Gut Grief: The Truth About Gluten Sensitivity

In the past decade, gluten sensitivity has captured the nation's attention, yielding a niche market for gluten-free products and questions for clinicians, especially about the somewhat ambiguous disorder known as *nonceliac gluten sensitivity*. This article will enable you to better diagnose the disorders and differentiate between fads and facts.

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IN THIS ARTICLE

Gluten has become a dietary pariah (see "So What Is Gluten?"). The American public's enthusiasm for a gluten-free diet has spurred a gluten-free food industry that has grown, on average, 34% per year since 2009, with annual sales predicted to reach an impressive $15.5 billion by 2016.[1] This trend coincides with the national media's intense focus on gluten sensitivity (GS), as well as best-selling books such as *Wheat Belly* and *Grain Brain*.[2,3]

Gluten-free food products, once relegated to boutique food shops and limited shelf space, now fill sections in large grocery and drugstore chains. Many restaurants have added gluten-free items to their menus (although gluten-free Big Macs have been available in Finland for more than 20 years).[4] Only celiac disease (CD), which affects approximately 1% of the American population, requires strict gluten avoidance; yet more than 30% of US adults report having reduced their gluten intake, most claiming they did so to promote a "healthier" diet or support weight loss.[1]

PREVALENCE AND PATHOLOGY OF GS DISORDERS

Gluten sensitivity, once used to denote CD alone, now includes a group of gluten-intolerant conditions unrelated to CD—primarily nonceliac gluten sensitivity (NCGS) and wheat allergy (WA)—although the nomenclature is likely to change. While these disorders differ in underlying pathogenesis, each demonstrates a resolution of symptoms when the patient is placed on a gluten-free diet. Of these GS disorders, only NCGS lacks clarity with regard to incidence, diagnosis, and pathology.[5]

Celiac Disease

Celiac disease is an autoimmune, T-cell–activated disease that manifests in genetically susceptible individuals (with gene variants *HLA-DQ2* and *HLA-DQ8*); it can occur at any age. The incidence of CD in the US has increased from 1 in 500 in 1974 to a current estimate of 1 in 100, although many with CD are believed to be undiagnosed.[4,6]

CD is the only autoimmune disease for which a trigger is known: gluten. Suspicion for CD should be heightened if the patient or a family member has a history of autoimmune disease. Nearly one-

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quarter of patients with CD will develop an autoimmune thyroid disorder.[7]

In CD, a significant enteropathy occurs in response to gluten intake, characterized by inflammation of the proximal small intestine. Individuals with CD produce tissue transglutaminase (tTG) or transglutaminase 2 (TG2) autoantibodies, resulting in gluten-specific CD4+ Th1 T-cell activation and an immune response that causes an upregulation of zonulin.[8] Zonulin, a protein that modulates the permeability of the intestinal mucosal wall, is believed to play a role in "leaky gut syndrome" and autoimmune disease. The upregulation of zonulin in CD creates a disruption of the intestinal mucosal lining, causing villous mucosal atrophy and impairment of intestinal permeability and absorption.[9]

Nonceliac Gluten Sensitivity

NCGS is a poorly understood condition first described in the 1980s and recently "rediscovered" as a gluten-related disorder.[10] Its actual prevalence is unknown because of unclear diagnostic criteria but is likely much higher than that of CD.[1,4] Unlike CD, there does not appear to be a genetic predisposition for NCGS, nor is it believed to be an autoimmune disorder. However, research does suggest that NCGS may increase the risk for autoimmune diseases, such as Hashimoto thyroiditis. NCGS can occur at any age but appears more commonly in adults than children, and in women than men.[4]

A small but meticulous 2013 study raised doubt about NCGS as a specific gluten-related disorder.[11] The results suggested that NCGS should be viewed as a variant of irritable bowel syndrome (IBS), not triggered by gluten but by poorly absorbed carbohydrates found in wheat known as *fructans* and *galactans,* and perhaps by other foods containing fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPS). It is believed those with diarrhea-prone IBS are particularly sensitive to gluten.[11] As a result, ardent claims of NCGS and improved health with gluten-free diets in those without CD are often discounted.

More recent research findings refute this conjecture, suggesting that NCGS is likely a reaction to *other* proteins within the gluten family, such as beta-, gamma-, or omega-gliadin, glutenin, wheat germ agglutinin, gluteomorphin, and deamidated gliadin. Development of GS is believed to be triggered by such factors as intestinal infections, altered microbiota, or food additives.[4]

So What Is Gluten?

Although the gluten family comprises nearly 200 proteins, *gluten* generally refers to a protein component (gliadin and glutenin) of cereal grains from the Triticeae tribe of grasses—primarily wheat, barley, and rye. It is relatively indigestible. Gluten is important in baking, as it provides elasticity and other characteristics to dough.

Over the past 100 years, plant breeding has increased the "gluten strength" in many wheat varieties. Additionally, vital gluten (gluten extracted from wheat flour) is added to many foods, leading to triple the gluten consumption in this country since 1977. It is estimated that 80% of this nation's vital gluten is imported from Australia, Europe, Canada, and China. Gluten is also a food additive found in a variety of products, such as soups, sauces, potato chips, candies, meat products, and ice cream—as well as pills, dietary supplements, and livestock feed (including farmed fish).[4]

Source: Brown. *Expert Rev Gastroenterol Hepatol*. 2012.[4]

In any event, the pathogenesis of NCGS remains unclear, and it does not present with the diagnostic antibodies or inflammatory enteropathy seen in patients with CD. Despite this, NCGS does present with gastrointestinal (GI) and extra-intestinal symptoms similar to those of CD.

Wheat Allergies

Wheat is frequently implicated in food allergies, especially in infants and children. The incidence of WA is not known, although up to 4% of adults and 6% of children are estimated to have food allergies. In WA, there is an IgE antibody–mediated reaction to one or more of the wheat proteins (albumin, gliadin, globulin, gluten) that occurs within minutes to hours after exposure to the offending food. Many children with IgE-mediated allergies may "outgrow" them with time.[12]

CLINICAL PRESENTATION OF GS

Although CD is a disorder associated with the GI system, the "classic" GI symptoms of bloating, flatulence, diarrhea, and/or constipation are often absent (*silent CD*), especially in older individuals. It is for this reason that the diagnosis of CD is easily missed.

Delaying diagnosis can have serious health consequences, as CD is associated with significant morbidities, such as malnutrition (worse in children), iron-deficiency anemia, neuropsychiatric aberrations (depression, anxiety, attention-deficit, and ce-

TABLE 1
Selected Symptoms of Celiac Disease

Gastrointestinal (GI)
Bloating
Constipation
Cramping
Diarrhea
Gas
Liver disease
Nausea
Non-Hodgkin lymphoma, other GI malignancies
Vomiting
Malabsorption
Anemia
Aphthous ulcers
Bone/joint pain
Dental defects
Failure to thrive in children
Fatigue
Muscle cramps
Osteopenia/osteoporosis
Weakness
Weight loss
Skin
Dermatitis herpetiformis
Reproductive
Infertility
Late menarche/early menopause
Miscarriage
Neurologic
Cerebral ataxia (cerebellar atrophy)
Concentration and memory problems
Dementia
Headaches or migraines
Mood swings, depression, anxiety
Peripheral neuropathy
Seizures

Sources: Capili et al. *J Nurs Pract*. 2014[1]; Rubio-Tapia et al. *Am J Gastroenterol*. 2013.[6]

rebral ataxia), osteoporosis, lymphoma, and death (see Table 1).[4,13] CD may also present with dermatitis herpetiformis, a chronic vesicular rash, seen most often in adult males.

The role of gluten in the development of autism spectrum disorders or schizophrenia, though not proven, remains hotly debated, especially as close biochemical links are now recognized between the gut and the brain. It is clear, however, that gluten intake in severely gluten-sensitive individuals can directly affect mood and brain function. Most CD-associated morbidities will resolve after one year of complete gluten avoidance.[1,13]

Prominent symptoms of NCGS occur soon after gluten ingestion and disappear within days to weeks of gluten avoidance. The classic NCGS presentation combines IBS-like symptoms, such as abdominal cramps, bloating, diarrhea, and constipation, with systemic manifestations that include "brain fog," fatigue, headache, joint and muscle pain, peripheral numbness, skin rash, aphthous stomatitis, anemia, and depression or anxiety. As with CD, GI symptoms usually predominate in children and abate with gluten avoidance.[14,15]

Allergic reactions to wheat will present within minutes to two hours of wheat exposure and may manifest with pruritic rash, hives, swelling of the lips or tongue, rhinitis, abdominal cramps, vomiting, diarrhea, constipation, and/or anaphylaxis. Subtle reactions may make diagnosis difficult.[12]

DIAGNOSTIC STUDIES FOR GS

The effectiveness of diagnostic testing for CD has been well established. Testing for antitissue transglutaminase antibodies (tTG-IgA) is the preferred laboratory test for CD, with a sensitivity of 93%, specificity of 98%, and few false-negative results. The endomysial antibody (EMA-IgA) test, though highly specific for CD, lacks the sensitivity of tTG-IgA. Newer antibody tests, such as deamidated gliadin peptide IgA and IgG, have not proven superior in detecting CD. Genetic testing for *HLA-DQ2* and *HLA-DQ8* may also be performed, but many people carry the gene without ever developing CD.[13]

To improve the reliability of CD antibody tests, the patient should have consumed gluten regularly for at least one month prior to testing. If the patient has been on a gluten-free diet for several weeks, then a *gluten challenge* should be done: The patient would be instructed to consume at least 3 g/d of gluten (two slices of bread) for a minimum of two weeks (versus eight weeks in previous protocols), after which the celiac antibody tests would be repeated.[16]

If these antibody test results are negative but the suspicion for CD remains high, an endoscopy with a duodenal biopsy should be performed. The appearance of villous atrophy would confirm the diagnosis of CD.[1,13,16]

Unlike CD, there are currently no reliable di-

TABLE 2
Selected Food and Products Containing Gluten

Important message: When in doubt, go without!

Grains (found in baked goods, cereals, pasta)
- Barley, including barley malt
- Bran
- Bulgur
- Communion wafers
- Cracked wheat
- Durum
- Farina
- Faro
- Kamut
- Matzo
- Oats (only if grown side by side with wheat)
- Orzo
- Semolina
- Spelt
- Wheat bran
- Wheat germ
- Wheat starch

Other foods processed with wheat starch, dextran, or barley malt
- Any product containing brown rice syrup
- Beer, ales, lagers (note: distilled alcohol and wine are gluten free)
- Bouillon cubes
- Breaded foods
- Candy (malted milk balls, licorice)
- Canned soup and broth
- Couscous
- Energy bars/granola bars
- Farmed fish (because of their diet)
- Frozen or canned vegetables in sauce
- Imitation bacon bits, artificial seafood
- Malt vinegar (other vinegars are gluten free)
- Malted milkshakes, some ice cream
- Pickles (because malt vinegar may be used)
- Prepared gravies
- Prepared sauces, marinades, salad dressings
- Processed meats (eg, hot dogs, lunch meat)
- Potato chips
- Restaurant or fast-food French fries
- Self-basting chicken, turkey
- Some cheesecake fillings
- Soy sauce (unless made with tamarind)
- Tabouli
- Tortilla chips

Nonfood items with gluten-containing filler or coating
- Herbal or nutritional supplements
- Lipstick, lip gloss, lip balm
- Play-Doh®
- Some prescribed or OTC medications

Gluten-safe foods
- Beans, lentils, and other legumes
- Fresh (not farmed) fish and seafood
- Fresh, unprocessed meat and poultry
- Fruits and vegetables
- Grains: rice, amaranth, potato, beans, tapioca, sorghum, quinoa, buckwheat, corn, chia, flax, cassava, and nut flours
- Nuts

Cross-contamination risk (unintentional contact)
- Colanders
- Cutting boards and baking sheets
- Flour-sifters
- Reused utensils (especially knives used to spread peanut butter, mayonnaise, etc)
- Toasters

Note: Gluten can remain airborne for hours after gluten flour has been used for baking.
Sources: Capili et al. *J Nurs Pract*. 2014[1]; Celiac Disease Foundation. Sources of gluten.[17]

agnostic tests for NCGS, although some researchers suggest testing for IgG antigliadin antibodies (AGA); NCGS is currently a diagnosis of exclusion.[7] In NCGS, celiac antibodies will be negative and the duodenal biopsy will demonstrate only mild inflammation without the mucosal atrophy of CD. As with CD, patients affected by NCGS will also test negative for the wheat allergy IgE response.

Another option is a gluten challenge. The patient is instructed to follow a gluten-free diet for six weeks and monitor for NCGS symptoms. If symptoms abate, a gluten-containing diet is then reintroduced and the patient is evaluated for the reemergence of NCGS symptoms. If symptoms are not reduced with a gluten-free diet, NCGS may be excluded. Newer GS laboratory tests will emerge that can assay more forms of gliadin antibodies, possibly aiding in NCGS diagnosis.[4,14]

To make a diagnosis of WA, skin prick tests and allergen-specific IgE testing are used, along with a medical history, clinical presentation, and possibly a food challenge.

MANAGEMENT OF GS

The hallmark treatment for GS, regardless of its causative factor, is a strict gluten-free diet (GFD). For

patients with CD, a 100% GFD is recommended for life. It is not yet known whether this lifelong duration is necessary for those with NCGS and WA, or if there is a safe threshold in these patients for gluten consumption. It is helpful for patients to keep a food diary, noting what they eat and how that affects the appearance or attenuation of symptoms.

Transitioning to a gluten-free lifestyle can be confusing, frustrating, and expensive for patients. Removing gluten from the diet is also challenging, as wheat is the predominant grain consumed in this country. Barley and rye (less so oats) also contain gluten, leaving limited alternatives, like amaranth, corn, quinoa, rice, and tapioca. Unlike CD and NCGS, WA requires only elimination of wheat-containing products; thus, it may not be necessary for affected patients to avoid barley and rye.[1,4]

Extensive patient education is important for success. Referral to a knowledgeable nutritionist is ideal but not always practical. Lists of foods to avoid on a gluten-free diet are readily available, but important points should be stressed, including how to read food labels. For example, the term *wheat-free* does not mean *gluten-free* (see Table 2, page S33).[1,17] As of August 2014, the food industry, by law, can only claim a product is "gluten-free" if it contains no more than 20 parts per million (ppm) of gluten.[1]

Due to malabsorption issues, it is recommended that patients with CD be monitored for micronutrient deficiencies (ie, iron, B_1, B_6, B_{12}, and zinc), and osteopenia/osteoporosis (dual-energy x-ray absorptiometry [DEXA] at the time of diagnosis) and be offered fertility counseling. What patients with GS need most of all are informed, caring providers to help guide them through diagnosis and treatment.[6,13]

CONCLUSION

Gluten-free diets are increasing in popularity, and many people who do not have CD claim improved health and vitality when they avoid gluten. Much is known about the incidence and pathogenesis of the gluten-associated disorders of CD and WA. Far less is known about the controversial disorder of NCGS. The symptoms and morbidities associated with NCGS have been well documented and present a curious mix of CD and IBS, yet neither condition fully accounts for the pathogenesis of NCGS. While CD is linked to more serious morbidities (including death if the disease is not readily diagnosed), NCGS and WA do produce significant manifestations and risks.

Research into NCGS remains limited and conflicting, and biomarkers for the disorder are not yet known. Unsupported or not, many patients attribute mood disorders, pain, and chronic ills to gluten intake and seek input from their health care providers. Rather than dismiss their claims, clinicians can provide pertinent instructions on a gluten-free lifestyle and healthy diet, and encourage the use of food diaries to document food-symptom associations. Gluten sensitivities are not benign and "going gluten-free" may be of great benefit for many patients with GS. That's a fact. **CR**

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