Non-celiac Gluten Sensitivity

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KEYWORDS

- Gluten sensitivity • Celiac disease • Antibody • Food challenge
- Irritable bowel syndrome

KEY POINTS

- Nonceliac gluten sensitivity (NCGS) has emerged as a frequently encountered entity in the clinical setting. Individuals with self-reported NCGS appear to far outnumber those with celiac disease, and may be increasing.
- A better understanding of NCGS is hampered by the lack of objective clinical diagnostic criteria and absence of specific biomarkers.
- The financial burden on patients is considerable.
- In countries where reimbursement or prescription for gluten-free diet exists, the clinician must be aware of the condition and carefully consider the health economic aspects.

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy triggered by ingestion of wheat gluten and related cereal proteins in genetically predisposed individuals.[1] The ensuing inflammatory response in the small intestine leads to villous atrophy, crypt hyperplasia, and lymphocytic infiltration. Elimination of the gluten proteins from diet generally leads to clinical and histologic improvement.[2] CD is a multigenic disorder, with genes for specific class II human leukocyte antigens (HLA) conferring about 40% of the genetic susceptibility. The primary HLA association is with DQ2 (DQA1 *05/DQB1 02) and DQ8 (DQA1 *0301/DQB1 *0302).[3] The HLA-DQ2 and HLA-DQ8 molecules confer susceptibility for CD by having the important role of presenting specific immunogenic gluten peptides to gluten-specific T cells in the small intestine. The major antibody responses in CD are targeted at (1) gluten proteins, (2) deamidated gluten sequences, and (3) the transglutaminase 2 (TG2) enzyme autoantigen.[4] Among these antibodies, the immunoglobulin A (IgA) anti-TG2 antibody is currently

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considered the most sensitive and specific serologic marker of CD.[5,6] Immunoglobulin G (IgG) and IgA antibodies to deamidated gliadin have also been shown to have high sensitivity and specificity for CD. Antibodies to native gliadin proteins have low specificity for CD, and have been reported to be elevated in several other conditions. The presence of these antibodies has been suggested in some studies to be a marker of immune sensitivity to gluten, even in the absence of CD. CD is now understood to have a wide range of clinical manifestations, both intestinal and extraintestinal.[4]

Some of the CD-associated symptoms experienced in response to ingestion of wheat are also reported by individuals who do not have the typical serologic, histologic, or genetic markers of CD, and who also do not experience the immunoglobulin E (IgE) serologic response associated with wheat allergy. The term nonceliac gluten sensitivity (NCGS) has been proposed to refer to the spectrum of conditions reported by these patients.[1] The term nonceliac gluten intolerance has also been used in the past, but is not recommended.[1]

DEFINITION OF NCGS

A precise and widely agreed definition of NCGS does not yet exist. NCGS is currently understood as a condition associated with the experiencing of various symptoms in response to ingestion of foods containing wheat, rye, and barley, and the resolution of symptoms on removal of those foods from diet in individuals in whom CD and wheat allergy have been ruled out. The symptoms may be accompanied with an increase in levels of antibody to gluten. The majority of symptoms associated with NCGS are subjective, including abdominal pain, headache, "brain fog," tingling and/or numbness in hands and feet, fatigue, and musculoskeletal pain. However, other symptoms such as rash and diarrhea, as well as more severe neurologic and psychiatric conditions including schizophrenia and cerebellar ataxia, have also been reported to be associated with NCGS. **Table 1** lists the most commonly reported symptoms associated with NCGS in comparison with those of CD and wheat allergy.

Table 1
Some of the symptoms reported to be associated with CD, wheat allergy, and NCGS

	CD	Wheat Allergy	NCGS
Gastrointestinal	Abdominal pain Diarrhea Constipation	Abdominal pain Vomiting Diarrhea	Abdominal pain Diarrhea Constipation Nausea Vomiting
Neurologic/ psychiatric	Headache Musculoskeletal pain Brain fog Tingling and/or numbness in hands and feet Fatigue Ataxia	Dizziness Headache	Headache Musculoskeletal pain Brain fog Tingling and/or numbness in hands and feet Fatigue Other neurologic and psychiatric conditions
Other	Dermatitis herpetiformis Weight loss	Eczema Asthma Rhinitis Nausea Itchiness	Rash Nausea Weight loss