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A Clinical Update

Nonceliac Gluten Sensitivity—Is it Really the Gluten?

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Abstract and Introduction

Abstract

Gluten-free diets are increasing in popularity among consumers and fueling a global market of gluten-free products. A gluten-free diet is the only treatment for celiac disease (CD). However, many patients are self-reporting and suspecting "gluten sensitivity" after gastrointestinal symptoms, such as bloating, abdominal pain, or diarrhea, resolve on a gluten-free diet without formal evaluation testing for food allergies or CD. The terms related to gluten and/or wheat intolerance, nonceliac gluten sensitivity or wheat sensitivity, CD, and wheat allergy can be confusing. These forms of intolerance combined affect approximately 10% of the United States population. In this article we clarify the range of gluten and/or wheat disorders, clinical features, diagnosis, and management.

Introduction

The American public is embracing the gluten-free diet, fueling a global market of gluten-free products approaching sales of $4.2 billion in 2012, up from global sales of $2.6 billion in 2010.[1] The media attention has exploded with magazine and newspaper articles, television segments, and advertising espousing the benefits of gluten-free diets. The global food company, General Mills, offers more than 300 gluten-free products, including their popular brands, Betty Crocker and Pillsbury. Walgreen's, Fresh Direct, and Drugstore.com all carry a variety of gluten-free packaged food products from cookies and crackers to canned soups, snack bars, and juices. In a recent market research poll of consumers, 30% of adults claimed cutting down on or avoiding gluten completely.[2] An online nationwide survey of 1,881 adults found that the top reason for buying gluten-free foods and beverages was a perception that they are "generally healthier."[3] In day-to-day practice, nurse practitioners (NPs) encounter clinical complaints, both gastrointestinal (GI) and non-GI, that are being attributed to the ingestion of gluten. Is there suddenly an epidemic of celiac disease (CD)? Is it a fad diet? Or, is something else going on?

CD is an immune-mediated disorder triggered by gluten in genetically predisposed individuals. CD is 4 times more common now than 50 years ago and affects about 1 in 100 people, with serious complications if untreated.[4] Undiagnosed or poorly treated CD has been associated with osteoporosis, iron-deficiency anemia, miscarriage, liver disease, and an increased risk for malignancies.[5,6] With CD, individuals cannot tolerate gluten and the role of gluten is clear. Some individuals cannot tolerate even minute amounts of gluten. The only treatment is strict adherence to a gluten-free diet (GFD), which requires significant patient education, motivation, and follow-up.[5] One of the most common reasons for a lack of response is inadvertent gluten ingestion.[5] (For an overview of CD, see *JNP*, Volume 7, Issue 7, July/August 2011).

Although CD affects up to 1% of the United States population, an entity known as nonceliac gluten sensitivity (NCGS) is estimated at between 0.55% and 6%.[7,8,9] NCGS manifests as GI and/or non-GI symptoms, which occur after ingestion of gluten and improve after gluten withdrawal from the diet. Patients often self-report and suspect "gluten sensitivity" after GI symptoms, such as bloating, abdominal pain, or diarrhea, resolve on a gluten-free diet without formal evaluation testing for allergies or CD.[10] Individuals are increasingly adopting a GFD on their own without the advice of their physician or health provider. A major concern is the risk of misdiagnosis. The reported improvement in symptoms by some patients may mask other conditions like inflammatory bowel disease or intestinal lymphoma. Another issue of concern is that a gluten-free diet, without the proper knowledge or supervision, can be low in fiber, high in fat and calories, and low in vitamins and minerals.[11,12] NPs can provide education on the wide range of symptoms, facilitate testing and diagnosis, discuss appropriate treatment plans, and play a role in optimal self-management.

What is NCGS?

NCGS is an entity distinct from CD and is currently defined as a nonallergic and non-autoimmune condition in which the consumption of gluten can lead to symptoms similar to those seen in CD.[8] Although it can occur at any age, gluten sensitivity seems to be more frequent in adults than in children and more prevalent in females than in males.[13] The pathogenesis of this condition remains unclear, but possible roles of the innate immune system and intestinal permeability are indicated.[8,14] The symptoms of bloating, abdominal pain, diarrhea, and constipation may also seem similar to irritable bowel syndrome, but more often with non-GI symptoms (headache, "brain fog," fatigue, skin disorders such as eczema or rash, and joint pain) (). More severe neurologic and psychiatric conditions have also been reported to be associated with gluten sensitivity, but data are insufficient and the topic remains controversial.[15]

Table 1. Signs and Symptoms of Gluten/Wheat-related Disorders

	Nonceliac "Gluten Sensitivity"	**Celiac Disease**	**Wheat Allergy**
Gastrointestinal	Abdominal pain Bloating Nausea Diarrhea Constipation	Abdominal pain Diarrhea Constipation Weight loss Vomiting Pale, foul-smelling, or fatty stool	Abdominal pain Abdominal cramps Vomiting Diarrhea Nausea
Non-gastrointestinal	Headache Fatigue Brain fog or "foggy mind" Joint and muscle pain Numbness in the hands and feet Depression Eczema and/or rash	Unexplained iron-deficiency anemia Headache Fatigue Bone or joint pain Brain fog Tingling or numbness in hands and feet Ataxia Dermatitis herpetiformis Osteoporosis or bone loss Depression Anxiety	Dizziness or light-headedness Difficulty breathing, Swelling, itching, irritation of the mouth or throat Eczema Hives Asthma Rhinitis Itchiness Angioedema

		Seizures Missed menstrual periods Infertility or recurrent miscarriage Dental enamel defects Aphthous stomatitis	Anaphylaxis Headache

Data from National Institute of Diabetes and Digestive and Kidney Diseases,[6] Sapone et al,[8] National Institute of Allergy and Infectious Diseases,[40] and Scibilia et al.[49]

Differences Between CD and NCGS

CD is an autoimmune disorder and disease of malabsorption that occurs in genetically susceptible individuals.[8] CD is associated with specific human leukocyte antigen (HLA) class II genes, known as HLA-DQ2 and HLA-DQ8.[8] HLA-DQ2 is found in up to 90% to 95% of patients with CD, whereas most of the remaining patients have HLA-DQ8.[16] With CD, the ensuing inflammatory response in the small intestine leads to mucosal villous atrophy, crypt hyperplasia, and lymphocyte infiltration.[15] Unlike CD, the small intestine biopsy in NCGS is usually characterized by normal mucosa or a mild increase in intraepithelial lymphocytes.[14] Based on current evidence, it appears that NCGS does not have a strong hereditary basis, is not associated with malabsorption, and does not have an increased risk for long-term complications, such as autoimmune disorders or intestinal malignancy.[5]

Diagnostic Testing for CD

For CD, serum IgA endomysial antibodies (EMA) and tissue transglutaminase (tTG) antibody testing have the highest diagnostic accuracy.[17] Immunoglobulin A (IgA) anti-tTG antibody testing is the preferred method for detection of CD in individuals over the age of 2 years.[5] Positive celiac serologic testing *on a gluten-containing diet* and endoscopy with duodenal biopsy with villous atrophy consistent with CD will confirm the diagnosis of CD.[5] For NPs, it is important to emphasize to patients that they must be ingesting gluten to test for CD. If a patient has started a gluten-free diet on their own for several weeks before testing, then the tests to diagnose CD may be negative and unreliable. If CD is still suspected, a gluten challenge may be done and tests repeated. For CD, the classic gluten challenge has been to consume at least 10 g of gluten (the equivalent of 4 slices of bread) per day for 6 to 8 weeks,[5,18] but a recent CD study suggested the gluten challenge may be shortened to 2 weeks with doses of 3 grams (1 slice of bread) per day.[19]

Diagnostic Testing for NCGS

For NCGS, there is currently no specific serologic marker.[8] Primary-care NPs need to be aware of the range of GI and non-GI clinical presentations and refer to appropriate specialists if necessary. The diagnostic process involves exclusion of CD and wheat allergy.[8] This involves detailed history-taking and clinical findings that include: negative immunoallergy tests to wheat by normal specific IgE; negative CD serology (anti-EMA and/or anti-tTG) in which IgA deficiency has been ruled out; normal duodenal histopathology; and the possible presence of biomarkers of native gluten immune reaction, anti-gliadin antibodies (AGA^+). In addition, patients present with clinical symptoms that can overlap with CD or wheat allergy symptoms, and patients show a resolution of symptoms when started on a GFD.[8] Although positive tests for deamidated gliadin antibodies, AGA-IgA, and IgG may occur in 50% of cases and provide some support for suspicion of NCGS, specificity and sensitivity have not been established.[13]

If symptoms do go away while on a GFD, the patient should undergo a gluten challenge to confirm. A gluten challenge may begin with one regular cracker or a one-quarter slice of regular bread; this is doubled every 1 to 3 days until significant symptoms develop or until one is eating the equivalent of 4 slices of bread or 2 cups/servings of pasta per day.[20] However, many patients often refuse to return to gluten if they have already started a GFD on

their own and have had symptom relief.

Nonceliac Gluten or Wheat Sensitivity: Is it the Gluten or the Wheat?

For individuals with NCGS, it is not entirely clear whether gluten is the sole responsible agent, as wheat contains other components that may induce symptoms.[21] Gluten is the main storage protein contained within the germ of wheat grains, which provides the elasticity in dough. Gluten is a complex mixture of proteins, mainly gliadin and glutenin. Proteins similar to gliadin found in wheat exist as secalin in rye and hordein in barley, and are collectively referred to as "gluten."[22] Gliadin binds to CXCR3 (a chemoreceptor) and leads to MyD88-dependent zonulin (protein that modulates intestinal permeability) release and increased intestinal permeability.[23] One recent study showed that gliadin did not induce any mucosal inflammation in patients with NCGS.[24]

Gluten is found mainly in foods, yet it can also be found in many commercially available food products (used as a protein filler). It may also be hidden in modified food starch, preservatives, and stabilizers made with wheat (). Gluten may also be found in everyday and unexpected products, such as medicines, vitamins, and lip balms.[6] Even products specifically targeted to dietary treatment of CD may contain small amounts of gluten proteins, either because of cross-contamination or because of the presence of wheat starch as a major ingredient.[25]

Table 2. Overlooked Foods and Other Products That May Contain Gluten and/or Wheat

Foods	Condiments/sauces/gravies	Beverages	Others	Drugs[a]
Wheat (in any form)[b] Barley (in any form)[c] Rye (in any form) Croutons Panko (breadcrumbs) Imitation bacon Imitation seafood, such as artificial crabmeat in sushi Batter, breading, coating mixes in fried fish, chicken wings Tortillas Soup bases—bouillon	Barbecue sauce Soy sauce Marinades Salad dressing Brown rice syrup	Nondistilledgluten-containinggrain (wheat, barley, rye, malt), alcoholicbeverages andvinegars, such asbeers, ales, lagers, and maltbeverages Flavored coffee/teas/tea mixes (flavorings	Craft supplies, such as play dough, paper mache, finger paints (may contain wheat flour) Communion wafers Lip gloss/lip balms/lipsticks ingredients: • Hydrolyzed wheat protein • Hydrolyzed wheat starch • Hydrolyzed wheat gluten • Triticum vulgare • Wheat	Fillers or excipients: • Wheat • Modified starch (source not specified) • Pregelatinized starch (source not specified) • Pregelatinized modified starch (source not specified) • Dextrates (source not specified) • Dextrimaltose (when barley malt is used)

cubes, cream-based soups (flour as a thickener) Processed luncheon meats Energy and snack bars Pickles (some pickling process may include malt vinegar) Candy, such as licorice and malted milk balls		may contain malt/barley)	germ oil • Wheat germ extract • Oat kernel flour • Avena sativa • Barley extract • Hordeum vulgare • Secale cereal	• Caramel coloring (when • barley malt is used) • Dextrin (source not specified, but usually by corn or potato)

[a]Drugs and over-the-counter medications, including vitamin, mineral, and herbal supplements.

[b]Einkorn, emmer, bran, durum, graham, wheatberries, farro, kamut, matzoh, semolina, spelt, bulgur, couscous, farina, triticale, orzo, udon, seitan, spelt.

[c]Brewer's yeast, malt, malt extract/syrup/flavoring, malt vinegar. Data from American Celiac Disease Alliance,[50] Celiac Disease Foundation,[51] American Society of Health Pharmacists,[52] and Thompson and Grace.[53]

Although the term "nonceliac gluten sensitivity" is used in the current literature, it may be possible that nongluten proteins of wheat are partially, or wholly, responsible for the associated symptoms.[21,26] Nongluten proteins, such as wheat amylase trypsin inhibitors, which are enriched in wheat and other related cereals, may trigger the innate immune response and induce intestinal inflammation.[27] The lectin, wheat germ agglutinin, may also have pro-inflammatory effects and increase intestinal permeability.[28] Hence, the term "nonceliac wheat sensitivity" has also been suggested and some researchers hypothesized that patients may actually have a non–IgE-mediated food allergy.[26,29] The lay press has focused on possible theories of modern wheat strains and hybrids, although scientific evidence is lacking, and this remains a controversial topic.[30] Currently, there is no genetically modified wheat commercially grown or approved in the US.

Another possibility is a family of poorly absorbed dietary short-chain carbohydrates known as FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols). FODMAPs are found in a variety of foods, including those containing lactose, fructose, fructans, galactans, and polyols (sorbitol, mannitol, and xylitol). Wheat and rye are common foods high in FODMAPs, as are milk, some fruits (eg, apples and watermelons), vegetables (eg, onions, garlic, and asparagus), and legumes (eg, lentils and chickpeas). FODMAPs are osmotic and, with their rapid fermentability, can lead to excessive fluid and gas accumulation and cause distention of the intestine, leading to functional GI symptoms.[31] Examples of low FODMAP food choices include almond and rice milk (instead of high FODMAP cow, sheep, and goat milk) or rice, oats, and quinoa (instead of wheat or rye). A low FODMAP diet is strict to follow and not intended to be a prolonged diet plan. It is best done with the help of an experienced dietitian as there is no data on nutritional adequacy or long-term consequences. The concept that FODMAPS may alter the intestinal microbiota composition has been suggested, but this remains to be determined.[32,33]

Low FODMAP diets for patients with irritable bowel syndrome have been associated with improvements in abdominal pain, bloating, gas, and diarrhea.[34,35,36] Reduced intake of foods with high FODMAPs may hold potential for those with similar GI symptoms, including NCGS. A recent study in patients with self-reported NCGS showed that GI symptoms consistently and significantly improved during reduced FODMAP intake, and there was no evidence of effects of gluten in patients with NCGS on a low FODMAP diet.[37]

Wheat Allergy

Studies in the US suggest that up to 6% of children and 4% of adults have food allergies.[38,39] Wheat is a food that commonly causes an allergic reaction, particularly in infants and children. One or more of the wheat proteins, albumin, globulin, gliadin, or gluten, can cause an allergic reaction involving IgE antibodies. The reactions usually take place within a few minutes to several hours after exposure to the allergen.[40] The symptoms may include: itching in the mouth; swelling of lips and tongue; hives; eczema; rhinitis; tightening of the throat or trouble breathing; drop in blood pressure; GI symptoms, such as vomiting, diarrhea, or abdominal cramps and pain; and, if severe, anaphylaxis.[40] Skin prick tests and allergen-specific IgE testing are useful in diagnosis, along with medical history, clinical presentation, and possible food challenge. For wheat allergy, strict avoidance of wheat and wheat products is necessary.

Although classic IgE-mediated allergic reactions are most common with wheat, non-IgE-mediated reactions to wheat may occur, usually with a slower onset and symptoms generally confined to the GI tract.[41,42] Wheat allergy and gluten sensitivity are both food intolerances, but classic wheat allergy should not be confused with NCGS.

Clinical Management

The lifestyle transition to a gluten-free or any restricted diet is often overlooked and can be confusing.[43] For most patients, upon initial diagnosis, they are given a list of foods to remember to avoid or limit and are left to manage this condition largely on their own. Extensive education and referral to a registered dietitian with expertise in social and emotional adaptation to living with food intolerances are vital. Some patients may consume processed or prepared gluten-free products, which can be loaded with excessive calories, fat, salt, and sugar, and may contribute to additional risk factors such high cholesterol and high blood pressure. Many fortified breads and cereals in the US are sources of B vitamins and dietary fiber. When patients omit gluten from their diet without proper substitutions, there exists the possibility of nutritional deficiencies.

Gluten and wheat are often interchanged and confused. A food labeled "wheat-free" may be safe for someone with wheat allergy but not necessarily for someone with NCGS or CD. For example, a person with a wheat allergy may tolerate bread labeled "wheat-free," but it may contain other grains, such as barley, rye, or malt, which a person with NCGS or CD may not tolerate. Identification and labeling of gluten-free foods is a significant issue in adhering to a GFD, particularly in those with CD. In 2013, the US Food and Drug Administration issued a federal ruling that standardized the definition of "gluten-free" claims across the food industry for voluntary labeling. The ruling requires that, to use the term "gluten-free" on its label, the food contains none of the following:

1. An ingredient that is any type of wheat, rye, barley, or crossbreeds of these grains.
2. An ingredient derived from these grains and that has not been processed to remove gluten.
3. An ingredient derived from these grains and that has been processed to remove gluten, if it results in the food containing 20 or more parts per million gluten.[44]

The deadline for compliance is August 2014. Because food manufacturers may frequently change product ingredients, it is always important to double check product labels each time a food is purchased, as the gluten-free status of a particular product may change at any time. The NP should also carefully review any of the patient's prescription and over-the-counter medications for gluten and/or wheat content.

For most individuals, in addition to the increased time and effort required to read and understand packages and product labels, difficulty arises with the increased costs. A 2007 study determined that, overall, gluten-free products

are far more expensive than comparable regular gluten-containing products, by a rate of 2- to 3-fold. In addition, the availability of gluten-free products was shown to vary between stores and regions.[45]

Because the role of gluten is still unclear for patients with NCGS, it is necessary to differentiate the triggers of their symptoms. A food/symptom diary can help highlight triggers for both patient and provider, as well as monitor compliance of dietary advice. For example, a patient may keep a diary while following a low FODMAP diet for 6 weeks, and then high FODMAP foods may be gradually reintroduced one at a time in small amounts to identify foods that could be triggers to symptoms of gas or bloating. NPs need to be aware that what benefits the patient may be a process of trial and error through gluten withdrawal, wheat exclusion, or a low FODMAP diet.

In guiding patients, it is important to emphasize that it is not only about avoiding gluten, wheat, and/or high FODMAPs, but maintaining optimal nutritional intake and dietary habits over the long term. The patient's weight needs to be carefully assessed at the time of diagnosis and initiation of a diet/lifestyle change and monitored for normalization of weight if under- or overweight. A gluten-free, wheat-free, or low FODMAP diet can be a well-balanced one if care is taken with food choices. Emphasize the variety of foods allowed and substitutions that will make the diet and/or lifestyle seem less restrictive, while highlighting the abundance of naturally gluten-free/wheat-free foods such as fruits and vegetables. Discuss the importance of nutritional issues (iron, vitamin B deficiencies, and fiber) and cross contamination. Demonstrate clear reading of labels, shopping points, and reliable sources of product information on the web and support groups. Encourage the pleasure of dining out with friends and family with easy restaurant and travel planning tips. Education can be tailored by providing appropriate meal-planning guidelines, with simple, cost-sensitive recipes to rely less on processed foods.

Living with any chronic condition requires demands and discipline on the individual due to the need to learn self-management. Among patients with CD, up to 60% are partially nonadherent to a GFD.[46] In 1 study, 51% of participants reported a minimal level of stress and 25% reported a moderate level of stress with regard to adherence to a GFD.[47] NCGS patients may require psychosocial support because the symptoms can be vague and the research is still limited. Thus, follow-up is paramount, as it remains unclear as to the duration of maintaining a GFD and tolerance amounts with NCGS. Patients with NCGS may be able to test their exposure to gluten as needed to avoid symptoms.[48] NPs can play a pivotal role by encouraging patients to return for regular follow-up in person, over the phone, or by setting up structured surveys.

Patients are increasingly discussing their "gluten sensitivity" and, with the recent interest in gluten-free diets, the topic of gluten-related disorders is often poorly understood. The diverse clinical presentation of NCGS with symptoms similar to other conditions adds to the confusion, so NPs need to be knowledgeable about how to diagnose and manage these patients. As the literature on NCGS is still evolving, NPs need to stay up to date on this clinical entity and best guide their patients as the standards of care based on scientific evidence become firmly established.

Sidebar

Resources

Academy of Nutrition and Dietetics Web site. http://www.eatright.org.

Celiac Disease Foundation Web site. http://www.celiac.org.

Gluten Intolerance Group Web site. http://www.gluten.net.

Gluten Free Drugs Web site. http://www.Glutenfreedrugs.com.

National Foundation for Celiac Awareness. Celiac Central Web site. http://www.celiaccentral.org.

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. National Digestive Diseases Information Clearinghouse Web site. http://www.digestive.niddk.nih.gov.

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