Celiac Center of Excellence
Hartford Healthcare
Connecticut GI PC

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Update on Celiac Disease

INTRODUCTION

Celiac disease is a chronic inflammatory disease of the small intestine, resulting from an inappropriate immune response to the dietary protein gluten. Gluten is a storage protein, found in wheat, barley and rye, that is responsible for the elastic texture of dough. The prevalence of celiac disease in the United States is approximately 1-2 % of the population, with an increased prevalence noted in patients with related symptoms, a family history of celiac disease and in patients with diabetes. The manifestations of celiac disease range from no symptoms to overt malabsorption (of essential nutrients) with involvement of multiple organ systems and an increased risk of some malignancies. Before 1981, over 90% of patients diagnosed with celiac disease presented to their physician with diarrhea and weight loss as their major symptoms. Currently, only 27% of patients present with these classic symptoms, while 21% of patients are asymptomatic and the majority (52%) of patients present with atypical symptoms such as constipation, anemia, osteoporosis, elevated liver function tests, neurologic disorders, reproductive disorders etc. These atypical presentations result from malabsorption of essential vitamins and minerals secondary to gluten-related injury to the small intestinal villi. The atypical presentation of celiac disease has led to a significant delay in the diagnosis of celiac disease (from onset of symptoms to establishing the diagnosis) to as much as 11 years in the1980s. As physicians have become more aware of the changing pattern of symptoms, the delay in diagnosis has reduced to less than 4 years; still much too long!! This delay in diagnosis has been associated with an increased risk of osteoporosis, autoimmune disease, and some malignancies as well as a poorer quality of life.

The Celiac Center of Excellence at Hartford Healthcare/Connecticut GI is composed of 20 GI providers from Connecticut GI servicing over 26 geographic areas, as well a pediatric gastroenterologist from CCMC, 4 nutritionists, and 3 GI fellowship-trained pathologists. It has been recognized as a Celiac Disease Recognized Unit by the prestigious Society for the Study of Celiac Disease (SSCD); one of only a handful of similar programs across the country, including Massachusetts General Hospital, Columbia, Vanderbilt, University of Chicago etc. Our hope is that we can continue to educate both physicians and patients regarding the changing presentation of celiac disease, so as to shorten the delay in diagnosis, while at the same time offering the most comprehensive care available to the patient with celiac disease.

CLINICAL PRESENTATION

Celiac disease has wide clinical spectrum depending on the severity and extent of injury to small intestinal villi from the ingestion of gluten. Most symptoms are due to malabsorption of essential vitamins and minerals and can affect multiple organ systems. GI symptoms may be absent, subtle or severe. Diarrhea and weight loss are the classic celiac symptoms but currently only 27% of patients present with those complaints. Other common GI symptoms include excess flatulence, abdominal pain, cramping, discomfort and bloating or distention. The majority of patients, > 50%, present with atypical symptoms such as nausea, constipation, anemia or abnormal liver function tests. Multiple extraintestinal manifestations can occur including osteoporosis and secondary hyperparathyroidism from calcium and Vit D malabsorption; ecchymosis, petechiae and bleeding from Vit K deficiency; peripheral neuropathy due to malabsorption of Vit B 12 and thiamine; amenorrhea, infertility or ED due to prolonged malnutrition; edema from hypoproteinemia. Other symptoms may include dermatitis, ataxia, persistent oral ulcers and prolonged fatigue. Due to the pervasive nature of celiac disease, awareness of the typical and atypical presentations is key to early diagnosis since prompt treatment can prevent detrimental health effects and improve quality of life.

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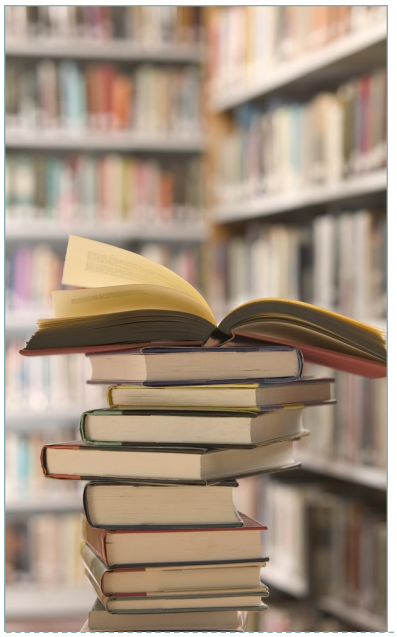
SPECIAL POINTS OF INTEREST

- Prevalence of celiac disease in the United States 1-2%
- Percentage of celiac patients that present with atypical symptoms 52%
- Average delay in diagnosis of celiac disease around 3—4 years

CELIAC-ASSOCIATED DISEASES/DISORDERS



Celiac Disease can affect almost any organ system, which leads to numerous extraintestinal symptoms present in roughly ½ to 1/3 of cases, equally common in children and adults. Short stature, fatigue and headaches are seen commonly in children; anemia, fatigue and headaches more commonly in adults. Some associated diseases are due to autoimmunity, but many can be attributed to nutritional deficiencies, especially of vitamins and minerals. For that reason, many patients with Celiac Disease and extraintestinal manifestations improve on a gluten free diet, though better and faster with children than adults.

Dermatologic: Dermatitis herpetiformis,

alopecia areata

Endocrine: autoimmune (Hashimoto's) thyroiditis, osteopenia/porosis, Type 1 Diabetes Mellitus,

Gynecologic: Infertility, recurrent miscarriages

Cardiac: myocarditis, dilated cardiomyopathy

Neuropsychiatric: Depression, migraine headaches, peripheral neuropathy, seizures, ataxia

Collagen Vascular: Sjogren 's syndrome, Rheumatoid Arthritis

Hematologic: anemia due to deficiencies of iron, B12, folate

Genetic: Down Syndrome, Turner Syndrome, Williams Syndrome

Renal: IgA nephropathy

Hepatic: Autoimmune hepatitis, benign elevation of liver enzymes

The estimated global prevalence of celiac disease is approximately 1-2%, with a higher prevalence noted in patients with a family history of celiac disease and /or personal history of Type I DM or autoimmune diseases.

HARTFORD HOSPTIAL'S DIGESTIVE HEALTH CENTER

For patients in Connecticut, Hartford HealthCare Digestive Health is a comprehensive resource for the prevention, diagnosis, and treatment of a full range of gastrointestinal disorders that affect the stomach, colon and digestive tract.

We provide expert care. But we also realize that when you visit us, you may be experiencing some discomfort. That's why we do everything we can to ensure that your visit is as pleasant and comfortable as possible. From routine screenings and common tests to advanced procedures and complex cases, we offer expert diagnostic and treatment capabilities, combined with the compassionate care every patient deserves. Learn more at Hartford Hospital's Digestive Health Center.

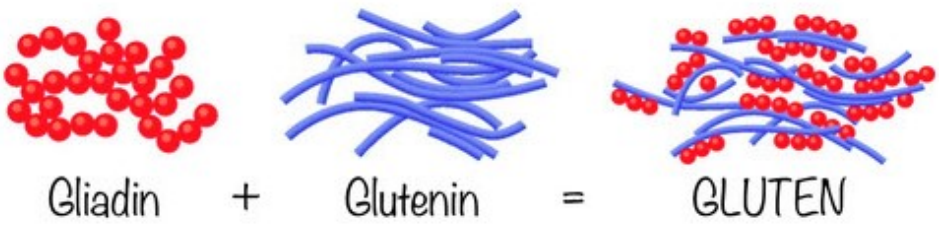
CELIAC DISEASE: PEDIATRIC PERSPECTIVE

The prevalence of celiac disease in children is approximately 1 %, which is like adult population. There are some distinctive aspects of presentation and management of celiac disease in children and adolescents that should be taken into consideration when taking care of this population.

The presentation of celiac disease in children has changed over years and there is a wide variation in symptoms. Symptoms may develop any time after gluten-containing foods are introduced into the diet, usually after 6-9 months of age. Gastrointestinal symptoms can range from mild such as abdominal pain, constipation, vomiting, diarrhea etc. to more severe symptoms such as weight loss and failure to thrive. They can also present with extraintestinal symptoms such as short stature, delayed puberty, aphthous stomatitis, and dental enamel defects and may have impaired bone health.

Prompt diagnosis and treatment of Celiac disease in children is important due to its potential of affecting their growth and development. Screening should be done in all patients who have concerning symptoms, family history, and associated autoimmune and genetic conditions.

Most children respond rapidly to gluten free diet and are able to achieve their growth potential. Compliance with gluten free diet can be very challenging in the pediatric population due to various reasons including their limited ability to understand the need of diet restriction, inability to resist temptation, feeling of deprivation, peer pressure etc. Therefore, it is essential that they have close follow ups with their physician, and dietitian, to reiterate, encourage and monitor compliance.



Structure of gluten

DIAGNOSTIC APPROACH

In a patient with suspected symptomatic celiac disease, a first degree relative with celiac disease, or an associated condition who needs testing for celiac disease, the diagnostic approach starts with blood work. Importantly, the patient must be regularly consuming gluten for this testing to be accurate. The recommended first step is measuring a tissue transglutaminase IgA level (tTG IgA) as well as a total IgA level. If the tTG IgA is >2X normal, a small bowel biopsy should be pursued. If the tTG IgA is positive but less than 2X normal, an endomysial IgA should be measured. As the endomysial IgA has nearly 100% specificity, if this test is negative, celiac disease is unlikely. If the endomysial IgA is positive, the next step is duodenal biopsy. If the tTG IgA is negative with a normal IgA level, celiac disease is unlikely. If the total IgA level is low, <7 mg/dl, the tTG IgA is unreliable and a deamidated IgG should be measured and duodenal biopsy pursued if positive. If negative, celiac disease is unlikely.

When evaluating celiac disease, the endoscopist should obtain at least four biopsies from the second portion of the duodenum and two biopsies from the duodenal bulb. If the biopsy shows villous atrophy in a patient with positive serology, a diagnosis of celiac disease is very likely. If biopsy findings demonstrate increased intraepithelial lymphocytes without villous atrophy, further testing with anti-endomysial IgA (if not already performed) and repeat assessment of tTG IgA is the next step. Also, measuring HLA DQ8 and HLA DQ2 should be considered because increased intraepithelial lymphocytes without villous atrophy is a non-specific finding that can be seen in many other disease processes. If the endomysial antibody is positive in a patient with permissive haplotypes, celiac disease is confirmed. If the endomysial antibody is negative, it is recommended to repeat serology with tTG IgA and endomysial IgA in 3-6 months. If the HLA DQ2 or HLA DQ 8 is negative, celiac disease is unlikely.

In a patient who has already begun a gluten free diet, the recommended approach is a gluten challenge during which the patient consumes gluten equivalent to one slice of wheat containing bread daily for a minimum of two weeks. A more prolonged gluten challenge of several months is preferred. Then, the patient may initiate testing with a tTG IgA and total IgA and follow the approach as above. If a patient declines to perform a gluten challenge, HLA DQ2 and HLA DQ8 can be measured and, if both are negative, celiac disease is unlikely. If one or both haplotypes are positive, the patient should again be encouraged to do a gluten challenge to allow accurate diagnosis.

There are a small percentage of patients with celiac disease who have negative serology. Thus, if there is a strong clinical suspicion for celiac disease, small bowel biopsy may always be pursued. If villous atrophy is present on the biopsy, the next recommendation is to measure haplotypes if not already performed. If the patient has permissive haplotypes and villous atrophy without another cause of villous atrophy identified, celiac disease should be strongly considered. The patient should be encouraged to follow a gluten free diet with repeat clinical assessment and repeat biopsy. The diagnosis of a seronegative patient is ultimately confirmed with clinical and histologic improvement on a gluten-free diet.

FOUR OUT OF FIVE RULE

Current standard of care is based on the "four out of five rule" which indicates that four out of five of the following criteria are enough to establish CD diagnosis:

1. Typical signs and symptoms (diarrhea and malabsorption)
2. Antibody positivity
3. HLADQ2 and/or HLADQ8 positivity
4. Intestinal damage (villous atrophy and minor lesions)
5. Clinical response to GFD

This helps physicians to identify the various subtypes of CD i.e. seronegative CD (absent point 2), potential CD (absent point 4), non-classic CD (absent point 1) and non-responsive CD (absent point 5).

TREATMENT OF CELIAC DISEASE AND NON-CELIAC GLUTEN SENSITIVITY

Consultation with a skilled dietitian

Education about the disease

Lifelong adherence to a gluten-free diet

Identification and treatment of nutritional deficiencies

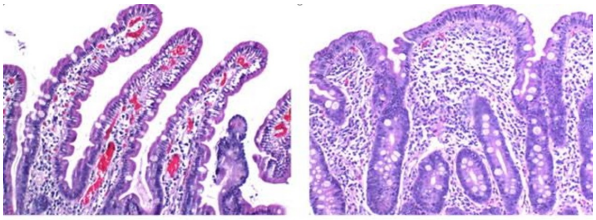
Access to an advocacy group

Continuous long-term follow-up by a multidisciplinary team

PATHOLOGY OF CELIAC DISEASE

In patients with celiac disease, the immune system abnormally responds to gluten, a protein found in certain foods and damages the lining of the intestines. The damage will limit the intestine's ability to absorb nutrients from foods and lead to various symptoms, including diarrhea, weight loss, and bloating. The disease develops as a combination of genetic factors and a trigger (gluten ingestion). Multiple tests can help in the diagnosis of celiac disease. A blood test can detect the immune system's response that forms immune proteins (antibodies) against a part of the small intestine lining (tissue transglutaminase). If this test is positive, the diagnosis can be confirmed by a microscopic examination of a tissue sample from the small intestine.

The small intestinal lining has finger-like structures, which are called villi. These villi increase the intestine's surface. The larger surface leads to more efficient absorption of the nutrients in the food. In patients with celiac disease, the gluten -induced immune system response will increase the number of lymphocytes (an immune response cell) in these villi. Eventually, those cells will cause damage leading to the flattening of the villi. In most patients, if they stop eating gluten-containing food, the immune response also stops and allows the healing of the villi. This response to gluten withdrawal is diagnostic of celiac disease. It also highlights the importance of continuing to eat gluten-containing foods during initial testing. However, a small subset of patients will not respond to a gluten-free diet (refractory celiac disease). Their small intestinal lining will show the same changes even after they stop eating gluten. In a few of these patients, the lymphocytes can become abnormal, grow out of control, and potentially develop lymphoma, a cancer of lymphocytes.



Normal **Celiac disease**

MANAGEMENT OF CELIAC DISEASE

The management of celiac disease involves the life-long adherence to a gluten-free diet. Patients with celiac disease should be referred to a registered dietitian to have dietary counseling.

Education of the patient and family about the significance of celiac disease and the intricacies of being on a gluten-free diet is essential to ensuring their success.

Patients with celiac disease are also commonly deficient in vitamins and minerals such as iron, calcium, magnesium, folate, vitamin b12 and vitamin D. Patients should have nutritional values checked periodically and supplementation should be given if needed.

After initiating a gluten free diet, patient should be seen for follow up visits every 3-6 months to assess response and adherence to gluten free diet, have serological testing and evaluate for complications of celiac disease.

If a patient has persistent or recurring symptoms despite gluten-free diet, clinicians should ensure that patients are not experiencing any gluten contamination and also exclude other diagnoses including microscopic colitis, exocrine pancreatic insufficiency, refractory celiac disease or enteropathy-associated lymphoma.

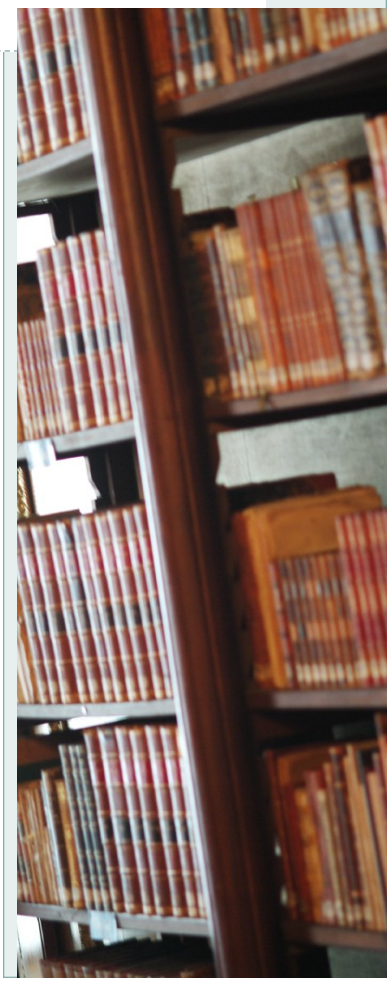
GLUTEN-FREE DIET

A strict gluten-free diet is essential for people diagnosed with celiac disease. Gluten is a protein found in wheat, rye, and barley and can be found in food and non-food sources including supplements and medications. All types of wheat, barley, rye, malt, and oats unless labeled as gluten-free must be avoided. Label reading is crucial in identifying gluten and gluten-containing ingredients. Gluten is not considered a major food allergen by the FDA, so is not required to be labeled as an ingredient. Manufacturers may voluntarily choose to indicate a product is gluten-free if it meets the FDA criteria. Wheat-free does not necessarily indicate gluten-free. Products labeled as certified gluten-free have been certified by an independent third party and may meet stricter criteria than those set by the FDA.

Avoidance of cross-contact with gluten is also essential by practicing good hand hygiene, keeping food and surfaces free of crumbs, storing gluten-free foods above gluten-containing foods in the pantry or refrigerator, using squeeze bottles for condiments, having a separate toaster for gluten-free and gluten-containing breads, avoiding bulk bins and buffets, being careful at the deli counter, thoroughly washing/sanitizing all utensils, pots, pans, and dishes, and identifying safe restaurants that can ensure avoidance of gluten cross-contact.

It is important to maintain a well-balanced diet that includes foods that are naturally gluten-free such as fresh fruits and vegetables, fresh fish/seafood, unprocessed meat, poultry, eggs, beans, legumes, nuts, seeds, milk, unprocessed cheese and dairy products, and gluten-free grains and plant foods. Avoidance of gluten is necessary to improve symptoms, allow intestinal healing, reverse or prevent nutritional deficiencies, and decrease risk for future health complications.

Delay in the diagnosis of celiac disease has not only been associated with a poor quality of life but also an increased frequency of developing autoimmune diseases, infertility, neurological problems, osteoporosis, cancer and anemia.



FOLLOW-UP OF PATIENTS WITH CELIAC DISEASE

Control of symptoms, facilitation of adherence to a gluten free diet and avoidance or early detection of complications are the general goals of monitoring celiac disease after a diagnosis. This is especially important in children to assure normal growth and development.

Periodic medical follow up with a health practitioner with knowledge of celiac disease is recommended, as is consultation with a dietician if gluten contamination is suspected. Monitoring of adherence to a gluten free diet is generally based on history provided by the patient as well as serologic testing of IgA TTG or IgA DGP antibodies and should demonstrate normalization of laboratory abnormalities detected during initial laboratory investigation. An upper endoscopy with intestinal biopsies may be an approach in cases where there is lack of clinical response or a relapse of symptoms despite a gluten free diet.

A follow up visit in 3-6 months after diagnosis is performed to assess symptoms, serology, and reevaluate for correction of abnormal baseline lab tests such as vitamin deficiencies, CBC and liver enzymes. If the response is adequate, the next follow up can be in 1 year for reassessment of symptoms and serologies as well as a DEXA scan. If there is an expected response, annual follow up can be continued.

If any follow up visits suggest an inadequate response, referral to a dietitian to assess for gluten free adherence is recommended. In cases where patients are strictly gluten free, work up for other causes of non-responsive celiac disease may be necessary.

Consideration may also be given to endoscopy for follow up biopsy to assess mucosal healing. In adults, the intestine will often fail to heal despite negative serology and absence of symptoms. This lack of healing may increase the risk of lymphoma, bone disease and ultimately lead to refractory celiac disease. In a US study, the median time from onset of a gluten free diet to achieve mucosal healing was 3 years.

CONNECTICUT GI PC

Our staff of physicians, advanced practitioners, physician assistants, clinical and administrative staff are here to provide our patients with comprehensive and compassionate care. Experts in diagnosis and intervention, our board certified gastroenterologists offer advanced treatment and diagnostic services for digestive and liver disorders.

Some of our doctors also have advanced training in areas such as biliary and pancreatic disorders, small bowel disease, pelvic floor dysfunction, and Barrett's esophagus. As a comprehensive gastroenterology practice we also offer on site infusion services for patients with inflammatory bowel disease in a comfortable environment

APPROACH TO THE NON-RESPONSIVE PATIENT

Celiac disease can be diagnosed in patients with symptoms of gastrointestinal bloating, flatulence, diarrhea, weight loss and other symptoms. It can be suspected and diagnosed in patients who exhibit minimal GI symptoms due to abnormal laboratory findings, such as iron deficiency, mild to modest elevation of liver enzymes, osteopenia, or associated with other medical conditions. Once the diagnosis is confirmed with serology and duodenal biopsies, the patient is advised to adhere to a lifelong gluten free diet (GFD).

Gastrointestinal symptoms usually improve within a few weeks after initiation of the GFD. However, not all patients will respond to a GFD. This presents a dilemma to the medical providers. This is referred to as nonresponsive celiac disease (NRCD). Primary nonresponse is when the patient's symptoms have not improved substantially despite maintaining a GFD for 6 months. Secondary nonresponse means that the patient has improved with the gluten free diet, but symptoms recur at a later time. The rate of NRCD in children is 20 -25%. In adults, it might be as high as 40 - 60%. One reason for the lower rate of nonresponse in children may be that parents are carefully controlling their diet. Also, their disease has not been present as long as in adults, where there is frequently a delay in making a diagnosis.

The most common causes of nonresponsive celiac disease in children are 1) exposure to gluten, 2) constipation, 3) lactose intolerance, 4) disorders of the brain-gut axis such as IBS/anxiety, or "functional abdominal pain". In adults one must also consider a diagnosis of small intestinal bacterial overgrowth syndrome (SIBO), microscopic colitis/collagenous colitis which may be seen in up to 4% of patients with celiac disease, and exocrine pancreatic insufficiency (EPI).

Many patients ingest gluten intentionally and unintentionally. A food can be labeled as gluten free if it contains <20 mg of gluten per kg of the food. In a recent study, 20% of breakfast cereals labeled as gluten free actually contained greater than the 20 mg/kg allowance. Therefore, the patients were eating gluten in a gluten-free product.

The designation "refractory sprue" refers to persistence of symptoms as well as villous atrophy despite adherence to a GFD. Refractory celiac disease (RCD) is thankfully rare, <1% of patients deemed to have NRCD.

Rare diagnoses include 1) Refractory celiac disease type 1, 2) RCD type 2, 3) Enteropathy associated T cell lymphoma (EATL), 4) autoimmune enteropathy, 5) Combined variable immunodeficiency disease (CVID), 6) drug induced villous atrophy such as from the antihypertensive drug class of -sartans, 7) collagenous sprue where a thick band of collagen has formed beneath the mucosa in the small intestine. This is analogous to "collagenous colitis".

Refractory celiac disease type 1 refers to high sensitivity towards minimal amounts of gluten, but the intraepithelial lymphocytes (IELs) are a normal population. In contrast, RCD type 2 has a clone of premalignant IELs, and can progress to EATL. EATL, which is rare, presents with small bowel perforation or obstruction and is usually diagnosed on the resected pathology specimen.

It is expected that the serologies should improve with adherence to a gluten free diet. One may expect the tTG-IgA to decrease by 20% within 6 months if the patient is on a GFD. It is assumed that normalization of tTG should correlate with mucosal healing of the duodenum. It is estimated that one third of patients will have duodenal healing by 2 years, and two thirds will have healing by 5 years. More recently additional studies have explored the role of gluten immunogenic proteins (GIP). These can be tested from stool or urine and can diagnose recent exposures to gluten. They are available OTC in Europe, and the United States.

For Patient Referrals:

CTGI: https://connecticutgi.org/celiac-info/#appt
HHC Digestive Health Center: 888 742-6257