Systematic approach to celiac disease: a comprehensive review for primary providers

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Abbreviations:

CeD: Celiac disease
 IgA-TTG: Immunoglobulin A anti-tissue transglutaminase
 IgG-DGPs: Immunoglobulin G anti-deamidated gliadin peptides
 EMA: Anti-endomysial antibody
 GFD: Gluten free diet
 NCGS: Non-celiac gluten sensitivity
 NRCD: Non-responsive celiac disease
 RCD: Refractory celiac disease
 HLA: Human leukocyte antigen
 ACG: American College of Gastroenterology
 North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)
 ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology, and Nutrition
 SIBO: Small intestinal bacterial overgrowth
 IBS: Irritable bowel syndrome

Celiac disease is an immune-mediated illness to gluten exposure in genetically susceptible patients. It is characterized by chronic lymphocytic inflammation of the small bowel leading to villous atrophy and its associated complications. The global prevalence of celiac disease is increasing, due in part to improved screening tests and simplified diagnostic criteria. Novel therapies are being developed and include proteolytic enzymes, sequestering agents, and immunotherapies. A strict gluten-free diet, however, remains the mainstay of treatment. In this comprehensive review, we discuss the epidemiology, definitions, diagnosis, and treatment of celiac disease.

Key words: celiac disease, gluten sensitivity, gluten-free diet, primary care, diagnosis.

INTRODUCTION

Celiac disease (CeD) is a chronic enteropathy triggered by gluten in genetically predisposed individuals. The illness was first described in 1888 amongst children in London and became treated with dietary modifications, such as following a strict diet of bananas [1]. In 1940, gluten, which refers to the cereal proteins of wheat, barley, and rye, was discovered as the trigger for CeD [2].

CeD is a systemic illness that may present in children and adults in various manners. Patients may present with signs of malnutrition, including failure to thrive, short stature, and weight loss, or with symptoms of abdominal pain, chronic diarrhea, or nausea [3]. Extra-intestinal manifestations,

including dermatitis herpetiformis, vitamin deficiencies, iron deficiency anemia, aphthous stomatitis, elevated aminotransferases, and neurological manifestations, such as ataxia or seizures, may occur as part of the initial presentation [3].

Gluten contains a high number of proline residues, which make it resistant to proteolytic digestive enzymes [4]. The gluten polypeptides, including gliadin, glutenins, secalin, and hordein, remain undigested and cross the intestinal submucosa through paracellular and transcellular mechanisms [4]. Tissue transglutaminase (TTG) deamidates the gluten polypeptides, making them recognizable by antigen presenting cells (APCs). The APCs present deamidated gliadin peptides on MHC class II molecules, encoded by human

leukocyte antigen (HLA)-DQ2 or HLA-DQ8 genes, to T helper cells (T_h1 and T_h2 cells), initiating an adaptive immune response. Cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells are recruited, leading to apoptosis of enterocytes and damage of the intestinal submucosa. Cytokines released by T_h2 cells induce differentiation of B-cells into plasma cells, which produce autoantibodies against TTG and gliadin peptides. The inflammatory milieu causes destruction of the villi leading to villous atrophy.

EPIDEMIOLOGY

Until recent decades, CeD had been considered an uncommon illness, mainly affecting children and individuals of European descent [5]. Between 1974 and 2003, the prevalence of CeD increased from 0.21% (about 1 in 476 patients) to 0.95% (about 1 in 105 patients) across all patients in the United States [6]. Non-Hispanic white individuals have the highest prevalence of CeD in the United States compared to Hispanic or African Americans [7]. Similarly, the incidence of CeD increased in Europe from 5.2 to 19.1 per 100,000 person-years between 1990 and 2011 [8]. The exact reason for the increased incidence and prevalence is unclear, but it is partially due to improved diagnostics and widespread availability of serological testing [9].

RISK FACTORS FOR CED

Certain genetic and environmental exposures have been implicated as risk factors for CeD. The HLA class II haplotypes DQ2 and DQ8 are necessary but not sufficient for the development of CeD and contribute 35–40% to the genetic susceptibility in the development of CeD [2, 10, 11]. Non-HLA genes contribute about 65% to the genetic susceptibility [11]. Heritability of CeD is estimated at 87% based on twin studies, which have shown high concordance in monozygotic twins regardless of HLA genotype [12].

Feeding practices during childhood have been extensively researched, and the higher quantity of gluten in an infant's diet is associated with the development of CeD [13]. Time to initiation of gluten ingestion, breastfeeding, and avoidance of cow's milk do not alter the risk of developing CeD [14]. Certain conditions, including type 1 diabetes, IgA deficiency, Down

syndrome, Turner syndrome, Williams syndrome, and having a first-degree relative with CeD, have a strong association with the illness [15].

The microbiome has been suggested to be involved in the pathogenesis of CeD, but the current evidence is mixed [16]. An international multicenter, prospective study, called the Celiac Disease, Genomic, Environmental, Microbiome, and Metabolomic Study (CDGEMM), is currently enrolling infants genetically predisposed to CeD to determine the impact of microbiome-derived metabolites in its development [16].

CLINICAL PRESENTATION

Celiac disease is a highly heterogeneous illness, which may have a wide spectrum of presentations. The Oslo definitions characterize the various presentations of CeD. The expert consensus discourages the use of certain terms, including atypical CeD, latent CeD, typical CeD, and silent CeD, given their imprecise definitions [11]. Instead, it recommends the use of five classifications, including classical CeD, non-classical CeD, asymptomatic CeD, symptomatic CeD, and subclinical CeD [11].

Patients with classical CeD present with signs and symptoms of malabsorption, such as diarrhea, steatorrhea, failure to grow, or weight loss. In contrast, patients with non-classical CeD present without malabsorption, and usually experience a monosymptomatic disease without diarrhea or steatorrhea. These patients may present with chronic abdominal pain and constipation, but without malabsorption.

Patients with asymptomatic CeD are discovered usually through screening programs of high-risk individuals [11]. Minor symptoms, including fatigue, may be recognized after the initiation of a gluten-free diet (GFD). Subclinical CeD has been defined as a disease state with symptoms or signs below the threshold required for clinical detection. Patients with subclinical CeD may present with abnormal laboratory results, including iron deficiency anemia, elevated aminotransferases, osteoporosis, enamel defects, or incidental findings on upper endoscopy. Additionally, they may present with only extra-gastrointestinal symptoms (Table 1). Finally, symptomatic CeD has been defined as clinically evident disease that manifests as gastrointestinal and/or extra-gastrointestinal symptoms related to gluten intake.

Table 1

Extra-gastrointestinal manifestations of celiac disease

Extra-Gastrointestinal manifestations of celiac disease	
Constitutional	Fatigue
Dermatologic	Dermatitis herpetiformis
Endocrinologic	Miscarriage, delayed puberty
Hematologic	Iron deficiency anemia
Liver	Elevated aminotransferases
Musculoskeletal	Arthritis, osteopenia
Neurological	Ataxia, peripheral neuropathy, seizures
Oncologic	T cell lymphoma
Oral	Aphthous ulcers, dental enamel hyperplasia

A number of neurological manifestations may occur with CeD.¹¹ Gluten ataxia is defined as idiopathic sporadic ataxia that occurs in patients with positive anti-gliadin antibodies with or without enteropathy [17]. CEC syndrome is rare and characterized by celiac disease (C), epilepsy (E), and cerebral calcifications (C) [18]. Vitamin deficiencies (folate and vitamin B12) from malabsorption underlie the mechanisms of gluten ataxia and CEC syndrome.

* A gluten challenge consists of 4 to 12 weeks of a normal diet with 3 slices of wheat bread daily

¥ Perform HLA DQ2/DQ8 screen if TG-IgA is weakly positive, defined as 2-3x upper limit of normal. If positive, then perform a small-intestine biopsy. If negative, CeD is excluded.

§ A positive biopsy consists of Marsh 3 histopathological findings, namely the presence of villous atrophy.

GFD: Gluten-free diet

TG-IgA: Tissue transglutaminase IgA

HLA: Human leukocyte antigen

EMA: Anti-endomysial antibody IgA

CeD: Celiac disease

Figure 1. Diagnostic algorithm for symptomatic or at-risk individuals.

DIAGNOSTIC EVALUATION

Whom to test?

1. Test patients with symptoms, signs, or laboratory findings suggestive of malabsorption, including diarrhea, steatorrhea, bloating, or weight loss [19, 20].
2. Screen first-degree relatives of patients diagnosed with CeD via serological testing, who present with probable signs and symptoms of CeD [19, 20].
3. Consider screening asymptomatic first-degree relatives of patients diagnosed with CeD [19, 20].
4. Test patients with type 1 diabetes if they have gastrointestinal symptoms suggestive of CeD, or in patients with elevated aminotransferases without a clear etiology [19, 20].

How to test?

IgA-TTG is the preferred first-line screening test for CeD [19]. Total IgA levels should be obtained concomitantly to determine if concurrent IgA deficiency exists as it is present in 2–3% of patients with CeD and may result in a false-negative result [21]. Ideally, testing should be obtained while the patient is following an unrestricted diet as a GFD prior to testing may give a false-negative result. Testing of HLA DQ2/DQ8 genotypes should be performed to exclude CeD in this scenario. Patients with positive HLA testing should have a gluten challenge consisting of 3 slices of wheat bread daily (~ 3 g gluten daily) for 4–12 weeks and then retested for IgA-TTG [22].

If IgA levels are normal, and titers of IgA-TTG are positive, then the next step involves an upper endoscopy with duodenal biopsies. If IgA levels are normal, but titers of IgA-TTG are negative, then CeD is excluded. If IgA-TTG levels are weakly positive, however, then duodenal biopsies are warranted [22]. If IgA levels are low, additional serological testing is indicated with immunoglobulin G (IgG) anti-deamidated gliadin peptides (DPGs). If IgG-DPG is negative, then CeD is excluded. If positive, then duodenal biopsies are indicated. If there is a high suspicion for CeD despite a negative IgA-TTG with normal IgA levels, i.e., seronegative CeD, then duodenal biopsies are recommended [22].

The American College of Gastroenterology (ACG) guidelines recommend duodenal biopsies

as a critical component in the diagnosis of CeD, including 2 from the duodenal bulb (9 o'clock and 12 o'clock positions) and at least 4 from the distal duodenum [19]. The histopathological findings of CeD are threefold, and involve intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy. Three classification criteria are used to grade the histopathological findings in CeD, and include the Marsh, modified Marsh, and Corraza classifications. The presence of villous atrophy separates a positive from a negative biopsy.

In cases with discordant results between the biopsy and serological tests, additional testing is indicated [19]. If the biopsy is equivocal (Marsh 1 to 2, i.e., absence of villous atrophy), HLA-DQ2/DQ8 genotyping is indicated. A negative HLA result excludes CeD given its high negative predictive value, whereas a positive result maintains CeD as a possibility [10]. In cases of negative serological testing but a positive biopsy, then other causes of villous atrophy should be considered and excluded before further considering CeD [19]. Anti-endomysial antibody (EMA) testing is primarily used in cases of discordant results, and may be used with HLA-genotyping and repeating IgA-TTG if biopsy results are negative [23].

American guidelines, including from the ACG and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), recommend obtaining a duodenal biopsy as the confirmatory test for CeD [15, 19]. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines, however, provides an alternative approach to diagnosing CeD without a biopsy in pediatric patients by using a quantitative test of IgA-TTG for first-line screening [24]. If IgA-TTG titers exceed 10 times the upper limit of normal in a symptomatic pediatric patient, then a second blood sample should be tested for EMA, repeat IgA-TTG, and HLA-DQ2/DQ8 [24]. If the IgA-TTG persistently exceeds 10 times the upper limit of normal, and the EMA is positive, then CeD can be diagnosed.

A recent prospective study showed a small bowel biopsy may not be required in pediatric patients with strong serological evidence of CeD as proposed by the ESPGHAN guidelines [25]. The presence of any symptom, an IgA-TTG titer greater than 10 times the upper limit of normal, and a positive EMA, had a positive predictive value (PPV) for CeD of 99.75%. The PPV was 100% when malabsorption was used as the only

symptom. Additionally, it found the inclusion of HLA genotyping did not improve the accuracy of the diagnostic algorithm. This biopsy-sparing approach would decrease the need of an upper endoscopy by 30–50% [25]. The American Gastroenterological Association (AGA) released a

clinical practice update of the utility of diagnostic testing and suggested a biopsy-avoiding diagnostic pathway based of this approach [26]. Nonetheless, the AGA suggests considering an upper endoscopy with duodenal biopsies in adults to evaluate for the differential diagnosis.

* Prospective studies have validated the biopsy-avoiding approach in pediatric patients. AGA Best Practice Advice 2a supports the biopsy-avoiding approach given its positive predictive value of 100%, but suggests proceeding with upper endoscopy in adults for differential diagnosis

GFD: Gluten-free diet

HLA: Human leukocyte antigen

CeD: Celiac disease

TG-IgA: Tissue transglutaminase IgA

EMA: Anti-endomysial antibody IgA

ULN: Upper limit of normal

Figure 2. Biopsy-avoiding diagnostic algorithm for symptomatic or at-risk individuals.

Celiac disease versus non-celiac gluten sensitivity

The Oslo definitions for celiac disease defined the illness as “a chronic small intestinal immune-mediated enteropathy precipitated by

exposure to dietary gluten in genetically predisposed individuals” [11]. Additionally, it defined CeD as a permanent condition which leads to mucosal pathology and reverses with the avoidance of dietary gluten [11]. The expert consensus defined the umbrella term “gluten-related disorders” as all

diseases precipitated by dietary gluten exposure and discouraged the use of gluten intolerance or gluten sensitivity as being synonymous with CeD. Instead, the group defined the term “non-celiac gluten sensitivity (NCGS)” to describe a set of manifestations, either immunological, morphological, or symptomatic, that arises from gluten ingestion in patients where CeD has been excluded.

To distinguish between CeD and NCGS, the expert consensus recommended a systematic evaluation to exclude CeD and other inflammatory disorders [11]. Similar to CeD, gastrointestinal and extra-gastrointestinal manifestations may occur in NCGS, which improve with the abstinence of gluten. In contrast to CeD, NCGS lacks the presence of an enteropathy, genetic predisposition, and autoantibodies. Negative serological testing with total IgA and anti-TTG antibody, and a negative small intestinal biopsy are recommended to distinguish NCGS from CeD. Separating CeD from NCGS is important as it determines the long-term treatment and management of patients as NCGS has been implicated to be a transient condition [27]. In patients with NCGS, expert consensus recommends a GFD for 12 to 24 months before reassessing for gluten intolerance [27]. In contrast, patients with CeD must follow a lifelong and strict GFD.

Treatment approach

The mainstay of treatment for CeD involves adhering to a strict GFD indefinitely [19]. Following a strict GFD may be challenging as gluten may be present at small amounts in medications, supplements, or food [22]. Although studies have found a possible role of probiotics as an adjunctive therapy in CeD, current guidelines do not recommend their use [4]. Recommendations suggest referring patients to dietitians and to pharmacists [19]. In addition to wheat, barley, and rye, patients should be advised to avoid oats for the first year following diagnosis because of cross-sensitivity [22]. In children, adhering to a strict GFD is of upmost importance as it will lead to normal growth and development, and avoidance of complications [19].

COMPLICATIONS

Adhering to a strict GFD leads to resolution of symptoms, mucosal healing, and avoidance of complications in the majority of cases [19].

Complications, including risk of malignancy and mortality, may arise in those patients who fail to adhere to a GFD, and consist of small-bowel adenocarcinoma, esophageal cancer, and intestinal T-cell lymphoma [19]. Nutritional deficiency secondary to decreased absorption of micro-nutrients, including iron, folate, vitamin D, B6 and B12, and zinc, copper and carnitine, is a well-known complication of CeD [19]. Osteoporosis, infertility, spontaneous abortions, and pre-term labor have also been shown to occur at higher rates in patients with CeD [19]. Given the numerous complications that are possible if patients fail to adhere to a strict GFD, routine follow-up visits are strongly recommended in patients with CeD [19].

SURVEILLANCE & FOLLOW-UP

The first return visit should occur at 3–6 months following the diagnosis of CeD and should involve determining the patient’s level of adherence to a GFD, symptom resolution, and performing repeat serological testing, including IgA-TTG or IgG-DGPs. Additional tests at this visit may include a complete blood count, liver function tests, and testing for micronutrients, such as copper, zinc, vitamins A, D, E, and B12, folic acid, iron, ferritin, and carotene. Eighty percent of patients will test negative for IgA-TTG after 6–12 months of adhering to a strict GFD [28]. After being on a strict GFD for 5 years, 90% of patients will have negative serological testing [19]. Additionally, symptom improvement may be expected by the first follow-up visit [19]. Mucosal healing is expected within 1–2 years of following a GFD. Therefore, a follow up duodenal biopsy is not generally recommended if patients are adherent to a GFD. [19] If patients fail to improve or have an inadequate response (i.e., no improvement of symptoms or lack of decrease in serological titers) at the first visit, then the patient should be referred to a dietitian and the clinical response should be monitored at the next visit. The role of the dietitian is to evaluate for unintentional ingestion of gluten by reviewing the patient’s diet habits. After six months of follow-up, subsequent visits may occur annually in patients who are strictly adhering to a GFD. Follow up duodenal biopsies are indicated in two scenarios, 1) in patients with potential CeD defined as having positive serologies but negative duodenal biopsies, and 2) to evaluate for an inadequate response, as discussed below. [19]

* Inadequate response defined as lack of symptomatic improvement or decrease in serological titers

[¥] Other testing may include a complete blood count, liver function tests, and testing for micronutrients, such as copper, zinc, vitamins A, D, E, and B12, folic acid, iron, ferritin and carotene

[§] After confirming diagnosis of CeD based off previous work-up, a repeat upper endoscopy with duodenal biopsies is indicated for the evaluation of NRCD.

CeD: Celiac disease

GFD: Gluten-free diet

RCD: Refractory celiac disease

NRCD: Non-responsive celiac disease

SIBO: Small intestinal bacterial overgrowth

IBS: Irritable bowel syndrome

Figure 3. Surveillance and follow-up of patients with celiac disease.

NON-RESPONSIVE AND REFRACTORY CELIAC DISEASE

If an inadequate response is observed, then non-responsive celiac disease (NRCD) should be suspected. NRCD is defined as persistent symptoms despite following a strict

GFD for 6–12 months and occurs in 7 to 30% of patients [29, 30]. The most common causes of NRCD are the unintentional ingestion of gluten, followed by other food intolerances, including lactose or fructose intolerance [29, 30]. Other considerations include small intestinal bacterial overgrowth (SIBO), pancreatic insufficiency,

irritable bowel syndrome (IBS), microscopic colitis, and refractory CeD [29, 30]. After reviewing the initial results that confirmed CeD, and excluding the other possible causes for NRCD, a repeat biopsy is indicated, which would show ongoing lymphocytic inflammation with villous atrophy [19]. Other causes of villous atrophy, such as autoimmune enteropathy, drug-induced enteropathy (olmesartan), intestinal lymphoma, infectious enteritis, Whipple disease, tropical sprue, hypergammaglobulinemic sprue, intestinal tuberculosis, acquired immune deficiency syndrome (AIDS) enteropathy, should be considered and evaluated if indicated [19]. The treatment approach to NRCD should be directed against the underlying etiology if discovered [19].

Refractory CeD (RCD) is defined as persistent symptoms of malabsorption despite following a strict GFD for at least 12 months with biopsy showing villous atrophy in the absence of other causes [19]. It is uncommon occurring in 1 to 2% of patients with CeD [31]. There are two types of RCD: Type I and Type II, which differs by the presence of CD3 T-cells with abnormal immunophenotype expression, including the lack of CD8 [31]. Treatment of RCD is not well established and involves using immunosuppressive medications, including glucocorticoids (budesonide), immunomodulators (azathioprine), monoclonal antibodies (anti-tumor necrosis factor agents) in addition to a GFD [19]. Nutritional support with total parenteral nutrition (TPN) may be implemented. Type II RCD carries a worse prognosis than Type I as it is less likely to respond [31]. Additionally, the 5-year survival of Type II RCD as compared to Type I, was 44% and 93, respectively [31]. Experimental treatments for Type II RCD have included bone marrow transplantation, anti-TNF agents, and cyclosporine [19, 31].

HORIZONS

A GFD may not resolve the gastrointestinal and extra-gastrointestinal symptoms associated with CeD as 7 to 30% of patients do not respond initially [4, 30]. Gluten is ubiquitous in the food preparation industry and can be found in trace amounts in unsuspecting areas. The strict observance of a GFD may be difficult and adherence rates plummet to 35% at four years

after diagnosis [32]. Additionally, about 20% of adults develop therapy-resistant CeD despite being adherent to a GFD [33]. Given the limitations of the GFD, additional therapies for CeD are being developed.

Novel nondietary therapies for CeD target its pathogenesis and include endopeptidases, gluten-sequestering polymers, and tight junction modulators. Endopeptidases are enzymes that catalyze the post-proline hydrolysis of peptides and reduce the immunogenicity of gluten [4]. Randomized clinical trials on these agents have shown mixed results with one trial demonstrating improvements in mucosal inflammation and clinical symptoms after 6 weeks on the highest dose of latiglutenase when compared to placebo [4]. BL-7010 is a non-absorbable polymer that sequesters intraluminal gliadin and prevents its degradation, which has been found to reduce gluten associated histological changes in a mouse model of CeD [4]. A phase I/II clinical trial of BL-7010 has been completed but results have not been published (NCT01990885). Larazotide is an octopeptide similar to the zona occludens toxin of *Vibrio cholerae* that stabilizes the tight junctions of the small bowel and prevent gliadin-induced permeability changes [34]. Randomized trials of larazotide have shown promising results with patients reporting symptomatic improvement when coupled with GFD [4]. Other therapies target the immunogenic pathways of gliadin presentation on T-cells to prevent or decrease the adaptive immune response. These agents are under investigation, and include HLA-DQ2/-DQ8 blockers, interleukin and CD-3/CD-20 antagonists, and chemokine receptor inhibitors [4]. Another potential treatment being explored is fecal microbiota transplantation (FMT) given the role of the microbiome on the pathogenesis of CeD [35–37]. Several randomized trials (NCT04706611, NCT04014413) are underway and seek to address the safety and efficacy of FMT in several diseases, including CeD.

CONCLUSION

Primary care providers are essential in the diagnosis and management of patients with CeD. We believe this comprehensive review will facilitate the understanding of the evidence behind the diagnosis and management of CeD.

Boala celiacă este o boală autoimună mediată de expunerea la gluten la pacienții susceptibili genetic. Este caracterizată prin infiltrat inflamator al intestinului subțire ce duce la atrofie viloză și complicațiile asociate. Prevalența globală a bolii este în creștere mai ales datorită screening-ului și a criteriilor de diagnostic simplificate. Sunt în curs de dezvoltare noi opțiuni terapeutice, printre care agenți secheștranti, imunoterapii și enzime proteolitice. Dieta strictă fără gluten rămâne prima opțiune de tratament. În acest articol sunt trecute în revistă epidemiologia, definiția, diagnosticul și tratamentul bolii celiace.

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