates, mainly lactose and FODMAPs (fermentable oligi-, di-, monosaccharides and polyols), which cause bloating or diarrhoea, can usually be excluded clinically or by simple tests. Recent studies and experimental data strongly indicate that NCWS exists in a substantial proportion of the population, that it is an innate immune reaction to wheat and that patients often present with extraintestinal symptoms, such as worsening of an underlying inflammatory disease in clear association with wheat consumption. Wheat amylase-trypsin inhibitors (ATIs) have been identified as the most likely triggers of NCWS. They are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa. Non-gluten containing cereals or staples display no or little TLR4 stimulating activity. Wheat ATIs are a family of up to 17 similar proteins of molecular weights around 15 kD and represent 2–4% of the wheat protein. With oral

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ingestion they costimulate antigen presenting cells and promote T cell activation in celiac disease, but also in other immune-mediated diseases within and outside the GI tract.

Clinical definitions and differential diagnoses

Non-celiac gluten sensitivity (NCGS) has been described about 40 years ago, being defined as mainly abdominal symptoms related to ingestion of gluten containing cereals, after celiac disease and wheat allergy have been (largely) excluded. Since it is possible if not likely that non-gluten components of wheat, barley and rye induce the disease, we prefer the term non-celiac (non-allergy) wheat sensitivity (NCWS), at least in scientific discussions. An increasing number of subjects claim to suffer from NCWS, and physicians are challenged to better define the condition. In view of the "gluten free fad" we have to separate mere claims of a health benefit of gluten free diet (GFD) from real disease, and rule out numerous other differential diagnoses before diagnosing a patient with NCWS, a subject of recent consensus conferences [1–3]. Here, patients with a clear worsening of symptoms and signs shortly after consuming gluten containing food, with rapid improvement on a GFD best fulfil the criteria of having NCWS. For the experienced clinician extraintestinal symptoms which are frequent serve as the best indicator of the disease, and accordingly, are increasingly recognized as hallmarks of NCWS [4,5]. When it comes to mainly intestinal symptoms, there may be a significant overlap with the spectrum of irritable bowel syndrome (IBS) [6], wheat allergy which is frequently missed with conventional blood IgE and skin testing [7–9] and (less likely) intolerance to FODMAPs (fermentable oligo-, di-, monosaccharides and polyols [10]. Wheat allergy can be revealed with mucosal challenge followed by confocal endomicroscopy but this technology is not yet generally available [11]. However, clinically allergies and FODMAP intolerance are usually characterized by a quick onset after ingestion of the offending foods (minutes to a few hours), whereas NCWS has a slower onset, with symptoms appearing after hours to a few days [12]. This also sets these entities apart from celiac disease in which symptom onset can take days to weeks after onset of gluten challenge (Table 1). Notably, there appears to be a large number of patients with IBS whose complaints are at least partly attributable to food intolerances or food sensitivities, especially FODMAP intolerance and undetected allergies [10–13].

Toxic wheat components?

Much research has been invested in identifying bioactive components in wheat. Apart from allergens, gluten peptides that trigger T cell activation in celiac disease and wheat proteins that activate innate immunity (see below), research has failed to identify toxic constituents, rather described

Table 1
Guide to differential diagnosis of the three wheat sensitivities.

	Celiac disease	NCWS	Wheat allergy
Time from wheat (gluten) exposure to onset of symptoms	Days–weeks	Hours–days	Minutes–hours
Pathogenesis	Th1: autoimmunity/ adaptive immunity	Innate immunity	Th2: Allergic immune response
HLA-DQ2/DQ8-restricted	Yes	No	No
Autoantibodies	Yes (anti-TG2)	No	No
Enteropathy	Yes	Minimal	Minimal
Symptoms	Intestinal and extra-intestinal	Intestinal and extra-intestinal	Intestinal and extra-intestinal
Complications	Co-morbidities, long term complications	Long term (extraintestinal) complications?	No co-morbidities, short-term complications (anaphylaxis)