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Review

Non-coeliac gluten sensitivity: A review of the literature

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ABSTRACT

Background: Non-coeliac gluten sensitivity (NCGS) is an emerging and still poorly defined clinical entity, which is part of the spectrum of gluten-related disorders (along with coeliac disease and wheat allergy) but also closely related to irritable bowel syndrome. It is characterized by a wide array of both gastro-intestinal and extra-intestinal symptoms. NCGS was first defined in the 1970s, but has gained critical relevance in recent years.
Scope and approach: This review covers the existing definitions, documented symptoms and methods of diagnosis, treatment via a gluten-free diet, history, prevalence in the general population and possible mechanisms for NCGS. It also looks into recent studies and their findings. All information is relative to studies published in the last 6 years (2011-present).
Key findings and conclusions: Despite recent advances in characterising NCGS as a clinical entity and gaining novel insights into its pathogenesis, further studies are needed to better understand its etiology and mechanism and to establish specific biomarkers.

1. Gluten and the spectrum of gluten-related disorders

Gluten is the main storage protein complex in cereals such as wheat, barley, rye and spelt. Its main protein constituents are gliadin and glutenin (Dupont, Vensel, Tanaka, Hurkman, & Altenbach, 2011). These proteins are rich in glutamines and prolamines, which causes them to be incompletely digested by gastric, pancreatic, and brush border peptidases, leading to the formation of large peptides (Shan et al., 2002). These pass through the intestinal epithelial barrier and enter the lamina propria by way of a transcellular or paracellular route (Visser, Rozing, Sapone, Lammers, & Fasano, 2009).

When flours which contain gluten are kneaded with water, the dough acquires viscosity and elasticity due to the action of gliadins and glutenins (Blomfeldt, Kuktaite, Johansson, & Hedenqvist, 2011). This happens by way of the formation of an elastic network which retains the gases resulting from fermentation, which allows the expansion and rise of the dough during the baking process (Moore, Schober, Dockery, & Arendt, 2004).

The proteins of gluten possess resistance to gastric and intestinal digestion and cause an increase in intestinal permeability through cytoskeletal rearrangement, zonulin (protein which modulates intestinal permeability) overexpression and dysfunction of tight junctions (Drago et al., 2006). Intestinal homeostasis is altered via the inhibition of epithelial cell growth and the induction of apoptosis (Dolfini et al., 2005).

The ingestion of gluten can trigger an array of conditions; these are designated by the broader term “gluten-related disorders”. They are divided into: disorders with autoimmune pathogenesis, including coeliac disease (CD); disorders characterized by allergic mechanisms, which include wheat allergy (WA); and the controversial non-coeliac gluten sensitivity (NCGS), whose causes are neither autoimmune nor allergic in nature (Sapone et al., 2012).

1.1. Coeliac disease

Coeliac disease (CD) is a systemic immune-mediated disorder caused by gluten and analogous prolamines (found in rye and barley) in individuals with a genetic susceptibility (Sapone et al., 2012). It is considered to affect between 1 and 2% of the general population (DiGiacomo, Tennyson, Green, & Demmer, 2013; Sapone et al., 2012).

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Abbreviations

AGA	anti-gliadin antibodies
ASD	autism spectrum disorders
ATI(s)	amylase trypsin inhibitor(s)
CCL2	chemokine (C-C motif) ligand 2
CD	coeliac disease
CD3, CD4, CD14	clusters of differentiation 3, 4 and 14
CLDN1, CLDN4	claudins 1 and 4
DBPC	double-blind placebo-controlled
DBPCFC	double-blind placebo-controlled food challenge
DQ2, DQ8	human major histocompatibility class II alleles
EMA	anti-endomysium autoantibodies
FABP2	fatty acid-binding protein 2
FODMAPs	fermentable oligo-, di-, and mono-saccharides and polyols
FOXP3	forkhead box P3
GFD	gluten-free diet
GI	gastrointestinal
GS	gluten sensitivity/gluten sensitive
HLA	human leukocyte antigen
IBS	inflammatory/irritable bowel syndrome
IBS-D	diarrhoea-predominant inflammatory/irritable bowel syndrome
IFN-γ	interferon-gamma
IgA, IgE, IgG	immunoglobulins A, E and G
IL-8	interleukin-8
LBP	ipopolysaccharide-binding protein
LPS	lipopolysaccharide
MD2	lymphocyte antigen 96
NCGI	non-coeliac gluten intolerance
NCGS	non-coeliac gluten sensitivity
NCWS	non-coeliac wheat sensitivity
RCD	refractory coeliac disease
sCD14	soluble CD14
TG2	transglutaminase 2
TGF	transforming growth factor
TLR-1, TLR-2, TLR-4	Toll-like receptors −1, −2 and −4
T_{REG}	regulatory T-cell
tTG	tissue transglutaminase
WA	wheat allergy

CD possesses well-documented genetic makeup and environmental triggers (such as gliadin peptides) (Sapone et al., 2010). Markers used in the confirmation of a diagnosis are IgA tissue transglutaminase (tTG or TG2) and anti-endomysial (EMA) antibodies (Sapone et al., 2010, 2011; Sollid & Jabri, 2011).

The common feature for all patients suffering from CD is the presence of a variable combination of gluten-dependent clinical manifestations, specific antibodies (tTG/TG2, EMA), human leukocyte antigen (HLA)-DQ2 and/or -DQ8 haplotypes (present in 90–95% of CD patients) and degrees of enteropathy varying from lymphocytic infiltration of the epithelium to complete villous atrophy (Sollid & Jabri, 2011).

The immune response to gluten in this disorder involves both the adaptive and innate immune systems (though the former is more heavily implicated in this mechanism) (Sollid, 2002). An adaptive immune reaction takes place within the lamina propria. Gliadin is deamidated by tTG, and the latter increases its immunogenicity by altering the charge of the gliadin fragments that aid in the binding between antigen presenting cells and the HLA-DQ2 or -DQ8 molecule (Sollid, 2002). This reaction leads to inflammatory responses in the small intestine that are mediated by $CD4^+$ T cells (Sollid, 2002). Said cells recognize gliadin peptides, leading to the subsequent production of pro-inflammatory cytokines, specifically interferon gamma (IFN-γ) (Sollid, 2002). The release of metalloproteinases and other tissue damaging mediators concurrent with the inflammatory cascade induce tissue injury (Mohamed et al., 2006).

Diagnosis is based on clinical symptoms (mainly chronic diarrhoea and weight loss), histopathological evaluation of biopsies of the small intestine with varying degrees of villous atrophy, as well as serological detection of TG2 and/or EMA IgA antibodies (Sollid & Jabri, 2011).

Until recently, CD was thought to be uncommon during infancy or childhood, while also being detected more frequently in individuals of that age (Matthias et al., 2011). However, it is now recognized that the majority of CD cases occur in adults in the 40–60 years age range (Matthias et al., 2011). This disorder is also more common in females than in males (Volta, Caio, Tovoli, & De Giorgio, 2013). First-degree family members of CD patients have been found to possess an increased risk for CD, which can vary from 2 to 20% depending on gender and HLA-haplotype (Vriezinga et al., 2014).

The foundation of treatment for CD is the permanent adherence to a strict gluten-free diet (GFD), which will usually lead to a rapid improvement, both clinical and histological (Green & Cellier, 2007). This treatment calls for the exclusion of wheat and other cereal grains from the diet (Green & Cellier, 2007). Patients on a GFD will have a quick response in most cases, leading to a resolution of clinical symptoms. Nonetheless, the resolution of histological changes is a longer process (Sestak & Fortgang, 2013).

Some patients will, however, develop refractory forms of CD (RCD), being unable to respond to the GFD and maintaining an inflammation. Repeated dietary transgressions and continuing gluten consumption (e.g., in non-diagnosed individuals) are thought to be contributing factors to the development of RCD (Hadithi & Peña, 2010).

Finally, regarding the association of CD and the risk of malignant lymphomas, a gluten-free diet does not appear to alter the risk of lymphoma. However, it is not possible to completely eliminate a cause-effect relationship (Olén et al., 2011). The risk of occurrence of malignant lymphoma in CD seems to be related with the small intestine histopathology, without raising the risk of latent CD (Elfström et al., 2011).

More recently, Lebwohl et al. (2013) found that the risk is mainly related with the T cell lymphoma, without a high level risk of the B cell lymphoma, and conclude that the follow-up biopsy may be a means to effectively stratify CD patients regarding subsequent malignant lymphoma risks.

1.2. Wheat allergy

Wheat allergy (WA) is an adverse immunological reaction to gluten and other proteins found in wheat (National Institute of Allergy and Infectious Diseases, 2010; Sapone et al., 2012). As it is mediated by IgE, the pathogenesis of CD and WA are believed to be unrelated, in spite of their optimal treatments being the same (Sestak & Fortgang, 2013).