SciMedCentral

Annals of
Pediatrics & Child Health

Special Issue on
Pediatric Gastroenterology Disorders

Edited by:
Hillel Naon, M.D.
*Acting Division Head, Pediatric Gastroenterology, Hepatology and Nutrition, Children's Hospital Los Angeles, University Southern California, Keck School of Medicine, Los Angeles, USA*

**Review Article**

# Celiac Disease and Non-Celiac Gluten Sensitivity

**Michelle Pietzak[1]* and Hillel Naon[2]**

[1]*Pediatric Gastroenterology and Nutrition, University of Southern California Keck School of Medicine, USA*

[2]*Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital Los Angeles, University Southern California Keck School of Medicine, USA*

**Abstract**

Wheat has been a staple in the human diet for over 10,000 years. However, in contrast to ruminant animals, humans did not evolve to digest wheat gluten completely before it leaves our one-chambered stomach. Response to the dietary proteins in wheat can result in a variety of symptoms and immunologic responses. In celiac disease, genetically predisposed patients react to the gliadin fraction of wheat gluten, and this result in a variety of intestinal and extra-intestinal manifestations. In contrast, wheat allergy is typically an IgE mediated response, resulting in gastrointestinal, skin and/or respiratory symptomatology. Non-celiac gluten sensitivity is a relatively new entity, and has an evolving definition. It is thought to occur when patients who have neither celiac disease nor wheat allergy exhibit symptom improvement upon dietary gluten withdrawal. Conditions in this category include dermatitis herpetiformis, irritable bowel syndrome, autism and gluten-sensitive ataxia. All of these entities respond to a gluten-free diet, but is it important for patients and health care practitioners to understand the distinctions. The potential health implications of differentiating among an "autoimmune" disorder, "allergy" and "sensitivity" are broad. Significant morbidity can result if the specific condition is not identified and treated correctly.

***Corresponding author**

Angeles Michelle Pietzak, Director, Celiac Disease Center, Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital Los Angeles, Children's Hospital Los, USA, Tel: 323- 226-5609; Fax: 323- 226-5692; Email: pietzak@usc.edu

**Submitted:** 05 November 2014

**Accepted:** 20 January 2015

**Published:** 04 February 2015



**Keywords**

- Gluten
- Casein
- Celiac disease
- Wheat
- Wheat allergy
- Gluten sensitivity
- Dermatitis
- Herpetiformis
- Ataxia
- Autism
- Irritable bowel syndrome

## ABBREVIATIONS

AGA: Anti-Gliadin Antibody; CD: Celiac Disease; DGP: Deamidated Gliadin Peptide; DH: Dermatitis Herpetiformis; EMA: Anti-Endomysial IgA; GFD: Gluten Free-Diet; GFCFD: Gluten-Free Casein-Free-Diet; HLA: Human Leukocyte Antigen; IBS: Irritable Bowel Syndrome; NCGS: Non-Celiac Gluten Sensitivity; tTG: Anti-Human Tissue Transglutaminase Antibody

## INTRODUCTION

### Background

As demand for gluten-free products has increased, their availability is no longer restricted to small specialty food stores and Internet distributors. Products labeled "gluten-free" is now more than a billion dollar business with exponential sales

increases [1]. Gluten-free foods are now perceived as "healthy" and "tasty" substitutes, as opposed to the dry and crumbling items of the past. However, the general public's recent embrace of the gluten-free lifestyle has been associated with a backlash from the medical community, with the perception of it is as a "fad diet" that will eventually disappear. The gluten-free diet (GFD), when used appropriately, is a medical nutritional therapy for celiac disease (CD), dermatitis herpetiformis (DH), and gluten-sensitive ataxia. Ongoing research is focusing on the use of the GFD for other medical conditions with gastrointestinal and neurologic symptoms, such as autism and irritable bowel syndrome (IBS).

In this paper, which is an updated version of a review published prior in chapter form [2], we will differentiate between CD, wheat allergy and NCGS. There are decades of research on CD showing both palliative and preventative benefits of the GFD. NCGS is evolving in definition, proposed pathophysiology and treatment. We will highlight the importance of CD as the prototype for an autoimmune disorder that responds to a GFD. CD can be differentiated from NCGS because of its well-documented complications of nutritional deficiencies, co-morbid autoimmune conditions, and an increased risk for malignancies. Wheat allergy will also be discussed, and how its symptoms and dietary treatment differs from those of CD and NCGS. The concept of NCGS will be elaborated, with emphasis on the conditions known to respond to gluten elimination, and recognition of those that still require further definition and examination.

To say that adhering to the GFD is challenging is an understatement. Patients and physicians should not take the GFD lightly just because it is nutritional therapy and not a pharmacologic agent. Food labeling in the United States presents many obstacles [3,4] . Unnecessary gluten restriction impacts a patient's ability to socialize, travel and eat out of the home [4]. Additional studies on NCGS are needed using more rigorous scientific methods to further define the benefits of the gluten elimination in those without documented CD.

## CELIAC DISEASE (CD)

Worldwide, CD is common, with a prevalence in the U.S. estimated to be between 0.5% and 1% of the general population [5,6]. There has been increased awareness and diagnosis of the condition. The incidence of CD is also thought to be rising in the U.S. over the past several decades [7]. CD is an immune-mediated reaction to gluten in wheat, rye and barley that occurs in genetically predisposed individuals. Patients with CD react to dietary proteins, called prolamins found in these grains. All grain products, including rice, contain prolamins. However, the specific prolamins found in wheat (gliadin), rye (secalin) and barley (horedin) are the ones implicated to induce immunologic reactions in CD [8]. Oats, which contain avenin, also cause a reaction in a small proportion of CD patients [9]. Oats have the greatest potential to be contaminated with wheat, as oats are crop rotated and milled in the same facilities with wheat. Because of this, U.S. oats are considered to have levels of contamination with wheat gluten high enough to make them unacceptable for the GFD in CD [10]. In well controlled adults with CD who have strictly eliminated gluten for many years it may be possible to incorporate pure and uncontaminated oats safely into the diet. These oat products contain less than 20 mg of gluten per kg of oats [11,12].

In many autoimmune diseases, both a genetic predisposition and an environmental trigger are required to manifest symptoms. In patients with CD, the ingestion of gluten (environmental) and a genetic predisposition with specific HLA (human leukocyte antigens) alleles are thought necessary. If an individual does not have the common HLA alleles found in CD (HLA DQ2 and HLA DQ8), the individual is at negligible risk to develop the condition. An infant who has not yet been exposed to gluten in the diet will not manifest the symptoms, even if he has the HLA alleles that put him at risk [13].

Even though these specific HLA alleles are present in up to 30% of healthy individuals, the majority do not develop celiac disease [13]. Research in different patient populations implicates several modifying factors which may contribute to disease development in genetically at-risk individuals. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition statement on complementary feeding recommends avoiding both early (less than 4 months of age) and late (greater than 7 months of age) introduction of gluten into the infant's diet [14]. This society states that, ideally, gluten should be introduced gradually, while the infant is still breastfeeding, to reduce not only the risk of CD but also of type 1 diabetes mellitus and wheat allergy [14]. However, a recent prospective Italian study found that neither breastfeeding nor delayed introduction of gluten decreased the risk of CD in infants with a high risk HLA genotype [15]. Another recent multicenter, randomized, double-blind, placebo-controlled dietary intervention study likewise showed that neither breastfeeding nor the introduction of small quantities of gluten at 4 to 6 months of age reduced the risk of CD at 3 years of age in those with HLA-DQ2 or HLA-DQ8 [16].

Cesarean delivery has also been associated with a higher incidence of CD in children [17]. Pediatric patients with CD have been reported to have a different seasonality of month of birth [18]. Girls diagnosed prior to the age of 24 months had a different seasonality of month of birth from those who were diagnosed after age 24 months [18]. Birth during summer months also carries a higher risk for CD [19]. Infections during early childhood may appropriately activate the Th1 immune response, but may also lead to a presentation of CD during the toddler years. This may explain why an increased risk for CD has been found in children with repeated rotavirus infections, as measured by anti-rotavirus antibodies [20].

Several non-HLA genes have been associated with CD susceptibility, including CCR3, IL12A, IL18RAP, RGS1, SH2B3 and TAGAP [21]. All of these code for proteins that regulate immune responses. Other autoimmune diseases in the patient or family (such as type I diabetes, autoimmune thyroid disease, rheumatoid arthritis and autoimmune liver disease) also put the patient at higher risk for CD [8]. Those with Down syndrome, Williams syndrome, Turner syndrome and cystic fibrosis are also at increased risk for CD over that of the general population [8,22,23]. Elevated anti-gliadin antibodies (AGA) can be seen in Down syndrome and cystic fibrosis patients, even in the absence of CD, perhaps due to increased intestinal permeability.

"Classic" CD occurs in toddlers who have been ingesting gluten for several months, and presents with diarrhea, weight loss, anorexia, vomiting and abdominal distension. In contrast to

adults in the U.S., who often see several health care practitioners before receiving the correct diagnosis of CD, these children exhibit protein-calorie malnutrition and thus receive more prompt medical attention. For developed countries, such as the U.S., "classic" CD is a misnomer, as the majority of patients now present in older age groups with intestinal and extra intestinal symptoms. Common misdiagnoses for these older patients include IBS, lactose malabsorption, inflammatory bowel disease and even depression and hypochondria.

When CD occurs without the "classic" gastrointestinal presentation, it can easily confuse the general practitioner. As in other autoimmune conditions, CD symptoms can manifest in virtually every organ system. After the gastrointestinal tract, the next most common system affected in CD is the musculoskeletal system, where arthritis, muscle pain, dental enamel defects and osteopenia/osteoporosis are commonly seen. Short stature, delayed onset of puberty, and even infertility, can be seen in both men and women, prompting an endocrinology workup. Women with undiagnosed or untreated CD have higher rates of infertility, spontaneous abortions, fetal neural tube defects and low birth weight infants [24,25]. Trace vitamin and mineral deficiencies in both adult and pediatric CD patients include iron deficiency anemia, protein-calorie malnutrition and low serum zinc, folic acid, selenium and vitamins B-6, B-12, D, E and K [4,26]. Neurologic and psychiatric manifestations are common, and include headaches, seizures, anxiety, depression, schizophrenia and peripheral neuropathy [27,28]. Improvement of long-standing neurologic symptoms is variable with the GFD and dietary supplements [28,29].

There are several excellent serum antibody tests readily available to screen for CD. The antibodies tested are of two types, those directed against gluten and those against "self". The "anti-gluten" antibodies, antigliadin (AGA) IgG and antigliadin IgA, were the first blood tests available, but they are not as sensitive or as specific as the anti-"self" antibodies. False positive AGAs can be seen in any condition in which there is increased intestinal permeability to gluten. Because of this pitfall, anti-endomysial (EMA) IgA and anti-tissue transglutaminase (tTG) IgG and IgA are better screening tests for CD. EMA IgA and tTG IgA have both high sensitivity and specificity. The likelihood of a false positive in an otherwise healthy individual is low. As young children will make food antibodies earlier than "self" antibodies, EMA IgA and tTG IgA may not be as sensitive in younger children. Because of their lower sensitivity and specificity, anti-gliadin IgG and IgA are no longer routinely recommended as a first line screen for CD in otherwise healthy adult patients. IgA and IgG antibodies to deamidated gliadin peptide (DGP, a synthetic peptide derived from gamma gliadin of wheat) shows improved sensitivity and specificity compared to AGA, and closely parallel the appearance in the blood of tTG IgA in CD [30,31]. IgA deficiency, which is more common in CD, may yield falsely low AGA IgA, DGP IgA, EMA IgA and tTG IgA titers. Hence, a total IgA level should also be measured at the time that antibodies are checked. Testing for tTG IgG may be a better screen under this circumstance [22].

The confirmation of CD requires an endoscopic intestinal biopsy to confirm enteropathy prior to the initiation of a GFD [22]. Biopsies from the proximal small bowel are graded based upon the Marsh classification, which grades the lesion according to the number of intra-epithelial lymphocytes, depth of crypt hypertrophy, and whether the villi are normal, mildly or markedly atrophic, or completely absent [32]. Recent European society recommendations involve using a combination of antibodies, genetic testing and response to a gluten-free diet as criteria for diagnosis, possibly eliminating the need for histopathologic confirmation [33].

How does gluten interact with the gastrointestinal immune system? As opposed to ruminant animals (which chew their cud and pass grains through a chambered stomach lined by bacteria), the human gastrointestinal tract incompletely digests gluten. Up to 50 different toxic fragments, which have potential to stimulate an immune response, survive digestion and are absorbed through the small intestinal mucosa. tTG modifies the shape of gliadin into a conformation which has a strong affinity for HLA DQ2 on antigen presenting cells. This stimulates the T helper 1 response, which leads to the intestinal damage [34]. In contrast to wheat allergy and gluten sensitivity, these manifestations of CD can cause permanent damage and result in nutritional deficiencies and higher rates of gastrointestinal malignancies.

## WHEAT ALLERGY

The top 8 food allergens in the U.S are milk, eggs, fish, crustacean shellfish, peanuts, tree nuts, soybeans and wheat. While food allergies affect approximately 5% of the population in industrialized nations, only about 0.1% has a documented wheat allergy. However, it is common for children with wheat allergy also to have reactions to other common food allergens. Wheat allergy, similar to CD, is an immune-mediated reaction to the proteins found wheat-containing food. In contrast to CD, wheat allergy is an IgE mediated reaction to the water and salt-insoluble gliadins, particularly omega-5 gliadin [35]. This protein fragment is also the major allergen of wheat-dependent exercise-induced anaphylaxis, commonly referred to as "Baker's asthma". Both total serum IgE and specific IgE to wheat can be elevated in the blood. Skin prick tests using wheat protein extracts may show reactions. It is important to differentiate CD from wheat allergy, since patients with the allergic response usually do not need to restrict other prolamin- containing grains (rye, barley and contaminated oats) from their diet. The wheat-free diet is therefore more liberal and less restricting from a social standpoint than the GFD.

Symptoms of wheat allergy are more common in the in the skin and respiratory tract than the gastrointestinal tract. Manifestations include wheezing, shortness of breath and swelling, itching and irritation of the lips, tongue, mouth, nose, eyes and throat. Wheat allergy rarely causes anaphylaxis. Hives and other simple pruritic rashes can occur. Gastrointestinal symptoms are non-specific, and include nausea, vomiting, gas, cramps, bloating, diarrhea and generalized abdominal pain. Unfortunately, the gastrointestinal manifestations of CD, wheat allergy and NCGS can be indistinguishable from each other. However, unlike CD, wheat allergy is not thought to cause permanent gastrointestinal or other organ damage once the acute event resolves.

Wheat allergy usually develops during the toddler years,

similar to "classic" CD. However, unlike CD (which is lifelong) wheat allergy is usually outgrown between the ages of 3 and 5 years. As in CD, the allergenicity of wheat is hypothesized to be strengthened by activated tTG in these patients [29]. Clinical improvement on the GFD cannot be used to discriminate between CD and wheat allergy, as both improve with elimination of wheat products from the diet. The best treatment of wheat allergy is secondary avoidance prevention. Antihistamines and corticosteroids may be of benefit for severe reactions. As with peanut and shellfish allergy, wheat-allergic individuals should have epinephrine readily available in case of a rare, life-threatening anaphylactic reaction [35]. Although the immunologic reactions with CD can be severe with emesis, diarrhea and dehydration, they do not cause anaphylactic reactions.

## NON-CELIAC GLUTEN SENSITIVITY (NCGS)

NCGS exists when a patient has symptomatic improvement upon gluten withdrawal. By definition, the subject does not meet the criteria for either CD or wheat allergy. A small bowel biopsy should be normal microscopically. There are no specific blood tests for gluten sensitivity, although some may have AGA IgG positivity, and there appears to be a higher incidence of HLA DQ2 [36]. In contrast to both CD and wheat allergy, NCGS does not manifest typical and measurable immunologic reactions. Unfortunately, the gastrointestinal complaints are non-specific, and it can be difficult to distinguish between these three conditions. Common symptoms reported by patients with NCGS include dyspepsia, nausea, vomiting, borborygmi, bloating, constipation and overt diarrhea [36]. Common extra-intestinal symptoms include joint pain, bone pain, muscle cramps, fatigue, headaches, rashes, and swollen tongue [36]. Similar to wheat allergy, and in contrast to CD, the manifestations of NCGS are thought not to cause permanent intestinal damage, nor result in nutritional deficiencies or higher rates of malignancies.

The pathophysiology of NCGS is unclear, as there are few published studies. One study involved a 4-month supervised gluten challenge given to subjects with biopsy-proven CD, NCGS or healthy controls who had undergone upper endoscopy and biopsies for dyspepsia [37]. By definition, those labeled with NCGS were negative for EMA IgA, tTG IgA and serum wheat IgE. However, about half had AGA IgG and/or AGA IgA and HLA DQ2 and/or HLA DQ8. Those with NCGS experienced gas, diarrhea, weight loss, abdominal pain, glossitis, muscle cramps, leg numbness, bone and joint pain and unexplained anemia upon gluten challenge. Immunologic markers in the NCGS group did not demonstrate elevations in interleukin-6 or interleukin-21 (as seen in CD). Biopsies of the NCGS group showed only a mild increase in intra-epithelial lymphocytes on intestinal biopsy, and a reduced expression of the T-regulatory cell marker FOXP3 (forkhead box P3) and TGFB1 (transforming growth factor $\beta_1$). Interestingly, those with NCGS demonstrated increased expression of the gene *CLDN4* (claudin 4, a tight junctional protein) and decreased intestinal permeability (as measured by urinary lactulose/mannitol), suggesting differences between this condition and CD in regards to the function of the intestinal epithelial cell tight junctions. These results signified a decreased recruitment of T-regulatory cells to the small bowel in those "gluten sensitive" compared with subjects who are "gluten tolerant", and indicated a generalized more limited involvement for the adaptive immune system (as opposed to CD). The innate immune system may play more of a role in those with NCGS, as their biopsies showed higher expressions of toll-like receptors 1, 2 and 4 compared to healthy controls [37].

## DERMATITIS HERPETIFORMIS (DH)

DH is thought by some to be the pathognomonic skin rash of CD, while others consider it part of the NCGS spectrum. Due to its evolving appearance over time, the rash can be difficult to diagnose clinically without biopsy. DH initially presents as an erythematous macule, progresses to an urticarial papule and eventually manifests as tense vesicles [38]. During the vesicular appearance, it is often mislabeled as chicken pox or varicella zoster. The condition may even mimic eczema or psoriasis, as patients will often unroof and scratch the lesions to the point that the skin is scarred and inflamed. Distinguishing features of this skin rash are severe pruritus and its symmetrical distribution on the face, trunk and extensor surface of the extremities. The majority of DH patients do not have gastrointestinal symptoms despite the fact that their small bowel biopsies are abnormal. The gold standard for diagnosis is the demonstration of its typical findings on a punch skin biopsy, which is an office procedure. This skin biopsy should be sent frozen for special IgA stains in the dermal papillae, which is likely dermal tTG IgA [38]. If the skin biopsy confirms DH, there is no need to proceed with upper endoscopy and small bowel biopsy. The medication of choice, in addition to a GFD, is Dapsone, an antibiotic that alleviates severe pruritus. Close monitoring of treatment with Dapsone is needed due to its potential side effects, including anemia, leukopenia and a flu-like syndrome. A strict GFD is recommended for those with DH to prevent flares and associated reported complications, such as vitiligo, alopecia areata, sarcoidosis, autoimmune thyroid disease, type I diabetes and systemic lupus erythematosis [39]. Some DH patients are also sensitive to products containing latex and iodine [38].

## ATAXIA AND OTHER NEUROLOGIC MANIFESTATIONS

"Gluten ataxia" was first described in 1998 in patients with progressive, idiopathic ataxia and elevated AGA IgG and AGA IgA [40]. In this initial description, all had gait ataxia; some had limb ataxia, and most had peripheral neuropathy. About 20% had evidence of cerebellar atrophy on MRI. Two subjects on autopsy demonstrated lymphocytic infiltration of the cerebellum, peripheral nerves and posterior columns of the spinal cord. About a third had distal duodenal biopsies consistent with CD [40]. Several studies have since examined the higher prevalence of AGA IgG and AGA IgA in patients with sporadic and familial ataxia [29]. Unlike CD patients, the 147 patients in one study with gluten ataxia (followed over 12 years in one center) had an equal male: female ratio, with a mean age of onset of 53 years. All were AGA IgG and/or IgA positive, 22% were EMA IgA positive, 56% were tTG IgA positive, and 70% were positive for HLA DQ2. Overall, 28% had biopsy-proven enteropathy and up to 60% had MRI evidence of cerebellar atrophy [29].

The mechanisms by which gluten interacts with the central nervous system have yet to be fully elucidated. *In vitro* research

demonstrates antibody cross-reactivity between gluten peptides and the Purkinje cells in the cerebellar cortex in human and rats [41]. There is also evidence for antibodies targeting Purkinje cell epitopes in the sera of patients with gluten ataxia [41]. tTG IgA deposits have been reported in both jejunal tissue and around the blood vessels of the cerebellum, pons and medulla of those with NCGS [42-44]. As in CD, the GFD is the mainstay of treatment for gluten ataxia, although one uncontrolled trial reported improvement in four patients after intravenous immunoglobulin [45].

The GFD has been reported to improve inflammatory myopathy both with and without concomitant immune suppression [46]. Sensory ganglioneuropathy has also been reported to respond to GFD alone [47]. Multiple sclerosis has been reported to be associated with elevated anti-gliadin IgG and anti-gliadin IgA. There is debate in the medical literature as to whether or not it should be considered part of the NCGS spectrum, or whether these patients have "occult" CD [48-49]. Biopsy-proven CD has also been associated with childhood partial epilepsy with occipital paroxysms [50]. A study of 75 biopsy-proven pediatric CD patients reported many had neurologic manifestations, including ataxia, febrile seizures, single generalized seizures, muscular hypotonia with retarded motor development, and T2 hyperintensive white matter lesions on MRI. These white matter lesions are hypothesized to be from vasculitis or inflammatory demyelination [51]. Another study from 2004 controversially found that 75% of patients with untreated CD exhibited at least one hypoperfused brain region as assessed by PET scan. These results were significantly different from healthy controls and CD patients who maintained a GFD [52]. These perfusion defects, as reported in the superior and anterior areas of the frontal cortex and anterior cingulated cortex, have also been reported in depression, anorexia nervosa and anxious-neurotic behaviors [53-55]. It is interesting to speculate as to whether these psychiatric disorders will eventually be included as part of the NCGS spectrum.

## IRRITABLE BOWEL SYNDROME (IBS)

In blinded studies of IBS patients, some types of IBS have shown symptomatic improvement with the GFD [56]. IBS has been recently associated with small intestinal bacterial overgrowth (SIBO). Its symptoms are primarily pain, gas, bloating and diarrhea with or without constipation [57]. After six months of a GFD, the majority of those with diarrhea-predominant IBS returned to normal stool frequency and gastrointestinal symptom score [58]. Predictors of this favorable clinical response included AGA IgG and tTG IgG positivity [59]. IBS is a common alternative diagnosis given to women with undiagnosed CD, as they may also complain of gas, bloating, abdominal pain and diarrhea alternating with constipation. It has also been reported that CD and IBS can co-exist in the same patient [60]. Before finalizing the diagnosis of IBS, most gastrointestinal experts and societies agree that it is cost-effective to first rule out CD [61].

## AUTISM AND THE GLUTEN-FREE CASEIN-FREE-DIET (GFCFD)

The opioid hypothesis proposes that autism results from excessive brain opioid activity during the neonatal period. Excessive opioid activity leads to inhibition of social motivation, resulting in aloofness and isolation. Arguments supporting this hypothesis include: Similar behaviors in animals after injections of exogenous opioids with decreased vocalization and increased aloofness; biochemical evidence of abnormal peripheral endogenous opioids in autistic patients; and case reports showing naltrexone (an opioid receptor blocking agent) to be therapeutic in autistic patients [62,63]. Reichelt theorized in 1991 that gluten and casein peptides, which have similar chemical structures, play a role in the pathogenesis of autism. A variety of disorders, including autism, schizophrenia and postpartum psychosis, were postulated to be due to an inability to adequately process gluten and casein [64]. These products of inadequate digestion, "gliadorphin" and "casomorphin" can be measured in the urine and cerebrospinal fluid of autistic patients. They theoretically cross both the gut and brain barriers, and then bind with endogenous opioid receptors, causing "interference of signal transmission". It has been proposed that "gliadorphin" and "casomorphin" have negative pharmacological effects on attention, learning, social interactions and brain maturation [65].

Children with symptoms consistent with the autistic spectrum disorders often receive complementary and alternative medications and diets. These include high-dose dietary supplements and different types of restrictive diets. Supplements and diets are perceived to be more acceptable and to have fewer safety issues and side effects compared with pharmaceuticals prescribed for autism. Even though diets and supplements are considered "food", their use should be scrutinized as to available evidence for efficacy and effectiveness as well as any associated risks. Cochrane Reviews published in 2004 and 2008 examined the evidence for the effect of diets on children, adolescents and adults clinically diagnosed with autism spectrum disorder [66-67]. Publications reviewed included trials in which GFD was compared to placebo (or no treatment); casein free diet was compared to placebo (or no treatment), GFCFS was compared to placebo (or no treatment), and GFD was compared to a casein free diet. Outcomes included standardized autistic behavioral assessments, communication and linguistic abilities, cognitive functioning, motor abilities, urine peptide concentrations, and disbenefits (harms, costs and impact on quality of life) [66-67].

Sixty-one studies were indentified from 1965 through 2007, of which only 3 were considered to be of high enough quality to be included in the analysis [66-69]. Studies excluded had significant bias, or were not randomized or blinded and consisted mostly of case reports. The three publications consisted of two small trials: The first with 10 participants in each arm and the second with a total of 15 participants. In the first trial, GFCFD reduced the autistic traits of "social isolation" and "bizarre behavior" only at the age of 12 months. In the second trial, there was no significant difference in outcome measures between the diet group and the control group in regards to cognitive skills at 12 months, motor ability at 12 months, communication and language sampling at week 6 of the diet, or Childhood Autism Rating Scale at week 6 of the diet. These two meta-analyses concluded "This is an important area of investigation and large scale, good quality randomized control trials are needed" [66-67].

What could be an adverse outcome to using the GFCFD in autism? For one, it costs significantly more than a standard diet

to purchase gluten-free substitutes for bread, pasta and other staples in the diet. Secondly, it involves extra effort in providing the special meals for the child with autism and normal meals for the rest of the family. In autism, many children have well-established, particular dietary preferences that are difficult to change in regards to texture and taste. Compliance with the GFCFD is also challenging as to identifying products that are guaranteed not to contain gluten or casein. While gluten is not an essential nutrient in the human diet, excluding casein and the associated nutrients found in cow's milk products, such as calcium, protein, magnesium, potassium and other vitamins and minerals, can lead to a nutritionally inadequate diet. And finally, the autistic patient is already perceived as "different", and further social restrictions via diet may place additional burdens on the family unit [66-67].

## THE IMPORTANCE OF KNOWING THE DIFFERENCE AMONG CD, WHEAT ALLERGY AND NCGS

While treatment for CD, wheat allergy and NCGS are similar, it is important for patients, families and health care practitioners to be able to differentiate between these disorders. For the following important reasons, CD must be differentiated from other conditions, even if the patient states improvement on the GFD:

1. **Familial risk:** Relatives of patients with CD are at much higher risk than those of the general population to develop CD and have other autoimmune disorders. Screening of first and second-degree family members should be performed for CD, once the index case has been identified. Screening family members for wheat allergy or NCGS is not currently recommended, although atopic diseases (food allergy, asthma) may also run in families.

2. **Nutritional deficiencies:** Patients with CD are at increased risk for malabsorption of protein, fat, iron and the fat-soluble vitamins A, D, E and K. Celiac patients often require iron and vitamin supplements for nutritional deficiencies and their consequences (i.e. anemia, decreased bone density). As there is less intestinal damage with wheat allergy and NCGS, these conditions do not share the increased risk for these nutritional deficiencies and their complications. Supplements, blood tests and X-rays are not usually required for these patients.

3. **Degree of dietary restriction:** In CD, a strict GFD, free of contamination, is required for symptomatic and histologic relief. In wheat allergy, only wheat restriction is needed, unless there are co-morbid food allergies. In NCGS, it is unclear if such strict adherence, as with CD, is required.

4. **Development of other autoimmune conditions:** Unfortunately, autoimmune conditions tend to travel together within the same patient and same family. Since CD is an autoimmune condition, the patient is at risk for others, such as thyroid disease, type I diabetes, joint diseases and liver diseases. Since wheat allergy and NCGS are not autoimmune conditions, patients with these diagnoses are not at increased risk to develop autoimmune conditions relative to that of the general population.

5. **Increased risk for malignancies:** CD involves the activation of a particular type of white blood cell, the T-lymphocyte. Patients are at increased risk to develop T-cell enteropathy lymphoma [70]. Other gastrointestinal malignancies, as well as skin cancer, have also been reported at higher rates in patients with CD that is either untreated or treated too late. Because food allergies and NCGS do not involve this particular immune system pathway, and do not cause severe GI tract damage, patients with these conditions are not at increased risk for these cancers.

6. **Increased mortality:** Patients with CD have a 2-4-fold increased mortality rate, at every age, compared to the general population. This is due to nutritional complications, co-morbid autoimmune conditions and the higher rate of malignancies [7,71]. Patients with wheat allergy and NCGS do not face this increased risk of death.

## REFERENCES

1. Gluten-Free Sector Still Hot in Tough Times.
2. Pietzak M. Celiac disease, wheat allergy, and gluten sensitivity. In: "Wheat and Rice in Disease Prevention and Health" (Ronald R. Watson, PhD, Victor R. Preedy, PhD, Sherma Zibadi, MD, PhD Eds) Elsevier Inc., New York, USA. 2014.
3. Pietzak M. Gluten-free food labeling in the United States. J Pediatr Gastroenterol Nutr. 2005; 41: 567-568.
4. Pietzak MM. Follow-up of patients with celiac disease: achieving compliance with treatment. Gastroenterology. 2005; 128: 135-141.
5. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003; 163: 286-292.
6. Hoffenberg EJ, MacKenzie T, Barriga KJ, Eisenbarth GS, Bao F, et al. A prospective study of the incidence of childhood celiac disease. J Pediatr. 2003; 143: 308-314.
7. Rubio-Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology. 2009; 137: 88-93.
8. Pietzak MM, Catassi C, Drago S, et al. Celiac disease: going against the grains. Nutr Clin Prac. 2001; 16: 335-344.
9. Arentz-Hansen H, Fleckenstein B, Molberg Ø, Scott H, Koning F, Jung G, et al. The molecular basis for oat intolerance in patients with celiac disease. PLoS Med. 2004; 1: 1.
10. Thompson T. Gluten contamination of commercial oat products in the United States. N Engl J Med. 2004; 351: 2021-2022.
11. Sey MS, Parfitt J, Gregor J. Prospective study of clinical and histological safety of pure and uncontaminated Canadian oats in the management of celiac disease. JPEN J Parenter Enteral Nutr. 2011; 35: 459-464.
12. Butzner JD. Pure oats and the gluten-free diet: are they safe? JPEN J Parenter Enteral Nutr. 2011; 35: 447-448.
13. Pietzak MM, Schofield TC, McGinniss MJ, Nakamura RM. Stratifying risk for celiac disease in a large at-risk United States population by using HLA alleles. Clin Gastroenterol Hepatol. 2009; 7: 966-971.
14. Agostoni C, Decsi T, Fewtrell M, Goulet O, Kolacek S, Koletzko B, et al. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2008; 46: 99-110.

15. Lionetti E, Castellaneta S, Francavilla R, Pulvirenti A, Tonutti E, Amarri S, et al. Introduction of gluten, HLA status, and the risk of celiac disease in children. N Engl J Med. 2014; 371: 1295-1303.

16. Vriezinga SL, Auricchio R, Bravi E, Castillejo G, Chmielewska A, Crespo Escobar P, et al. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med. 2014; 371: 1304-1315.

17. Decker E, Engelmann G, Findeisen A, Gerner P, Laass M, Ney D, et al. Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children. Pediatrics. 2010; 125: 1433-1440.

18. Lewy H, Meirson H, Laron Z. Seasonality of birth month of children with celiac disease differs from that in the general population and between sexes and is linked to family history and environmental factors. J Pediatr Gastroenterol Nutr. 2009; 48: 181-185.

19. Ivarsson A, Hernell O, Nyström L, Persson LA. Children born in the summer have increased risk for coeliac disease. J Epidemiol Community Health. 2003; 57: 36-39.

20. Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, Emery L, et al. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. Am J Gastroenterol. 2006; 101: 2333-2340.

21. Hunt KA, Zhernakova A, Turner G, Heap GA, Franke L, Bruinenberg M, et al. Newly identified genetic risk variants for celiac disease related to the immune response. Nat Genet. 2008; 40: 395-402.

22. National Institutes of Health Consensus Development Conference Statement on Celiac Disease, June 28-30, 2004. Gastroenterology. 2005; 128: 1-9.

23. Gravholt CH. Clinical practice in Turner syndrome. Nat Clin Pract Endocrinol Metab. 2005; 1: 41-52.

24. Bradley RJ, Rosen MP. Subfertility and gastrointestinal disease: 'unexplained' is often undiagnosed. Obstet Gynecol Surv. 2004; 59: 108-117.

25. O'Leary C, Wieneke P, Healy M, Cronin C, O'Regan P, Shanahan F. Celiac disease and the transition from childhood to adulthood: a 28-year follow-up. Am J Gastroenterol. 2004; 99: 2437-2441.

26. Harper JW, Holleran SF, Ramakrishnan R, Bhagat G, Green PH. Anemia in celiac disease is multifactorial in etiology. Am J Hematol. 2007; 82: 996-1000.

27. Häuser W, Janke KH, Klump B, Gregor M, Hinz A. Anxiety and depression in adult patients with celiac disease on a gluten-free diet. World J Gastroenterol. 2010; 16: 2780-2787.

28. Cascella NG, Kryszak D, Bhatti B, Gregory P, Kelly DL, Mc Evoy JP, et al. Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. Schizophr Bull. 2011; 37: 94-100.

29. Hadjivassiliou M, Sanders DS, Woodroofe N, Williamson C, Grünewald RA. Gluten ataxia. Cerebellum. 2008; 7: 494-498.

30. Ankelo M, Kleimola V, Simell S, Simell O, Knip M, Jokisalo E, et al. Antibody responses to deamidated gliadin peptide show high specificity and parallel antibodies to tissue transglutaminase in developing coeliac disease. Clin Exp Immunol. 2007; 150: 285-293.

31. Marietta EV, Rashtak S, Murray JA. Correlation analysis of celiac sprue tissue transglutaminase and deamidated gliadin IgG/IgA. World J Gastroenterol. 2009; 15: 845-848.

32. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol. 1999; 11: 1185-1194.

33. Murch S, Jenkins H, Auth M, Bremner R, Butt A, France S, et al. Joint BSPGHAN and Coeliac UK guidelines for the diagnosis and management of coeliac disease in children. Arch Dis Child. 2013; 98: 806-811.

34. Qiao SW, Bergseng E, Molberg Ø, Xia J, Fleckenstein B, Khosla C, et al. Antigen presentation to celiac lesion-derived T cells of a 33-mer gliadin peptide naturally formed by gastrointestinal digestion. J Immunol. 2004; 173: 1757-1762.

35. Inomata N. Wheat allergy. Curr Opin Allergy Clin Immunol. 2009; 9: 238-243.

36. Catassi C, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, et al. Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. Nutrients. 2013; 5: 3839-3853.

37. Sapone A, Lammers KM, Casolaro V, Cammarota M, Giuliano MT, De Rosa M, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Med. 2011; 9: 23.

38. Zone JJ. Skin manifestations of celiac disease. Gastroenterology. 2005; 128: S87-91.

39. Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Br J Dermatol. 1997; 136: 315-318.

40. Hadjivassiliou M, Grünewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, Jarratt JA, et al. Clinical, radiological, neurophysiological and neuropatholgical characteristics of gluten ataxia. Lancet. 1998; 352: 1582-1585.

41. Hadjivassiliou M, Boscolo S, Davies-Jones GA, Grünewald RA, Not T, Sanders DS, et al. The humoral response in the pathogenesis of gluten ataxia. Neurology. 2002; 58: 1221-1226.

42. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997; 3: 797-801.

43. Korponay-Szabó IR, Halttunen T, Szalai Z, Laurila K, Király R, Kovács JB, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. Gut. 2004; 53: 641-648.

44. Hadjivassiliou M, Mäki M, Sanders DS, Williamson CA, Grünewald RA, Woodroofe NM, et al. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. Neurology. 2006; 66: 373-377.

45. Bürk K, Melms A, Schulz JB, Dichgans J. Effectiveness of intravenous immunoglobin therapy in cerebellar ataxia associated with gluten sensitivity. Ann Neurol. 2001; 50: 827-828.

46. Hadjivassiliou M, Chattopadhyay AK, Grünewald RA, Jarratt JA, Kandler RH, Rao DG, et al. Myopathy associated with gluten sensitivity. Muscle Nerve. 2007; 35: 443-450.

47. Hadjivassiliou M, Rao DG, Wharton SB, Sanders DS, Grünewald RA, Davies-Jones AG. Sensory ganglionopathy due to gluten sensitivity. Neurology. 2010; 75: 1003-1008.

48. Pengiran Tengah CD, Lock RJ, Unsworth DJ, Wills AJ. Multiple sclerosis and occult gluten sensitivity. Neurology. 2004; 62: 2326-2327.

49. Hadjivassiliou M, Sanders DS, Grünewald RA. Multiple sclerosis and occult gluten sensitivity. Neurology. 2005; 64: 933-934.

50. Labate A, Gambardella A, Messina D, Tammaro S, Le Piane E, Pirritano D, et al. Silent celiac disease in patients with childhood localization-related epilepsies. Epilepsia. 2001; 42: 1153-1155.

51. Kieslich M, Errázuriz G, Posselt HG, Moeller-Hartmann W, Zanella F, Boehles H. Brain white-matter lesions in celiac disease: a prospective study of 75 diet-treated patients. Pediatrics. 2001; 108: 21.

52. Addolorato G, Di Giuda D, De Rossi G, Valenza V, Domenicali M, Caputo

F, et al. Regional cerebral hypoperfusion in patients with celiac disease. Am J Med. 2004; 116: 312-317.

53. O'Connel RA. SPECT brain imaging in psychiatric disorders: current clinical status. In: Grünwald F, Kasper S, Biersack HJ, Möller HJ, eds. Brain SPECT Imaging in Psychiatry. Berlin, New York: W. De Gruiter; 1995: 35–57.

54. Grasby PM, Bench C. Neuroimaging in mood disorders. Curr Opin Psychiatry. 1997; 10: 73–78.

55. Davidson RJ, Abercrombie H, Nitschke JB, Putnam K. Regional brain function, emotion and disorders of emotion. Curr Opin Neurobiol. 1999; 9: 228-234.

56. Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. Am J Gastroenterol. 2011; 106: 508-514.

57. Yamini D, Pimentel M. Irritable bowel syndrome and small intestinal bacterial overgrowth. J Clin Gastroenterol. 2010; 44: 672-675.

58. Wahnschaffe U, Schulzke JD, Zeitz M, Ullrich R. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. Clin Gastroenterol Hepatol. 2007; 5: 844-850.

59. Häuser W, Musial F, Caspary WF, Stein J, Stallmach A. Predictors of irritable bowel-type symptoms and healthcare-seeking behavior among adults with celiac disease. Psychosom Med. 2007; 69: 370-376.

60. Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with celiac disease: a meta-analysis. Clin Gastroenterol Hepatol. 2013; 11: 359-365.

61. Paul SP, Barnard P, Bigwood C, Candy DC. Challenges in management of irritable bowel syndrome in children. Indian Pediatr. 2013; 50: 1137-1143.

62. Panksepp J, Najam N, Soares F. Morphine reduces social cohesion in rats. Pharmacol Biochem Behav. 1979; 11: 131-134.

63. Leboyer M, Bouvard MP, Launay JM, Recasens C, Plumet MH, Waller-Perotte D, et al. [Opiate hypothesis in infantile autism? Therapeutic trials with naltrexone]. Encephale. 1993; 19: 95-102.

64. Reichelt KL. Peptides in schizophrenia. Biol Psychiatry. 1991; 29: 515-517.

65. Knivsberg AM, Reichelt KL, Høien T, Nødland M. A randomised, controlled study of dietary intervention in autistic syndromes. Nutr Neurosci. 2002; 5: 251-261.

66. Millward C, Ferriter M, Calver S, Connell-Jones G. Gluten- and casein – free diets for autistic spectrum disorder. Cochrane Database Syst Rev. 2004: CD003498.

67. Millward C, Ferriter M, Calver S. Gluten- and casein –free diets for autistic spectrum disorder. Cochrane Database Syst Rev. 2008: CD003498.

68. Knivsberg AM, Reichelt KL, Høien T, Effect of dietary intervention on autistic behavior. Focus Autism Other Dev Disabl. 2003; 18: 247-256.

69. Elder JH, Shankar M, Shuster J, Theriaque D, Burns S, Sherrill L. The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. J Autism Dev Disord. 2006; 36: 413-420.

70. Smedby KE, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. Gut. 2005; 54: 54-59.

71. Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet. 2001; 358: 356-361.

**Cite this article**

*Pietzak M, Naon H (2015) Celiac Disease and Non-Celiac Gluten Sensitivity. Ann Pediatr Child Health 3(2): 1041.*