GLUTEN-RELATED DISORDERS: SYMPTOMS, DIAGNOSIS AND MANAGEMENT

Patricia Jackson Allen highlights the symptoms nurse practitioners need to be aware of to help screen and support patients with gluten-related conditions

Abstract
Gluten intolerance is thought to affect many people worldwide and results in a myriad of symptoms that adversely affect quality of life. Those with an innate or adaptive immune-mediated enteropathy to gluten (coeliac disease), an antigen-triggered allergic reaction to gluten (gluten allergy) or sensitivity to ingested gluten-containing foods (non-coeliac gluten sensitivity) have gluten-related disorders. Signs and symptoms of these disorders are often indistinguishable, but the pathogenic processes vary, with potential health consequences. The nurse practitioner must: have a high index of suspicion for gluten-related conditions in individuals with a history of gastrointestinal symptoms; assure appropriate screening and testing is undertaken; assist in establishing a gluten-free diet; and manage associated health conditions so that optimal health and quality of life can be attained.

Keywords
coeliac disease, gluten allergy, gluten-related disorders, non-coeliac gluten sensitivity, wheat allergy, nurse practitioner, primary care nurse

THE GASTROINTESTINAL (GI) system is the largest epithelial surface in the body and provides the greatest interface between the environment and the person's individual immune systems, both innate and adaptive. Ingested proteins, such as gluten, are digested in the small intestines. Lymphatic tissue in the small intestine and the intestinal intercellular tight junctions attempt to balance the development of gut immunity, protecting the individual from potentially harmful proteins, while allowing absorption and use of beneficial proteins and the development of gut tolerance.

A hypersensitive immune-mediated response to gluten can occur in genetically susceptible individuals, resulting in elevated immunoglobulin A (IgA), cellular inflammation and structural changes of the small intestine. An allergic response can occur due to an immunoglobulin E (IgE) mast cell response to a specific protein, such as gluten proteins, resulting in a hypersensitivity reaction.

In addition, dysregulation of the 'brain-gut axis', the role of serotonin, the neuroendocrine response and alterations in autonomic or central nervous system processing of information or stress can alter GI motility and contribute to increased sensitivity to visceral function, motility or pain that may be associated with gluten ingestion (McCance et al 2014).

Gluten-related disorders
Coeliac disease Coeliac disease (CD) is an autoimmune enteropathy of the small intestine precipitated by ingestion of gluten-containing foods in genetically predisposed individuals. Gluten-related proteins are found in wheat, rye and barley, and in many processed...
foods and food seasonings. These proteins, known as gliadins, are the external antigens that cause the innate and adaptive immune response resulting in CD (Lebwohl et al 2015).

Recent studies have identified dozens of genetic risk loci indicating CD is a polygenetic immune-based disorder (Lebwohl et al 2014, Ludvigsson et al 2014). Individuals with the human leukocyte antigen (HLA) DQ2 or DQ8, found in approximately 30% to 40% of people, have the genetic susceptibility for developing CD, but most do not. Interestingly, more than 60% of the genetic susceptibility loci for CD is shared with at least one other autoimmune condition, suggesting a shared autoimmune pathogenic process (Troncone and Discepolo 2014); and 30% of adults with CD has at least one other autoimmune condition, compared to 3% of the general population (Reilly and Green 2012).

When an autoimmune enteropathy occurs it causes inflammation of the mucosa, resulting in increased intra-epithelial lymphocytosis, crypt hyperplasia and characteristic histological atrophy of the villi reported as Marsh Stage 0-3 (Ludvigsson et al 2014). Atrophy of the villi results in reduced absorption of nutrients, leading to many of the clinical manifestations associated with CD. The inflammatory response to gluten results in the loss of the normal tight junction barrier of the mucosa, enabling the autoimmune response to be released into the systemic system. This results in extra-intestinal signs and symptoms, and an increased incidence of other autoimmune conditions (Bai et al 2012).

Triggers other than exposure to gluten in genetically susceptible people are being studied to explain the more than doubling of positive CD serum samples collected and tested over the past four decades (Ludvigsson and Green 2014). Dramatic increases in the prevalence of CD over a relatively short time do not support a change in the general population genetics, but some other unknown trigger that leads to serum conversion in individuals with the genetic susceptibility and gluten exposure (Lebwohl et al 2014).

Changes in the microbiome of the GI system or viral illnesses altering the immune response to gluten, the increased rate of caesarean births, early or delayed introduction of gluten in the diet of infants and wheat processing changes potentially altering the gluten protein complex and use of antibiotics have all been proposed as possible triggers resulting in the significant increase in seroconversion (Fasano and Catassi 2012, Lebwohl et al 2015). The increased rate of seroconversion (Fasano and Catassi 2012, Lebwohl et al 2015). While the estimated prevalence of CD in Europe and North America is 1%, there are regional variations: Finnish rates are as high as 2% to 2.8%, while Germans rates were only 0.3% for adults aged 30 to 64 when screened by tissue transglutaminase (tTg) antibody test (Mustalahti et al 2010).

Large surveillance studies in the Asia-Pacific region have not been reported, but smaller studies indicate a prevalence rate of 1:50 to 1:500 in Australia, Iran, New Zealand, Syria and Turkey (Cummins and Roberts-Thomson 2009). In contrast, CD appears to be extremely rare in Japan and has an unknown incidence in China, where consumption of wheat is on the increase (Cummins and Roberts-Thomson 2009, Yuan et al 2013).

Certain people are at higher risk of developing CD and should have regular screening regardless of symptoms: first degree and second degree relatives of people diagnosed with CD have a 10% and 5% incidence of developing CD respectively; people with other autoimmune conditions such as type 1 diabetes mellitus (2-5%), thyroid dysfunction (2-7%), autoimmune hepatitis (3-6%) or Addison’s disease all have increased risk of CD and should have serological screening every few years regardless of symptoms (Bai et al 2012). In addition, people with the genetic condition of Down’s or Turner syndrome have a 6% incidence of CD (Bai et al 2012).

Most people with CD have not been diagnosed. Reasons for the prevalence of undiagnosed CD are that it can occur at any age and has a wide clinical variability of symptoms. In classic CD, the symptoms are primarily gastrointestinal: diarrhoea, steatorrhoea, malabsorption, weight loss, abdominal discomfort and bloating (Bai et al 2012). Classic CD was initially thought to be a paediatric condition; affected children appeared healthy for the first year of life, but when wheat-containing cereals were introduced into their diet they developed progressive GI symptoms of bloating, muscle wasting, poor weight gain and irritability that only resolved with the removal of gluten products from their diet.

In non-classic CD, which can present at any age, the GI symptoms may be accompanied by extra-intestinal signs and symptoms, including fatigue, skin lesions such as dermatitis herpetiformis, iron-deficiency anaemia, headaches, dental hypoplasia, reduced bone density and unexplained infertility or pregnancy loss (Ludvigsson et al 2014). There are also individuals with asymptomatic CD who deny symptoms but have positive
serological testing and the presence of characteristic intestinal villous changes on small bowel biopsy. Often these individuals report a ‘new normal’ of feeling well on a gluten-free diet (GFD) and elect to continue treatment (Bai et al 2012).

**Gluten allergy** There are multiple wheat protein groups with varying allergic potential. These proteins can trigger an adaptive immune response that is cross-linked to IgE. This immunoglobulin response releases histamine from basophils and mast cells affecting, to varying degrees, the GI tract, skin and the respiratory tract in a similar fashion to cow-milk protein allergy (Sapone et al 2012). This IgE immune response does not require the presence of either HLA DQ2 or DQ8 and does not cause atrophy of the mucosa villous as occurs in CD.

The current incidence and prevalence of IgE-mediated gluten allergy is unknown. Research indicates that skin-prick-tests (SPT) and serum food allergen-specific IgE measurements may not be sensitive enough to measure allergic reactions occurring in the GI system in response to allergens such as wheat (Mansueto et al 2015). Studies in individuals diagnosed with irritable bowel syndrome (IBS), with symptoms of abdominal pain, bloating and diarrhoea but negative SPT to wheat or elevated wheat-specific IgE, determined that elimination diets for foods, most commonly wheat, milk and eggs, resulted in marked reduction of symptoms (Mansueto et al 2015). It is possible that gluten allergy is a more common cause of chronic GI symptoms than is currently recognised by standard testing measures. As with other allergies, there is often a family pattern of atopy and presence of multiple allergies in the affected individual.

Food allergies in adults often result in mild GI clinical manifestations that are difficult to diagnose (Ellis et al 2015). Symptoms in individuals with an elevated IgE to wheat include abdominal pain, diarrhoea, bloating, vomiting, cutaneous symptoms of eczema and pruritus, and respiratory symptoms of rhinitis and asthma (Lundin and Alaedini 2012). Baker’s asthma, or baker’s rhinitis, occurs when wheat flour or gluten-containing dust is inhaled and was a relatively common occupational health risk for bakers in the past (Tatham and Shewry 2008).

**Non-coeliac gluten sensitivity** Non-coeliac gluten sensitivity (NCGS) is a disorder characterised by intestinal and extra-intestinal symptoms correlated to the ingestion of gluten-containing foods in people who have been determined not to have either CD or wheat allergy (Catassi et al 2013, Mansueto et al 2015). There are no laboratory biomarkers specific for NCGS and the pathophysiology is unclear (Lebwohl et al 2015).

The incidence and prevalence of NCGS is unknown. Volta et al (2014) studied people referred to a gastroenterology centre for NCGS and found the most frequently associated disorders were IBS (47%), food intolerance (35%) and IgE-mediated allergy (22%). Since IBS is one of the most prevalent GI disorders, estimated to affect 12%-30% of the general population, the possible correlation or causation with gluten is important and needs further research (Mansueto et al 2015). A recent population-based convenience sample of over 1,000 people in England found 13% of the study population reported gluten sensitivity (0.8% with diagnosed CD), with 20% of the study population also fulfilling the Rome III criteria for IBS by questionnaire. Individuals reporting gluten sensitivity also reported a greater prevalence of anxiety, depression, chronic fatigue syndrome and food allergies/intolerances than other study participants (Aziz et al 2014).

Symptoms reported with NCGS are similar to those reported with IBS: abdominal pain, bloating, diarrhoea or constipation, and systemic symptoms including fatigue, headache, depression, anaemia, numbness in legs, arms or fingers, joint and muscle pain, dermatitis and ‘foggy mind’ (Sapone et al 2012, Mansueto et al 2015).

**Diagnosing gluten-related disorders**

Diagnosing gluten-related disorders is important for the management of conditions and determining appropriate follow up. Frequently, individuals with perceived gluten-related symptoms will eliminate gluten from their diet before diagnostic evaluations have begun. It is important for the primary care nurse or nurse practitioner (NP) to try to initiate diagnostic testing while the individual is still consuming a diet containing gluten.

**Diagnosing CD** The variability of symptoms and variable age at presentation of CD requires the NP to have a high index of suspicion for CD, identify individuals with a greater risk of CD by either family history or associated health conditions, and screen accordingly.

Serological screening for the autoimmune inflammatory response of the gut mucosa and villous to gluten ingestion has been possible for the past 20 years. The most commonly used screening tests measure elevated levels of IgA antibodies to human recombinant tissue transglutaminase (tTG IgA), anti-endomysial antibodies (EMA IgA),
Diagnosing gluten allergy

Obtaining a careful history of allergies in the patient and family and the perceived temporal relationship of symptoms associated with ingesting gluten are the first steps the NP must take in the diagnostic process. An initial screening for elevated wheat-specific serum IgE may result in a false-negative result, and referral to an allergist who can administer SPT with multiple wheat protein formulations is appropriate, especially in people with a history of other allergies (Fasano and Catassi 2012). These tests must be performed while the person is on a gluten-containing diet and not taking any allergy medications.

Due to the low sensitivity of many SPT wheat allergen solutions, and low specificity of in vitro specific IgE findings, the final diagnosis of gluten allergy is often made by controlled oral food challenge (Sapone et al 2012, Elli et al 2015). The person is placed on a GFD for a few weeks to determine the changes in perceived symptoms, then gluten-containing foods are given either at home or in a controlled clinical setting and symptoms monitored. Resumption of symptoms with the reintroduction of gluten is regarded as a positive challenge and diagnostic of wheat allergy, irrespective of the SPT and serum IgE findings. The NP should work closely with an allergist in making the diagnosis, remembering that often multiple food allergies are present.

Diagnosing NCGS

People with NCGS are often frustrated by the lack of a diagnosis when tests for CD and gluten allergy are negative. Better understanding of NCGS is difficult due to lack of objective diagnostic criteria and specific biomarkers (Lundin and Alaedini 2012). The prevalence of NCGS is unknown. Many individuals self-diagnose gluten sensitivity and initiate GFDs without evaluation by a health professional, which complicates diagnosis.

Currently, NCGS is diagnosed in individuals who have screened negative for CD and wheat allergy but have reduced clinical manifestations while on a GFD for six to 12 months, with relapse of symptoms with a gluten challenge for one month (Lundin and Alaedini 2012). It is recommended that the NP consults with a gastroenterologist when making the diagnosis of NCGS. Figure 1 is a proposed algorithm for the differential screening and diagnosis of gluten-related disorders.

Management of gluten-related disorders

The only currently approved treatment for gluten-related disorders is a GFD. For individuals with CD, even minuscule amounts of gluten can trigger an autoimmune response and therefore must be avoided. For people with gluten allergy or gluten sensitivity, gluten-containing foods should be avoided to control symptoms associated with ingestion, but absolute avoidance of all gluten, including in processed foods, seasonings, cosmetic products and medications, may not be necessary to control clinical manifestation.

Research is ongoing to develop alternative treatment options to a GFD. Attempts to develop gluten-free wheat, enzymatic pretreatment of wheat flour to remove the gluten trigger, oral enzyme
supplements to process the gluten in the small bowel, mechanisms to create gluten tolerance or to modify the intestinal permeability are all being explored and hold promise (Mukherjee et al 2012, Stoven et al 2012).

Management of CD People diagnosed with CD must avoid all wheat (gluten), barley (hordeins) and rye (secalins) proteins (Ludvigsson et al 2014). Grains, starches and flours not permitted in a GFD include couscous, semolina, durum flour, farro, triticale and malt (Bai et al 2012). Oats uncontaminated by wheat, barley or rye are usually safe for people with CD and are a good source of soluble fibre. Rice, corn, bean or nut flour, arrowroot, quinoa, seeds and potatoes are all good sources of starch if not contaminated or part of processed foods (Bai et al 2012). Gluten is often found in sauces, condiments, soups, gravy, pies and processed meats, requiring people with CD to read labels carefully and ask when eating out. Even some medications and personal care products may contain gluten and should be avoided by people with CD (www.glutenfreedrugs.com). The amount of tolerable gluten that will not cause histological changes in the small bowel may vary from person to person, but is generally thought to be 10mg or less (Ludvigsson et al 2014). A slice of whole-wheat bread has 4.8grams of gluten (www.celiac.com). Fortunately, due to the increased recognition of gluten-related disorders, the number of food products available with gluten-free options has increased dramatically during the past decade. Most individuals with CD begin to feel better after instituting a GFD and this reduction in symptoms provides a positive reinforcement to continue the diet. Poor dietary adherence often results in continued clinical manifestations of CD and may put the individual at greater risk of additional autoimmune conditions, non-Hodgkins lymphoma or small intestine adenocarcinoma (Ludvigsson et al 2014, Lebwohl et al 2015).
Persistent symptoms are most often due to inadvertent gluten ingestion, so additional evaluation of the diet and other possible exposures to gluten, such as cross-contamination with other grains, should be done, preferably by a dietician with expertise in GFDs (Bai et al 2012). Recently, a urine test for gluten immunogenic peptides has been found to be sensitive to ingestion of even small amounts of gluten and may be useful in determining gluten-free compliance (de Lourdes Moreno et al 2015).

When symptoms persist or recur, the NP must also consider secondary diagnoses, such as lactose or other food intolerance, irritable bowel syndrome, pancreatic insufficiency, colitis, small bowel bacterial overgrowth or the wrong diagnosis all together, requiring further evaluations (Bai et al 2012). Unfortunately, some people have refractory CD, a diagnosis made when symptoms persist and villous healing does not occur while on a strict GFD.

Individuals newly diagnosed with CD benefit from consultation with a dietician to plan a well-balanced diet that contains sufficient calories, nutrients, iron, vitamins, fibre and calcium, and eliminates hidden sources of gluten (Ludvigsson et al 2014). Any dietary insufficiencies acquired prior to diagnosis, such as iron, vitamin or mineral deficiencies, should be treated and monitored by the NP during the first few months of therapy while the gut is healing and on an annual basis. Thyroid function, dental screening and evaluation for osteoporosis are recommended. Annual follow-up is recommended, but annual biopsies are not mandatory if the person is asymptomatic on a GFD and has a normal serological screening. Annual small bowel evaluation and biopsies do help identify those at increased risk of intestinal malignancy or with refractory CD (Ludvigsson et al 2014).

Family involvement in the dialogue regarding a GFD is imperative for successful management. It is also helpful for newly diagnosed individuals to be referred to a coeliac support group, for example, Coeliac UK (tinyurl.com/z4fbv86), for creative recipes, tips on where to buy or order gluten-free foods, social support for adjustment to the diagnosis and implementation of a GFD, and the latest information or research on CD. Unfortunately, the cost of gluten-free foods is greater than the equivalent wheat-based foods and often health insurance will not cover this additional expense.

Management of gluten allergy
The management for gluten allergy is a GFD. Although gluten allergy may result in inflammation of the GI mucosa, it has not been associated with villous atrophy or long-term health complications or autoimmune conditions (Sapone et al 2012). People with allergy to ingested gluten rarely run the risk of anaphylactic reaction and many are able to consume small amounts of gluten, such as in processed foods, without significant symptoms. Usually, people with gluten allergy learn through trial and error what amount of gluten-containing foods will result in symptoms.

As with other food allergies, the tolerance level may vary over time and the person may be allergic to multiple foods, making control of symptoms difficult. Further studies are needed to determine the gluten threshold and condition-duration of gluten allergy as compared to CD and gluten sensitivity (Sapone et al 2012).

Management of non-coeliac gluten sensitivity
The treatment for NCGS is a GFD. As with the diagnosis of CD and gluten allergy, consultation with a dietician is recommended when instituting a GFD. Because of the apparent overlap between NCGS and IBS, consultation with a dietician familiar with management of people with symptoms attributed to IBS would be ideal. Symptom control is the indicator of management success and the level of perceived symptoms determines dietary restrictions. Similar to lactose intolerance, some ingestion of gluten may be tolerable. Continued studies are needed into the pathophysiology and management of NCGS.

Nursing care
Many individuals live for years with undiagnosed gluten-related conditions. This affects their quality of life and social interactions, and may result in multiple health problems.

The nurse must help identify people with possible gluten-related conditions by careful attention to recurrent or chronic GI symptoms, the association of symptoms with gluten ingestion, family history of gluten-related conditions, and physical examination findings.

Diagnostic evaluation should not be delayed. A delay in diagnosis in symptomatic people, or an incorrect diagnosis and continuation of symptoms, adversely affects quality of life and frequently leads to frustration with the healthcare system and healthcare providers (Ludvigsson et al 2015). It is important that the nurse takes reported symptoms of GI distress seriously and orders or refers for diagnostic testing before the person initiates a GFD. Collaboration with a gastroenterologist is often indicated for accurate diagnosis and initial management of gluten-related conditions.
People diagnosed with gluten-related conditions need to be educated on their condition and the complexity of a GFD. Working closely with a skilled dietician, the nurse can help the client and family adapt to a healthy GFD, identifying gluten-free alternatives commonly consumed by the family. ‘Normalising’ the GFD will reduce the possibility of perceived stigma and increase the potential for compliance (Olsson et al. 2009).

All medications and personal hygiene products currently used by the individual must be evaluated to determine whether they contain gluten. If dietary deficiencies have developed prior to diagnosis, the nurse should educate the client on these health concerns and the management plans to alleviate them. Associated nutrient deficiencies, osteoporosis, dental enamel deficiency, mental health symptoms and fertility problems should all be monitored and addressed when present.

Ongoing evaluation of symptom resolution and adjustment of the individual and family to the management plan is indicated for the optimum health of the individual.

During the first year after diagnosis, frequent evaluation by the NP or primary care nurse is warranted to monitor resolution of symptoms. Once stabilised, annual visits are usually sufficient to monitor the condition.

References


