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Review Article

New Approaches to the Diagnosis and Management of Celiac Disease in Children

Rishi A and Absah I*

Division of Gastroenterology and Hepatology, Mayo Clinic, USA

***Corresponding author**

Imad Absah, Division of Gastroenterology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA, Tel: 507-266-0114; Fax: 507-293-0366; Email: absah.imad@mayo.edu

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Abstract

Celiac Disease (CD) is a chronic immune-mediated disease that is triggered by the consumption of gluten present in wheat, barley and rye in genetically predisposed individuals. The increment in the prevalence and incidence of CD in recent years may reflect a true increment, rising awareness among physicians or use of highly sensitive serologic tests. The clinical presentation of pediatric CD has changed in recent years and a number of patients are presenting with "atypical" and "silent" forms. Physicians should be aware of these unique presentations and high-risk populations in order to avoid under-diagnosis of CD. Recent European guidelines suggested that the diagnosis can be made without biopsy. These new guidelines should be followed with caution as persistent villous atrophy may be associated with a risk of morbidity and mortality. Initial screening at the time of diagnosis should include checking for autoimmune disorders (hepatitis and thyroiditis) and inadequate response to Hepatitis B Virus (HBV) vaccination. However, evaluation for vitamin deficiencies and low bone mineral density (BMD) may not be necessary. All first-degree relatives should be screened by serologic testing owing to the higher risk of CD. Human leukocyte antigens (HLA)-DQ2 and DQ8 are important but not sufficient to predispose to CD. However, HLA testing could be utilized in screening infants born to families with CD. Compliance to gluten free diet (GFD) is particularly difficult for teenagers because of social and psychological factors. Novel therapeutic strategies which may improve quality of life for these patients include gluten detoxification, modulation of intestinal permeability and modulation of aberrant immune response.

ABBREVIATIONS

CD: Celiac Disease; GFD: Gluten Free Diet; HLA: Human Leukocyte Antigen; Ig: Immunoglobulin; TTG IgA: Tissue Transglutaminase Immunoglobin A; EMA: Endomysial Antibodies;GI: Gastrointestinal; HBV: Hepatitis B Virus; HBsAg: Hepatitis B surface Antigen; BMD: Bone Mineral Density; AGA: Anti Gliadin Antibodies; DGP: Deamidated Gliadin Peptide

INTRODUCTION

Celiac Disease (CD) is a chronic immune-mediated disease that is triggered by consumption of gluten present in wheat, barley and rye [1]. It occurs in individuals carrying specific Human Leukocyte Antigens (HLA)-DQ2 or DQ8 and is associated with an inconsistent combination of elevated titers of CD-specific antibodies, an inflammatory enteropathy of variable severity and a wide range of extra-intestinal manifestations [2]. Lifelong adherence to a strict gluten free diet (GFD) remains the only available treatment for patients with CD [3]. Occurrence of CD is not age-restricted but adolescents seem to have the greatest trouble in coping with this disease [4]. This may be related to compliance with a GFD which may be difficult for teenagers because of social and psychological factors [5].

CD follows the iceberg model of diseasewhere classic malabsorption represents the tip of the iceberg whereas less typical manifestations of the disease are below the waterline and are thus invisible [6]. CD affects about 1% of the American population [7]. Recent data suggest that for every patient identified as having CD, 7 to 8 remain undiagnosed [8]. The prevalence of CD has increased dramatically in the United States during the last 50 years [9]. It has also been demonstrated that the incidence of CD has increased both in adults and children over the last decade [10]. The increment in the prevalence and incidence of CD in recent years may reflect a true increment, rising awareness among physicians or use of highly sensitive serologic tests

Clinical Presentation

"Typical" CD is characterized by the presence of obvious intestinal manifestations characterized by malabsorption, while "atypical" and "silent" CD are associated with extra-

intestinal manifestations and asymptomatic presentation respectively [11]. Atypical CD is characterized by few or no gastrointestinal (GI) symptoms, and predominantly extra-intestinal features including but not limited to osteoporosis, iron deficiency anemia, delayed puberty, short stature, infertility, and recurrent spontaneous abortions [12]. In recent years, the proportion of children presenting with diarrhea, weight loss and abdominal distension (typical CD) has decreased while patients presenting with extra-intestinal manifestations (atypical CD) and asymptomatic patients (silent CD) identified by targeted screening of high-risk groups (positive family history of CD, presence of type 1 diabetes mellitus, immunoglobulin A (IgA) deficiency, and Down syndrome) have increased [13]. Since increasing number of patients are presenting with atypical and silent forms of CD, physicians should be aware of these unique presentations and high-risk populations in order to avoid under-diagnosis of the disease.

Diagnostic Criteria

The guidelines from North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPHGAN) for CD diagnosis recommend screening with serologic testing using anti Tissue Transglutaminase Immunoglobin A (TTG IgA) followed by confirmatory small bowel biopsy [14]. However, recent European guidelines suggest that the diagnosis of CD can be made without duodenal biopsy in a select group of patients when the likelihood of villous atrophy is high [15]. This group consists of individuals who have manifestations suggestive of CD and high titers of anti TTG IgA (>10 times upper limit of normal). However, to avoid life-long mislabeling of a patient with CD due to false positive serology, an anti-endomysial antibody immunoglobulin A (EMA) test should be conducted to confirm positivity of CD-specific antibodies in these patients [15]. In most patients with CD, symptomatic improvement is observed in the few weeks after starting GFD [16]. This surprisingly quick clinical response with GFD is not always associated with mucosal recovery [17]. The latest data suggest that the rate of mucosal healing in treated children is only 64% after a period of 24 months [18]. More importantly, persistent villous atrophy has been found to be associated with an increased risk for lymphoproliferative disorders [19]. Hence, a prospective assessment of the true rate of mucosal healing in treated children with CD or developing a noninvasive test that can assess the mucosal healing is very important before omitting the need for duodenal biopsy.

Antigliadin antibodies (AGAs) are produced in the small intestine and have been used in the past as an adjunct for diagnosis of CD. However, AGAs are not very specific which led to the development of deamidated gliadin peptide (DGP) assay which is more specific for CD.Most recent data suggests that a new time-resolved immunoflurometric assay for detecting anti-deamidated gliadin peptide (DGP) antibodies is associated with high sensitivity and specificity for the diagnosis of CD in children [20].

Role of "bulb" biopsy

Involvement of the smallintestine in pediatric CD is often patchy and may be associated with variable severity even within a single biopsy fragment which cannot be predicted clinically [21]. It has also been shown that mucosal injury associated with CD may be limited to the duodenal bulb [21,22]. Recent European and American guidelines suggest that multiple endoscopic biopsies, including the duodenal bulb, should be obtained in patients when there is suspicion of CD to maximize the diagnostic yield [15,23].

Recommended screening in pediatric patients with newly diagnosed Celiac Disease

Autoimmune thyroid diseases such as Hashimoto thyroiditis and Graves' disease are associated with CD [24]. A recent study showed an increased prevalence (~3 fold) of thyroid autoimmunity among children with CD compared to healthy age and sex-matched controls and GFD did not seem to be protective in these patients [25]. Thus, all newly diagnosed pediatric patients with CD should be checked for the presence of thyroid autoimmunity.

The most common liver abnormality in patients with classic CD is hypertransaminasemia which responds rapidly to a GFD [26]. In addition to this celiac hepatitis, CD may be associated with other autoimmune liver disorders such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis all of which do not respond GFD [27]. It can be recommended that all newly diagnosed pediatric patients with CD should be evaluated for liver disease

CD has been historically associated with malabsorption that can result in deficiency of fat-soluble vitamins (A, E, D and K) and other trace elements [28]. A recent study showed that fat-soluble vitamin deficiencies seem to be uncommon in pediatric patients with CD, and the cases of mild deficiencies are corrected with GFD and vitamin supplements [29]. This may be due to an increase in the prevalence of "atypical" CD which is not associated with malabsorption. It can thus be suggested that routine measurement of fat-soluble vitamins levels in newly diagnosed pediatric CD patients may not be necessary unless there are symptoms of malabsorption [29].

The response rate to Hepatitis B Virus (HBV) vaccination in CD patients is found to be lower than the response inthe general population [30]. Both hepatitis B surface antigen (HBsAg) protein fragments and gliadin peptides bind to HLA-DQ2 molecules, and the resulting competition may lead to aberrant antibody response to the recombinant HBsAg vaccine in patients with "active" CD [31]. This problem of unresponsiveness to HBV in CD patients with "active" disease could represent a global problem [32]. It can be recommended that all children with a new diagnosis of CD should be tested for adequate response to HBV vaccination. Those who have inappropriate response should be revaccinated only after the decrease of CD-specific antibodies which usually occurs after one year of strict GFD so that adequate response to vaccination can be obtained [32].

Low bone mineral density (BMD) of the skeleton is a common complication of untreated pediatric CD [32-34]. This may be related to bone resorption due to increased secretion of parathyroid hormone as a compensatory response to negative calcium balance [35]. However, low BMD in children responds after short term treatment with GFD [33,36]. Thus, early diagnosis and treatment of CD should protect pediatric patients from osteopenia. It can be recommended that routine evaluation

of BMD in children with a new diagnosis of CD may not be necessary.

Screening of family members of patients with Celiac Disease

Genetics plays a crucial role in the predisposition to CD. The frequency of CD is significantly increased in patients who have a first-degree relative affected with CD [37]. The latest American guidelines suggest that all newly diagnosed patients with CD should inform their first-degree relatives and recommend them for testing owing to the risk of CD [23]. Routine testing of symptomless first-degree relatives is reasonable but debatable [23]. However, it is important to note that even those patients who initially thought themselves to be without symptoms will often report improved health after starting GFD [38]. It was thus suggested that untreated children with CD may have minor symptoms that are recognized only retrospectively after initiation of GFD [38]. Although 30%–40% of Caucasians carry the HLA-DQ2 or DQ8, less than 3% of these individuals will suffer from CD [39]. Thus, the result of DQ2 and DQ8 testing is only helpful when it is negative because it will help rule out CD. Based on aforementioned reason, the recommended test for screening first-degree relatives of patients with CD is TTG IgA.

Different approach could be suggested for infants born into family with CD, because the latest data showed that neither the timing of gluten introduction nor breast-feeding modified the risk of CD genetically predisposed infants to CD[40].The only predictiverisk factor in infants is the genetic predisposition to CD which results from carrying the HLA-DQ2 [40]. Based on that, it may be reasonable to recommend the genetic testing for infants at higher risk of CD and consider delaying gluten introduction until age of 2 years when vital organs like the brain have completely developed.

Novel Therapeutic Strategies

Treatment based on GFD is troublesome for patients and is associated with poor compliance in some people.This has led to the development of new therapeutic strategies which may improve quality of life in these patients including gluten detoxification, modulation of intestinal permeability and modulation of immune response[41].

Gluten detoxification is a process by which the gluten present in food is removed or degraded, thus decreasing the pathologic immune response which is responsible for CD. This can be achieved by genetic engineering of grains with deletion of a specific gene (alpha- gliadin locus) which reduces the amount of gluten present in the grains [42]. Moreover, a protease (ALV003) which degrades gluten present in diet into non-immunogenic fragments before it can cross the intestinal epithelium is in clinical trials [43].

Modulation of intestinal permeability could also help treat CD as immunogenic particles cross the mucosal barrier by both trans-cellular and para-cellular mechanisms. Larazotide acetate has been shown to inhibit translocation of gliadin in *in vitro* studies [44]. A phase II clinical trial has also shown Larazotide acetate to be safe candidate for the treatment of CD [45].

Gluten specific vaccination could induce tolerance in patients with CD. Nexvax 2 is a therapeutic vaccine that has been shown in a randomized clinical trial to be well tolerated (Clinical Trials registration number NCT00879749). Moreover, pathogenesis of CD involves production of cytokines (TNF-alpha and interleukin-15) which could be a target for monoclonal antibodies. Humanized HuMikBeta antibody that blocks interleukin-15 signalling is under study in patients with complicated CD (Clinical Trials registration number NCT01893775).

CONCLUSION

Prevalence and incidence of CD is increasing. However, the exact cause of this increment is unknown. Physicians should be aware of "atypical" and "silent" forms of CD in order to avoid under-diagnosis of the disease. Although recent European guidelines suggested that the diagnosis of CD can be made without biopsy, these guidelines should be followed with caution as persistent villous atrophy may be associated with a risk of morbidity and mortality. Initial screening at the time of diagnosis of pediatric patients with CD should include checking for autoimmune disorders and inadequate response to HBV vaccination. All first-degree relatives of patients with CD should be tested for possible CD with serology. HLA testing may be utilized in evaluating infants born to families with CD. Compliance to gluten free diet (GFD) is particularly difficult for teenagers because of social and psychological factors. Novel therapeutic strategies that may improve quality of life for these patients are currently being tested in clinical trials.

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