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An Overview on Diagnosis of Celiac Disease in Children

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Abstract:

Celiac disease is an immune-mediated systemic disease triggered by intake of gluten in genetically susceptible individuals. The prevalence of celiac disease in the general population is estimated to be 1% in the world. Its prevalence differs depending on geographical and ethnic variations. The prevalence of celiac disease has increased significantly in the last 30 years due to the increased knowledge and awareness of physicians and the widespread use of highly sensitive and specific diagnostic tests for celiac disease. Despite increased awareness and knowledge about celiac disease, up to 95% of celiac patients still remain undiagnosed. The presentations of celiac disease have significantly changed in the last few decades. Classical symptoms of celiac disease occur in a minority of celiac patients, while older children have either minimal or atypical symptoms. Serologic tests for celiac disease should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation, and in children who belong to specific groups at risk. Early diagnosis of celiac disease is very important to prevent long-term complications. Currently, the only effective treatment is a lifelong gluten-free diet. In this review, we will discuss the epidemiology, clinical findings, diagnostic tests, and treatment of celiac disease in the light of the latest literature.

Keywords: Celiac Disease, Children, Diagnosis.

Introduction:

The clinical symptoms of celiac disease are very diverse. Celiac patients may present with symptoms of GIS or extra-intestinal symptoms or no symptoms at all. Therefore, serologic tests for celiac disease should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation **(1)**.

Furthermore, celiac disease should be investigated in patients with high risk of developing celiac disease, such as type 1 DM, Down syndrome, autoimmune thyroid disease, Turner syndrome, selective IgA deficiency, autoimmune liver disease, and first-degree relatives of celiac patients, even if they are asymptomatic **(1)**.

Celiac disease is diagnosed by a variable combination of symptoms, positive celiac antibodies, presence of HLA-DQ2/DQ8, and duodenal histology. ESPGHAN guidelines from 2012 recommend tissue tTG-IgA test, which is highly sensitive and specific and less costly compared to EMA IgA antibody test, as an initial screening test for suspected celiac disease, and the total IgA test to rule out selective IgA deficiency. The analysis of deamidated gliadin peptide (DGP) IgA test is recommended for children under 2 years of age. If there is IgA deficiency, the tTG-IgG test or the EMA-IgG test or the DGP-IgG test should be performed **(1)**.

Diagnosis of CD requires that physicians have a high clinical suspicion for the diagnosis of celiac disease are extremely accurate when compared with the other antibody-based tests used to identify other autoimmune disorders. Serological tests for celiac disease are comparable only with anti-mitochondrial and anti-thyroid autoantibody tests, which aim to evaluate primary biliary cirrhosis and autoimmune thyroiditis, respectively **(2)**.

For this reason, serological testing should be the initial approach to assess individuals in whom celiac disease is being considered. Before serological testing for celiac disease, patients should be on a gluten containing diet for at least a month, as serum antibodies have a half-life of 30–60 days. Most commercially available antibodies, including IgA-endomysial antibody (EMA), IgA-tissue transglutaminase antibody (tTG) and IgA or IgG de-amidated gliadin peptide antibody (DGP) have a sensitivity and specificity greater than 90% **(3)**.

IgA-tTG antibody:

In the late 1990s, tTG was identified as one of the antigens detected by the EMA assay, which enabled the development of high-accuracy ELISA-based tests in celiac disease. Initial assays used guinea pig antigen, resulting in higher numbers of false-positives compared with newer recombinant protein-based antigens. Currently, assays are produced by a variety of manufacturers with high accuracy rates **(4)**.

IgA-tTG-based assays have a higher sensitivity than (and a similar specificity to) those of IgAEMA-based testing, with lower cost. IgA-tTG antibody is the preferred serological test for diagnosing celiac disease on individuals over 2 years of age **(5)**.

IgA-EMA antibody:

Prior to the development of IgA-tTG, IgAEMA antibody was the preferred diagnostic tool for diagnosing celiac disease. Whilst, in a reference laboratory, EMA is still the most sensitive test, it is more technically difficult, raising concerns related to inter-observer and inter-site variability. Measurement of IgA anti-endomysial antibodies (EMA) is nearly 100% specific for CD, but it is also expensive and operator dependent and therefore is better used as a secondline test **(1).**

IgG-DGP antibody:

Gluten peptides are de-amidated by intestinal tTG; resulting peptides will subsequently bind to HLA-DQ2 or DQ8 on APCs to stimulate a T-cell response **(Schuppan et al., 2009)**. The resulting antibody reaction constitutes the basis of DGP antibody testing in patients with celiac disease. IgG-DGP is more sensitive and specific than IgG-tTG and, for this reason, is the preferred test in patients with IgA deficiency. In addition, DGP may be more sensitive than tTG in children under the age of 2 years **(2)**.

Special circumstances:

1. **Co-existing IgA deficiency:** Patients with IgA deficiency have a 10–20 times greater risk of developing celiac disease. Ideally, serum IgA should be initially assessed in celiac disease patients with a high pre-test prevalence. In patients with low IgA levels, IgG-based DGP and/or tTG testing should be considered to be part of the serological assessment **(5)**. **Wang et al. (6)** have reported that IgG anti-tTG was more specific (although less sensitive) for celiac disease than IgG anti-DGP **(6)**.

2. **False positive results:** Despite having high sensitivity and specificity rates, a positive serological test does not confirm the diagnosis of celiac disease. In most individuals, IgA-tTG antibody testing has a very high negative predictive value. In rare circumstances, IgA-tTG can yield a false positive result due to cross-reaction of antibodies. Some conditions that can render a false-positive result are—but are not limited to—an enteric infection, congestive heart failure, chronic liver disease and hypergammaglobulinemia **(2)**.

3. **False negative results:** The most common reason for a 'false negative' tTG is that the patient is already on a low-gluten diet. IgA-tTG antibody testing is less sensitive in younger children (under 2 years) because the immune system is immature.

Primary IgA deficiency is another medical condition that could potentially show a negative IgA based testing. Point-of-care tests (POTC) based on transglutaminase 2 (TG2) auto-antibodies are increasingly being marketed as a replacement for serum-based testing. Evidence for and against POCT is still in a nascent stage. Despite the skepticism displayed by clinicians towards these 'off-the-shelf' tests, POCT kits may have a key role in increasing disease detection rates in countries with limited health resources and large numbers of potential celiac subjects **(7)**.

Genetic markers (HLA typing):

The most important recognized genetic risk factor for celiac disease is the presence of HLA-DQ2 or DQ8, of which one or both will be present in virtually all patients with celiac disease. Most of the remaining celiac disease population (less than 1%) will carry half of the HLA-DQ heterodimer **(8)**.

HLA-DQ2 and DQ8 genetic testing have a very high negative predictive value (more than 99%). This feature has been proven to be useful in ruling out celiac disease in patients with equivocal duodenal biopsies, or in those who are already following a GFD and are reluctant to have a gluten challenge. The utility of HLA testing has also been critical in differentiating non-celiac gluten sensitivity from celiac disease **(9)**.

Genome-wideassociation studies [GWAS] have identified many novel non-HLA loci that have partially explained some of the genetic variants in celiac disease. The existence of a large number of non-HLA genes, partly shared by each individual patient, suggests that celiac disease may be more heterogeneous than previously considered **(10)**.

Gluten challenge:

Celiac disease is a unique autoimmune disorder in which a GFD is the only effective and accepted treatment. The GFD resolves celiac-related immune dysregulation characterized by abnormal serological titers and mucosal injury. Patients with celiac disease who are on a GFD prior to diagnostic testing will usually yield negative serologies and normal duodenal histologies**(11)**.

The gluten challenge is clinically relevant in patients with suspected but unproven celiac disease that has been previously treated with a GFD. Its aim is to return to a normal, gluten-rich diet under medical supervision that will enable diagnostic testing. This test is not suitable for individuals with suspected celiac disease who experience severe symptoms or neurological manifestations after gluten ingestion. The gluten challenge remains the 'gold standard' for diagnosis of celiac disease in positive HLA patients on a GFD **(12)**.

The gluten challenge involved consuming at least 10 g of gluten per day for a 6–8 week period. One to two servings (> 3 g) of gluten daily for two weeks, followed by serological testing and duodenal biopsy, are sufficient to induce histological and serological changes in the majority of individuals with celiac disease **(12)**.

Its diagnosis can be definitely excluded if serological and duodenal biopsy results are normal following the 6–8 weeks of the gluten challenge. However, this approach can be troublesome and many patients are unwilling to undergo classical- or even the modified gluten challenge, due to exacerbation of symptoms. For this reason, novel techniques have been explored, including in vitro exposure of duodenal biopsy specimens to gluten. Tortora et al. found that in vitro gliadin-induced HLA-DR expression is an accurate tool for the diagnosis of celiac disease **(13)**.

Vanga et al. (14) analysed the difference in cytokine release in gluten-stimulated-, compared with nonstimulated, biopsies between celiac disease subjects and healthy controls. The study showed a significant increase in several cytokines including TNF-a, IFN-c, IL-6 and IL-10: all crucial in the pathogenesis of celiac

disease. Moreover, a score based on the increments of three of these cytokines (TNF-a, IFN-c and IL-10) appeared to provide a 100% diagnostic accuracy in differentiating healthy controls from treated celiac disease patients with normal duodenal histology*;* however, none of these tests are clinically available at this time.

The gluten challenge has also supported the development of other reliable diagnostic tools. Intestinal fatty acid binding protein (I-FABP) is a cytosolic protein that is release by necrotic enterocytes. I-FABP has previously been studied as a possible marker to evaluate mucosal damage. This protein has been proposed as a sensitive diagnostic test in the evaluation of ischemia in mechanical small bowel obstruction **(15).**

On the other hand, I-FABP has demonstrated a positive predictivevalue of 98% in children with a positive serological test for celiac disease. I-FABP levels increased significantly after two weeks of gluten challenge, while lower levels of I-FABP were seen in individuals following two weeks on gluten withdrawal. I-FABP may be considered as a future diagnostic tool that could assist in the diagnosis of celiac disease **(16).**

Small intestinal mucosal biopsy:

Although the diagnosis of CD can be suspected on clinical or laboratory grounds, or as a result of serological tests, histology of the proximal small intestinal mucosa is still the diagnostic gold standard and must always be performed. Small intestinal histopathology of CD biopsy samples are characterized by typical architectural abnormalities. Marsh has pioneered the theory of a sequence of progression of the CD lesion in the small intestinal mucosa **(17)**.

The Marsh-Oberhuger system was developed, where stage 3 was split into three sub stages (a, b and c). The Marsh-Oberhuber classification was based on a 6-stage grading, namely:

(1) Type 1 infiltrative lesions, characterized by normal mucosal architecture with an increased number of IELs.

(2) Type 2 hyperplastic lesions, characterized by an increase in crypt depth without villous flattening.

(3) Type 3a, 3b, and 3c destructive lesion, characterized by mild, marked, and complete villous flattening, respectively.

(4) Type 4 hypoplastic lesions, characterized by villous atrophy with normal crypt height and IEL count.

Considering the broad spectrum of lesions possibly present in CD, the Marsh-Oberhuber system is undoubtedly valid under optimal clinical conditions, but the considerable number of diagnostic categories involved makes it prone to a low inter-observer and intra-observer agreement**(18)**.

False-positive and false negative test results may occur due to patchy mucosal damage, inter-observer variability, low-grade histopathological abnormalities and technical limitations. Hence, reliance on standard histological findings alone may result in failure to diagnose CD **(19)**.

Furthermore, some patients with isolated intraepithelial lymphocytosis, who are not clinically suspected of having CD, may develop CD during follow-up.Although the mucosal changes in CD are thought to develop gradually, whether minor mucosal lesions in asymptomatic patients indicate CD in an early stage is not yet clear **(20)**.

In case of strong clinical suspicion of CD, duodenal biopsy must be performed regardless of serological analysis **(21)***;* in cases of low suspicion of disease or screening, duodenal biopsy probably only needs to be performed in seropositive patients. Hence, the new system for routine use of simplified grading system with uniform diagnosis and increase validity of the pathologic diagnosis of CD was developed by using only three categories (A, B1 or B2) with A representing normal villous with lymphocytic infiltration and B1 and B2 representing partial and complete villous atrophy, respectively **(22)**.

The new proposed grading system classified the CD lesions into non-atrophic (grade A) and atrophic (grade B). Grade A was characterized by the isolated increase of IELs (> 25/100 enterocytes), whereas grade B was split into B1, in which the villous/crypt ratio is less than 3/1, with still detectable villi, and B2, in which the villi are no longer detectable. **(23)**.

Quantitative measurements of villous height, apical and basal villous widths, and crypt length (morphometry) have been used to determine changes in duodenal morphology, particularly after the introduction of a GFD, in correlation with Marsh grade, self-reported adherence to GFD, and changes in serology. GFD resulted in increase in villous area and a progressive decrease in crypt length, with a plateau after 6-12 mo and mean villous area half that of control subjects **(24)**.

Differential diagnosis:

The finding of villous atrophy on biopsy is not specific for celiac disease. Therefore, if a patient is not responding to a gluten-free diet, the diagnosis of celiac disease needs to be reconsidered. Table (1) lists some possible alternative diagnoses.3 A referral to a gastroenterologist may be warranted in such cases.

Table (1): Differential diagnosis of villous atrophy other than celiac disease **(25)**

Autoimmune enteropathy	Intestinal lymphoma
Collagenous sprue	Intolerance of foods other than gluten (e.g., milk, soy, chicken, tuna)
Common variable immunodeficiency	Radiation enteritis
Crohn disease	Tropical sprue
Eosinophilic gastroenteritis	Tuberculosis
Giardiasis	Whipple disease
Human immunodeficiency virus enteropathy	Zollinger-Ellison syndrome

Special circumstances:

1. **Duodenal lymphocytosis with normal villous architecture:** This histological finding can be found either in individuals with partially treated celiac disease or several other conditions that include (but are not limited to) helicobacter pylori infection, bacterial overgrowth, non-steroidal anti-inflammatory drugs use, inflammatory bowel disease (IBD), tropical sprue, and lymphocytic enteritis **(26)**.

2. **Villous atrophy with negative serology:** This finding represents a diagnostic dilemma. Sero-negative celiac disease, medication-related villous atrophy and unclassified sprue were the most common differential diagnoses among 72 patients with villous atrophy, assessed over a 10-year period **(27)**.

The development of highly sensitive and specific serological assays, in addition to genetic markers and novel diagnostic tools, has positively influenced current diagnostic algorithms (figure 1). The recent European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines have proposed serological evaluation as an alternative to invasive techniques, such as endoscopically guided biopsies, in the pediatric population, but further evidence is still required to support this approach in the general population.

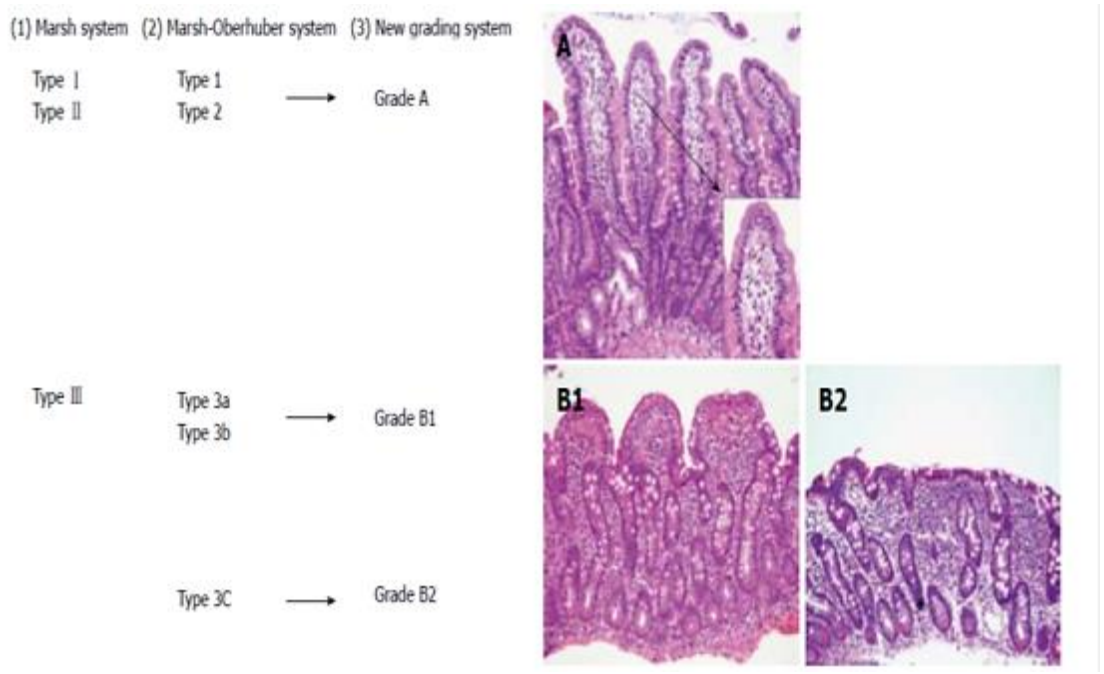

Figure (1): A comparison between the Marsh classification for celiac disease. **1:** Marsh-Oberhuber. **2:** Grading system for celiac disease, and the new grading system. **3:** Representative pictures of the grades A (original magnification, 20×; insert, 60×), B1 (20×), and B2 (20×), proposed in the new grading system. An alternative classification may simply describe "mild", "moderate" or "severe (flat)" architectural changes (printed with permission) **(23)**.

Complications:

Refractory celiac disease:

Celiac disease refractory to therapy is predominantly seen in the classic and atypical forms, where no suffcient response to a gluten-free diet can be achieved despite positive serology and also usually characteristic histology. In fact, in rare cases, disease progression is observed in spite of diet and is accompanied by increased infflamatory activity, the formation of subepithelial collagen bands beneath the intestinal epithelium (collagen celiac disease) and increased malabsorption **(28)**.

It is unclear in this context whether the disease, in the presence of a normal T-cell phenotype, is further triggered by incomplete gluten abstention (compliance), whether other infectious antigens are having a pathogenetic effect, whether related gastrointestinal allergies are present (e.g. gluten substitutes, lupin flour, corn) or whether, in the presence of aberrant T-cell populations (possibly malignant mutations), an autonomous dysfunction of the intestinal immune system already moving in the direction of lymphoma development has occurred **(29)**.

At all events, in the case of celiac disease refractory to therapy or collagen celiac disease, classic dietary interventions are inadequate, making it necessary to take recourse to immunosuppressive approaches, such as systemic or local glucocorticoids, azathioprine or, in particularly refractory cases, anti-tumor necrosis factor (TNF) antibodies.

The therapy of refractory celiac disease is divided into two subtypes according to the intraepithelial lymphocyte phenotype: subtype II is made distinct from subtype I by the loss of normal surface markers (CD3, CD4, CD8), as well as T-cell receptor chain rearrangement. The likelihood is greater in subtype I that, by intensifying treatment as described above, symptoms will improve. The prognosis for subtype II, however, remains poor **(30)**.

Celiac crisis:

A lifethreatening "celiac disease crisis" can occur, which is characterized by explosive watery diarrhea, dehydration, lethargy, electrolyte imbalance, and hypotension. This malabsorption presentation has been termed the "classic presentation" of CD, which is somewhat of a misnomer currently, as the presentation of CD in the pediatric population has been changing, and CD presenting with malabsorptive-type symptoms has become less common overall **(31)**.

Increased risk of some cancers:

The risk of mortality is increased in proportion to the diagnostic delay and clearly depends on the diet; subjects who do not follow a gluten-free diet have an increased risk of mortality, as high as 6 times that of the general population. The increased death rates are most commonly due to intestinal malignancies that occur within 3 years of diagnosis **(32).**

Rare complications:

Rare complications include the development of gastrointestinal ulcers, which in turn increase the risk of hemorrhage, perforation or structure forma-tion. In addition, patients with various forms of celiac disease exhibit an increased risk for the development of enteropathy associated T-cell lymphoma of the small intestine, which has a considerable effect on the prognosis of this otherwise effectively treatable disease. However, there are a number of other rare complications seen in undetected celiac disease, such as the development of "brown bowel" syndrome due to severe vitamin E deficiency, and dysregulation of epithelial DNA repair genes depending on the duration and degree of intestinal inflammation, which in turn bears the further risk of causing epithelial neoplasms **(33)**.

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