Muralidhar Jatla, Ritu Verma, Series Editors

Overview of Celiac Disease: Differences Between Children and Adults

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INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. It presents as symptomatic subjects with gastrointestinal and non-gastrointestinal symptoms, as well as subjects without specific CD symptoms that are affected by type I diabetes, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency, and first degree relatives of individuals with CD (1). Although the classic patient with malnutrition and a distended abdomen is readily diagnosed, it is becoming increasingly evident that symptomatic CD patients represent just the tip of the celiac iceberg (Figure 1).

Affecting 1% of the general population in the United States, including children, untreated CD poses long-term adverse health consequences including osteoporosis, anemia, poor growth, increased risk of autoimmune conditions and intestinal lymphoma (2). This review describes the epidemiology, pathophysiology, associated conditions, and treatment of CD, with an emphasis on aspects specific to the pediatric population.

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CLINICAL FEATURES AND EPIDEMIOLOGY OF CELIAC DISEASE

Once thought to be a rare childhood disorder characterized by malabsorption, abdominal distension, lethargy, and failure to thrive, celiac disease is a prevalent (~1/100) food hypersensitivity disorder caused by inflammation induced by ingestion of gluten, a protein found in wheat, barley, rye and other grains (3). This classic presentation makes for an easy diagnosis but in many patients the disease can be clinically silent or have predominant extra-intestinal manifestations (4). Clinical presentation depends on age, sensitivity to gluten, gluten load, and other undetermined factors. Increased awareness and widespread serologic evaluation has resulted in a shift in the presentation of celiac patients (5).

A multitude of signs and symptoms have been ascribed to celiac disease (Table 1). Weight loss and diarrhea are not present in the majority of patients. A significant lag between onset of symptoms and diagnosis can exist because the overall onset of symptoms is gradual (6). Occasionally, a triggering event such as gastroenteritis, travel, stress or a change in diet can be identified. Frequently, non-specific, constitutional symptoms such as fatigue, lethargy, headache, poor appetite, and depression are concomitantly reported (7). Commonly, patients present with symptoms of bloating, abdominal pain, altered bowel habits and have been diagnosed with irritable bowel syndrome. Patients satisfying the Rome II criteria for irritable bowel syndrome have a 5% risk for having undiagnosed celiac disease as the cause of their symptoms (8).

(continued on page 21)

(continued from page 18)

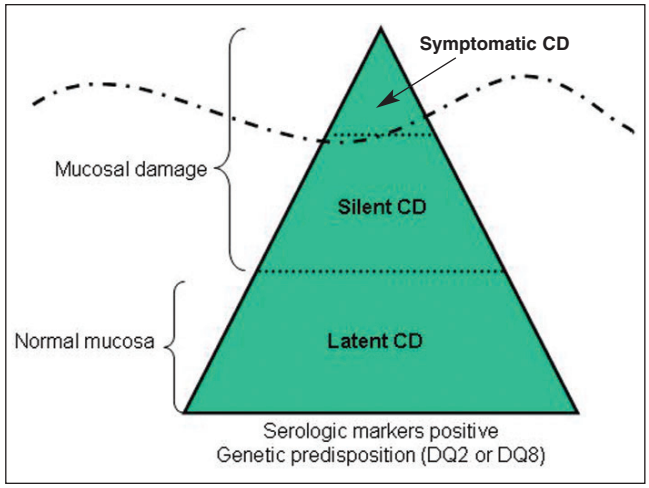

Figure 1. The Celiac Disease Iceberg.

In children, the most common age of presentation is 6–24 months. The most common gastrointestinal symptoms are chronic or recurrent diarrhea, abdominal distension, anorexia, failure to thrive or weight loss, abdominal pain, vomiting, constipation, and irritability (9). Celiac crisis is a rare presentation. Non-gastrointestinal manifestations tend to predominate in older children and adults (10). These include dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, (11) short stature, delayed puberty, iron deficiency anemia refractory to oral iron, hepatitis, arthritis and epilepsy with occipital calcifications (12).

CLASSIFICATION OF CELIAC DISEASE

The prevalence of celiac disease in children between the ages of 2.5 years and 15 years is three-to-13 per 1000 children or 0.3% to 1.25%. There are a substantial number of missed diagnoses of CD, possibly 10–50 times as many as have actually been diagnosed (13). Silent celiac disease is defined as having no or minimal symptoms, while manifesting mucosal damage on biopsy and positive serologic testing (Figure 1). These patients are identified by screening asymptomatic individuals from groups at risk such as first-degree relatives of CD patients, Down syndrome patients and Type 1 diabetics (14). These patients represent the middle of the iceberg. The bulk of the iceberg, the base, is comprised of patients with latent celiac disease. These asymptomatic patients may show positive serology, have DQ2 and/or DQ8 haplotype, but have normal mucosa on biopsy. They are typically asymptomatic individuals identified by screening groups at risk. These individuals, under the right circumstances, will develop mucosal changes and/or symptoms at some point (15).

Table 1
Signs and Symptoms Associated with Celiac Disease

Children	*Adults*
Fatigue	Abdominal pain
Bloating	Weight loss
Constipation	Chronic diarrhea
Abdominal pain	Infertility
Chronic diarrhea	Recurrent spontaneous abortion
Irritability	Dermatitis herpetiformis
Growth failure	Peripheral neuropathy
Osteopenia/osteoporosis	Depression
Delayed puberty	Fatigue/malaise
Hepatitis	Hepatitis
Dental anomalies	Aphthous stomatitis
	Alopecia
	Anemia
	Malignancy
	Seizures
	Ataxia
	Osteopenia/osteoporosis
	Arthritis

EXTRAINTESTINAL MANIFESTATIONS

The classic form of celiac disease presents with diarrhea, weight loss, abdominal pain, and deficiencies of nutrients such as iron, folate, calcium, and vitamin D. However, there are myriad presentations of celiac disease where extraintestinal manifestations dominate. These manifestations include persistent hypertransaminasemia, osteopenia, affective disorders, features of hyposplenism and autoimmune diseases. Other manifestations include dental enamel hypoplasia, short stature, delayed puberty, ataxia (16), peripheral neuropathy (17), and in adults, iron-deficient anemia unresponsive to treatment with oral iron (18).

Patients with minimal or no gastrointestinal symptoms may also present with cutaneous stigmata. Skin diseases presenting as extraintestinal manifestations are diverse and include dermatitis herpetiformis, urticaria, angioneurotic edema, cutaneous vasculitis, erythema nodosum, necrolytic migratory erythema, psoriasis, vitiligo, Behçet's disease, oral lichen planus, dermatomyositis, porphyria, alopecia areata, and pyoderma gangrenosum (19). Most of these skin conditions improve when a gluten-free diet is maintained (20).

Dermatitis herpetiformis (DH) presents as an itchy, chronic, papulovesicular eruption that may result in scarring (3). Typically seen as a symmetric eruption on extensor surfaces, DH tends to occur more in males in a 2:1 ratio in adults, with a reversed ratio in children. Characteristic histologic findings include microabscesses within the dermal papillae (20). Antigliadin, antiendomysial, and antitissue transglutaminase antibodies have been found in patients with DH (21). It is estimated that 90% of patients with dermatitis herpetiformis have gluten-sensitive enteropathy and gluten must be present in the diet for development of DH. The rash of DH is felt to be an external marker of intestinal sensitivity to gluten and is likely the result of molecular mimicry between the CD auto antigen tissue transglutaminase and skin derived epidermal transglutaminase. Topical application of gluten does not induce DH, whereas oral ingestion of gluten will induce DH in susceptible patients (22). Although patients with DH may lack gastrointestinal symptoms, they do manifest characteristic histologic changes on small bowel biopsies. Dermatitis herpetiformis may need to be treated with dapsone in addition to a gluten-free diet. Patients with DH are at increased risk for malignancy if not compliant with a GFD, regardless of gastrointestinal symptoms (23).

Liver disease is also described in celiac disease and presents as mild liver dysfunction, chronic liver disease, or autoimmune liver disease. Central theories of a common pathogenesis include impaired gut mucosal integrity, malnutrition, and generation of autoantibodies (24). Mild liver dysfunction characterized by elevated transaminases (aspartate aminotransferase and alanine aminotransferase) at the time of CD diagnosis is reported in up to 42% of adults (25) and 54% of children (26). Gamma glutamyl transferase and bilirubin are usually normal. Liver enzymes normalize within 12 months of gluten elimination in most cases. Mild, non-specific changes are seen in cases where a liver biopsy has been performed. Occasionally, mild hepatic steatosis is seen on histology and this also responds to a GFD. Asymptomatic CD has been found in 9% of adults being investigated for raised transaminases (27). Adults and children had normalization of their transaminases on a GFD (28).

Table 2
Conditions Associated with Celiac Disease

- IgA deficiency
- Type I diabetes
- Trisomy 21
- Autoimmune disorders
- Thyroid disease
- Turner syndrome
- Williams syndrome
- Sjögren's syndrome
- IgA nephropathy
- Idiopathic dilated cardiomyopathy

Severe liver disease including chronic hepatitis, severe fibrosis, and cirrhosis responsive to a GFD has been reported in adults and children (29). Four adults in whom liver transplantation was being considered were subsequently diagnosed with CD and after GFD initiation, hepatic function improved and transplantation was avoided (30). Italian literature reports an increased risk of CD in children with autoimmune hepatitis, with most having typical gastrointestinal symptoms. These children achieved remission with immunosuppression and GFD initiation, with relapse after gluten reintroduction (31–32).

Young adults with celiac disease have been found to have a higher prevalence of neurologic disorders and symptoms (33). Over half of these patients had neurologic disorders including hypotonia, developmental delay, learning disorders, ADHD, headache and cerebellar ataxia (34). Epileptic disorders were only marginally more common in CD. Tic disorders were not found to be different between CD and control patients. A gluten-free diet did result in therapeutic benefit for patients with transient infantile hypotonia and migraine headache (35).

Celiac disease has been known to cause metabolic bone disease, particularly in adults. In a large adult study from the United Kingdom (UK), the hazard ratio was determined to be 1.3 (95% CI, 1.16–1.56) for overall fracture risk, 1.9 (1.2–3.02) for hip fracture, and 1.77 (1.35–2.34) for wrist fracture (36). Interestingly, no overall increased risk of fracture has been found in this group of patients (37). Bone mineral density improves in patients with CD after initiation of a gluten-free diet. Consistent with findings of other centers, spine and whole body bone mineral composition abnormalities were not seen in pediatric CD at diagnosis at our institution.

HIGH-RISK POPULATIONS

A higher prevalence of celiac disease is seen in certain genetic, autoimmune, and relative groups (38). The frequency of CD is 5% in first degree relatives of diabetics or CD patients (10), 5% in type I diabetics, 4%–8% in autoimmune thyroiditis, 7% in IgA deficiency, 4%-19% in Down syndrome (39), 8% in Williams syndrome, and 4%–10% in Turner syndrome. These preceding groups have a celiac disease incidence rate roughly five times greater than the general population. Screening is recommended in these groups beginning at age three years and if they have negative serologic tests, be re-screened at intervals (40). Other conditions that have a higher prevalence of CD include arthritis (1.5%–7.5%), autoimmune liver diseases (6%–8%), Sjögren's syndrome (2%–15%), idiopathic dilated cardiomyopathy (5%), and IgA nephropathy (4%) in adult studies (41).

A common genetic and immunologic mechanism and the existence of CD itself are believed to play a role in the increased frequency of autoimmune conditions and celiac disease. The prevalence of autoimmune disorders in CD is related to duration of gluten exposure (42). It has been shown that if celiac disease is diagnosed before two years of age, there is a 5% chance of developing an autoimmune disorder by early adulthood. If CD is diagnosed at age two-to-10 years, the chance increases to 17%, and to 24% if age greater than 10 years. The prevalence of autoimmune disorders in diabetic patients with celiac disease was significantly higher than in subjects with Type I diabetes alone. The prevalence of autoimmune disorders in these patients' relatives with celiac disease was significantly higher than in those who tested negative for anti-endomysial antibodies (32).

GENETICS

A genetic predisposition, environmental triggers, and dietary factors contribute to initiate the underlying mucosal damage that results in celiac disease. Inheritance of CD is most likely multigenic although a strong HLA association exists. The vast majority of patients (90%–95%) have genetic markers encoded on chromosome 6 called human leukocyte antigen (HLA) DQ2 and most of the remainder have HLA-DQ8. HLA are cell surface markers that facilitate immune responses. Ten percent of patients have an affected first degree relative. Concordance in monozygotic twins is 70% and concordance in HLA-identical siblings is only 30%–40%, suggesting other genes are involved (43). HLA-DQ transcription may not be complete in some individuals and this may help to explain the late-onset in these patients. A homozygous cis genotype confers 100% transcription, heterozygous (cis and trans) confers 50% expression, and partial (cis or trans) confers 25% expression (44).

PATHOGENESIS

The degree of damage induced by gluten is influenced by immunity, genetics, cytokines, and environmental factors. Gluten digestion is not complete in humans and gliadin is one of the resultant peptides resistant to enzymatic processes (45). Protein binding receptors on antigen presenting cells recognize a 33 amino acid peptide in gliadin that contains critical epitopes high in glutamine and proline. This peptide is resistant to digestion in the lumen and penetrates the epithelial barrier (46). Zonulin, a protein that can increase intestinal permeability by promoting tight-junction disruption, is upregulated and this mechanism or alterations in permeability caused by infections may facilitate entry (47).

The enzyme tissue transglutaminase modifies this peptide as it deamidates glutamine residues to glutamic acid resulting in high affinity binding to HLA-DQ2 molecules on the surface of antigen-presenting

(continued on page 27)

(continued from page 23)

cells. This results in activation of the mucosal cytokine system by upregulation of interleukin-2 (IL-2) receptor expression, increased interferon (IFN) gamma mRNA expression, activation of nuclear factor kappa B (NF-kB) and upregulation of IL-15. Presentation of modified gliadin peptides in the context of HLA-DQ2 leads to activation of CD4+ lamina propria T cells. Gliadin-specific T cells produce IFN-gamma, which in turn enhances expression of DQ2/DQ8 molecules (44).

Epithelial cell infiltration comprised of increased intraepithelial lymphocytes (IEL) (>90% CD8, <10% CD4) and increased mucosal gamma/delta T cells (normal <10%) is seen. The role of gamma/delta cells in CD is unknown. Mucosal surface alterations including loss of epithelial cells, and proliferation of crypt epithelial cells are seen, although the mechanisms that lead to the typical CD lesions are still unclear (43). The humoral response includes enhanced antibody production, mainly anti-tissue transglutaminase (TTG), antigliadin, and other autoantigen (anti-actin) antibodies. The mechanism of antibody production is unknown. When antibodies to TTG are formed, enterocyte destruction ensues and signs and symptoms such as malabsorption, and bloating result and the characteristic blunted villi are seen on biopsy (44).

Tissue transglutaminase is an enterocyte enzyme released during injury and it stabilizes the cross-linking of proteins in granulation tissue (48). Its role in CD includes modification of gliadin epitopes. Formation of antibodies against TTG correlate with active celiac disease (49), particularly with more severe mucosal damage (50).

Malabsorption of nutrients, especially iron, folate, calcium, and vitamin D ensues and increased intestinal permeability may permit entry of other toxins which might induce autoimmune diseases (51). Unanswered questions include the mechanisms for failure of gliadin tolerance, the role of innate immunity, which epitopes are immunodominant, whether gluten has a direct effect on the mucosa, and how the mucosal Th1 response is induced and maintained.

DIAGNOSTIC STUDIES

It is crucial to confirm a diagnosis before treating as the diagnosis mandates a strict gluten-free diet for life. Following the diet is not easy and there can be significant quality of life (QOL) implications. More importantly, failure to treat has potential long-term adverse health consequences including increased morbidity and mortality. The classic diagnosis of CD require 1) characteristic small intestinal histology in a symptomatic child and 2) complete symptom resolution on a gluten-free diet. The gold standard for celiac disease diagnosis in at-risk or asymptomatic patients remains characteristic histology on small intestinal biopsies. Serologic tests may support diagnosis but they are most helpful to decide which patients to biopsy. Select cases may need additional diagnostic testing such as HLA haplotype testing (44).

SEROLOGIC TESTING

The role of serologic testing is primarily to identify symptomatic or at-risk individuals who need a biopsy. Because of high sensitivity and specificity, they are excellent for screening asymptomatic "at risk" individuals. Serologic testing can be used for monitoring dietary compliance. Serologic testing consists of antigliadin antibodies (AGA), antiendomysial antibodies (EMA), and antitissue transglutaminase antibodies (TTG). The first generation (guinea pig protein) tests were inferior to the second generation (human recombinant) tests (52).

AGA testing consists of antibodies (IgG and IgA) to the gluten protein in wheat, rye and barley. AGA testing has the advantage of being relatively cheap and easy to perform but it has poor sensitivity and specificity. EMA is an IgA based antibody against reticulin connective tissue around smooth muscle fibers. EMA testing has very high sensitivity and specificity but unfortunately, false negatives do occur in young children. Endomysial antibody testing is operator dependent, expensive and time consuming (53). Not surprisingly, EMA testing results in false negatives in IgA deficiency states. TTG Ab testing is IgA based antibody against tissue transglutaminase (CD autoantigen) (54). It has high sensitivity and specificity (human TTG), is not operator dependent (ELISA/RIA), and is relatively cheap. It also results in false negatives in young children and IgA deficiency. Studies have shown that tissue transglutaminase antibody testing is possibly less specific than endomysial antibody testing (18). Reported sensitivity and speci-

Table 3
Performance of Common Serologic Tests

	Sensitivity	*Specificity*
AGA-IgG	69%–85%	73%–90%
AGA-IgA	75%–90%	82%–95%
EMA-IgA	85%–98%	97%–100%
TTG-IgA	90%–98%	94%–97%

ficity ranges found in hospital and research lab settings for the most common serology tests are listed in Table 3, although recent studies (55) have reported lower sensitivity and specificity rates in commercial labs and in clinical practice (56).

IgA levels are reported with most grouped celiac panel tests to decrease false negative interpretation. Consider IgG based tests (EMA IgG and TTG IgG) in IgA deficiency states (57). Indications for serologic testing in children are listed in Table 4.

HLA HAPLOTYPE TESTING

The HLA-DQ2 is found in up to 95% of patients with celiac disease, and most of the remaining patients are HLA-DQ8 positive. These alleles are also found in 40% of the general population. They are necessary but not alone sufficient for developing CD. There is a low concordance between a positive HLA-DQ2 and celiac disease development. HLA testing has high negative predictive value and can be useful in certain situations such as when a diagnosis is unclear, when serologic or biopsy testing is performed when on a gluten-free diet, or in determining which family members to screen for CD (43).

ENDOSCOPY AND DUODENAL BIOPSY

Endoscopy guided duodenal biopsy is the gold standard of testing for celiac disease. Nodularity and scalloping can be seen in the duodenum during endoscopy but are not specific findings for CD. Histologic features of celiac disease include increased IEL's (>30/100 enterocytes), loss of nuclear polarity, change from columnar to cuboid cells, lamina propria cellular infiltration, crypt elongation and hyperplasia, increased crypt mitotic index, and progressive villous flattening or blunting.

Table 4
Indications for Serologic Testing in Children

- Diarrhea and failure to thrive
- Recurrent abdominal pain
- Unexplained anorexia, constipation, or vomiting
- Delayed puberty
- Weight loss
- Growth failure
- Dermatitis herpetiformis
- Unexplained transaminitis
- Dental enamel hypoplasia of permanent teeth
- Osteoporosis
- Iron deficiency anemia resistant to oral iron
- Asymptomatic children with conditions listed in Table 2

The Marsh criteria are the most commonly used grading scale of mucosal damage ranging from 0 (normal) to IIIa-c (various degrees of villous atrophy) (58).

MANAGEMENT

Primary management of a new diagnosis of CD consists of education about the underlying gluten induced enteropathy, need for strict adherence to a gluten-free diet (GFD), and monitoring for complications of CD.

DIETARY THERAPY FOR CELIAC DISEASE

Dietary therapy consisting of avoiding gluten is currently the only definitive treatment for celiac disease. Patients may ingest any foods not containing gluten, and all fruits and vegetables are safe foods. Adherence must be strict and life-long. Nutrition counseling about looking for gluten in unusual sources such as lipstick, medications, and supplements is crucial for success and compliance. Numerous resources, listed in the reference section, are available online, in bookstores, and through local support groups and national as well as global organizations.

Gluten-free Diet and Nutritional Counseling

Forth-five percent to 85% of children adhere to a GFD. Factors decreasing gluten free diet compliance include the inability to manage emotions, to resist temptation

(continued on page 33)

(continued from page 28)

and to exercise restraint. Feelings of deprivation and the fear generated from inaccurate information can be barriers as well. Time pressures including time to plan and prepare food must be considered. Assessing gluten content in foods, label reading and safely eating out can present challenges (9).

Social events, not wanting to look or be different and a lack of support of family and friends and statements like "Just a little bit—it won't hurt you" can impair compliance. Compliance can be increased by optimizing patient knowledge about the gluten-free diet with the help of a dietitian. Understanding the risk factors and serious complications that can occur to the patient as well as empowering them with the ability to break down big changes into smaller steps can help. Positive reinforcement and the ability to simplify or make behavior routine help greatly in increasing GFD adherence.

Follow-up visits and testing measure the health effects of eating gluten and provide important feedback. Test results can be a powerful motivator, especially for those who do not have symptoms when they eat gluten. Patients and parents look to the physician to tell them when follow-up testing is needed. Proactive follow-up measures can increase adherence (1).

FOLLOW-UP CARE

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines for monitoring include periodic visits for assessment of symptoms, growth, physical examination and adherence to a gluten-free diet. Tissue transglutaminase antibody testing at six months after gluten-free diet initiation and approximately 12 months after that if the patient is asymptomatic is recommended. TTG testing should occur at any time the patient is symptomatic after GFD initiation.

Pharmacotherapy for Celiac Disease

Future potential drug therapies include oral administration of bacterial endopeptidases that digest the toxic 33mer of gliadin, inhibitors of the zonulin pathway (47), and peptides that block the binding groove of DQ2 and DQ8. Other potential therapies being investigated include cytokine therapy (IL-10, IFN-gamma, and IL-15) and selective adhesion molecule inhibition (59). These therapies may alleviate some of the difficulties in maintaining a life long gluten-free diet. ■

RESOURCES

Celiac.com
www.celiac.com
National Institutes of Health
www.niddk.nih.gov
American Dietetic Association
www.eatright.org
The Gluten Intolerance Group—GIG
www.gluten.net
Celiac Disease Foundation—CDF
www.celiac.org
National Foundation for Celiac Awareness
www.celiaccentral.org
Center for Celiac Research
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