

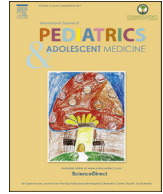
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Invited review

The approach to Celiac Disease in children



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1. Introduction

Celiac Disease (CD) is a permanent, irreversible but treatable multifactorial disease triggered by the ingestion of gluten (a plant storage protein contained in wheat, barley and rye) in genetically predisposed individuals and resulting in an autoimmune small intestinal inflammation with systemic implications.

While the gastrointestinal manifestations secondary to an inflammatory enteropathy with variable degrees of severity are what defined it for many decades, CD is in fact characterized also by a wide range of extra-intestinal complaints and elevated titers of celiac-specific autoantibodies.

1.1. Epidemiology and pathogenesis

The prevalence of CD is increasing at a remarkable pace during the past few decades [1–3]. Once thought to be a rare condition,

affecting no more than 1/10,000 people, thanks to the availability and widespread use of specific and sensitive serological markers, CD is now recognized worldwide as a common disorder, with a prevalence varying between 0.3 and 3 per 100. Only a limited portion of the expected celiac patients are however actually identified, with proportions varying between different countries: in the USA, even though overall CD prevalence is estimated to be around 1%, only about 15% of this population (including children and adults) has been diagnosed and can therefore be treated [4].

This phenomenon of under-diagnosis is likely due to a combination of inadequate awareness and a high prevalence of asymptomatic or oligo-symptomatic patients.

Like most multifactorial disorders, CD is the result of a complex interaction between genes, immune status of the host, and environmental triggers.

Gluten is a heterogeneous molecule. The gluten fractions that are toxic to celiac patients are a mixture of alcohol-soluble proteins called gliadins. Gliadins are rich in glutamine and proline residues, which even the healthy human intestine cannot fully digest. As a result, intact gliadin peptides are left in the lumen, and some cross the intestinal barrier. These fragments come into contact with the intracellular enzyme tissue transglutaminase (tTG), which deamidates them, leading to a change in shape and increased negative charge. This creates peptides that can easily be captured by the HLA-DQ2 and/or DQ8 molecules expressed on the surface of the

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lamina propria-associated antigen-presenting cells (APCs) and are presented to CD4⁺ T cells triggering an inflammatory reaction [5].

The end result of this autoimmune-triggered inflammatory reaction is a varied degree of small intestinal mucosal damage, typically more severe proximally than distally.

The role of additional environmental factors is still the object of an intense research. Recently, our group showed evidence for a plausible role of an otherwise innocuous viral infection (Reovirus) in creating a pro-inflammatory milieu conducive to the development of overt CD [6].

1.2. Clinical presentations

A wide variety of clinical presentations have also been described for CD both in children as well as in adults, including “Typical,” “Atypical,” “Silent,” and “Potential” forms. The “typical” form, so called because CD for a long time was thought to be presenting only with malabsorption-related manifestations, consists of gastrointestinal symptoms; the “atypical” form is instead characterized by predominantly extra intestinal symptoms (see Table 1, from Ref. [7]). “Silent” CD describes asymptomatic patients with positive blood serology and characteristic intestinal inflammation on biopsy; lastly, “potential” CD refers to individuals with positive blood serology who may or may not have symptoms, but show no apparent intestinal inflammation on biopsy. Though the typical presentation was most prevalent in the early and mid-twentieth century, there appears to have been a dramatic change from the 1980s onward with a shift from classical gastrointestinal symptoms to higher rates of atypical and asymptomatic presentations [8,9].

Furthermore, it has been found that in general, presentations have become milder and poor growth less common [10]. The reason for this shift is uncertain, but may partly be the result of an increased awareness of the disease resulting in earlier detection and higher rates of screening at risk individuals. Furthermore, CD has been found to occur more frequently in association with other

Table 1
Typical and atypical forms of Celiac Disease (from Ref. [7]).

Sign or symptom	Age most commonly involved
Typical Celiac Disease	
Vomiting	Infancy
Anorexia	Infancy to early childhood
Failure to thrive	Infancy to early childhood
Diarrhea	All ages
Abdominal bloating	All ages
Abdominal pain	Child to adult
Constipation	Child to adult
Weight loss	Child to adult
Atypical Celiac Disease	
Sad mood	Infancy to early childhood
Elevated AST, ALT	All ages
Fatigue	All ages
Delayed puberty	Adolescent
Short stature	Child to adult
Anemia	Child to adult
Dermatitis Herpetiformis	Adolescent to adult
Dental enamel defects	Child to adult
Oral aphthae	Child to adult
Arthritis	Child to adult
Osteopenia	Adolescent to adult
Osteoporosis	Adult
Unexplained infertility	Adult
Headaches/migraine	Adolescent to adult
Peripheral Neuropathy	Adult
Idiopathic seizures	Child to adult
Psychiatric disorders	Adolescent to adult

Table 2
Individuals at increased risk for Celiac Disease (From Ref. [7]).

- Subjects with signs and symptoms of Table 1 otherwise unexplained
- First degree relatives of celiac patients
- Autoimmune conditions
 - Type 1 diabetes
 - Autoimmune thyroiditis
 - Autoimmune hepatitis
 - Addison disease
- Genetic disorders
 - Down syndrome
 - Turner syndrome
 - Williams syndrome
 - IgA deficiency

autoimmune disorders, such as type 1 diabetes; in some syndromic disorders such as Down syndrome, and in first degree relatives of CD patients. Table 2 reports all conditions that are known to be possibly associated with CD. Therefore, the clinician needs to have a high degree of suspicion for CD in order to appropriately screen for this condition all individuals who are at increased risk, and not just those presenting with obvious malabsorptive signs.

1.3. Diagnosis

It is universally recommended that tTG IgA and total serum IgA be the first line of screening, given their very high sensitivity [11,12]. It is also important to remember that total serum IgA have to be determined to make sure that the patient is able to produce tTG IgA: in fact, celiac patients have higher rates of IgA deficiency (about 2–3%) than the general population [13] and therefore may have a falsely negative tTG IgA. Under these circumstances, both tTG IgG and DGP IgG can be useful surrogate markers of CD [14,15].

In 2012, an ad hoc task force of ESPGHAN published new evidence-based diagnostic criteria. The proposed diagnostic algorithm allowed skipping the duodenal biopsy under certain circumstances: namely, in children and teenagers showing a history and genetic asset compatible with CD, tTG-IgA levels >10 times the upper limit of normal and a positive titer of endomysial antibody (EMA) [11].

This simplified approach has been validated very recently by a large multicenter European study [16]. The results of this large prospective study on over 700 children have shown that children can be accurately diagnosed with celiac disease without biopsy. Diagnosis based on level of TGA-IgA 10-fold or more the ULN, positive results from the EMA tests of 2 blood samples, and the presence of 1 symptom, could avoid risks and costs of endoscopy for more than half the children with celiac disease worldwide. Interestingly, the study was able to document that HLA analysis was not required for accurate diagnosis. One needs however to be mindful that children with gastrointestinal complaints diagnosed without endoscopy may have additional disorders that would go undiagnosed by skipping this procedure. In fact, we have shown in a retrospective study performed at the University of Chicago that although the positive predictive value in our series of children who would have fulfilled these diagnostic criteria was indeed 100%, about 12% of them were found to have additional diagnoses that were disclosed at the time of endoscopy [17]. Hence, once a diagnosis is reached without the biopsy, the child simply needs to be monitored very carefully for full symptomatic remission.

1.4. Treatment and follow-up

The only treatment currently available for children and adults diagnosed with CD is a lifelong gluten-free diet (GFD). Notably,

Table 3
Recommendations for follow-up of celiac children.

Test	At diagnosis	At 3–6 months	At 1 year and yearly thereafter
EMA	○		
TTG-IgA	○	○	○
DGP-IgG	○	○	○
CBC	○	○	○
Fe studies	○		
TSH + T4	○	○	
Vitamin D	○		
Dietitian review	○	○	○

given the pervasive presence of gluten besides the obvious grains (wheat, barley and rye), a universally accepted definition of GF foods allow the presence of no more than 20 parts per Million (or 20 mg per kg) of gluten. How effective is it? We have recently examined our series of CD patients, measuring the time needed after diagnosis for individual signs and symptoms to subside [18]. A total of 554 patients (227 children) with CD were included. Abdominal pain, diarrhea and failure to thrive were the most common GI symptoms in children while diarrhea, bloating, and abdominal pain were most common in adults. Short stature, fatigue, and headache were the most common extra-intestinal symptoms in children while iron deficiency anemia, fatigue and headache/psychiatric disorders were most common in adults. Children had significantly higher and faster rates of extra-intestinal as well as gastrointestinal symptom resolution as compared to adults, with greater rates of improvements in gastrointestinal versus extra-intestinal symptoms at over 2 years after beginning of the diet. Long duration of symptoms, female sex and scarce adherence to a GFD were the most important significant predictors of failure to clinically improve.

Of interest, in a large international collaborative retrospective study in the US and in Italy on 265 CD children and matched controls (*manuscript in preparation*) that we recently completed, we found that while the majority of patients had normal BMI in both countries, 6% of Italian celiac children and 17% of US celiac children were overweight/obese at the time of diagnosis. After following a GFD, there was a significant increase in height ($P < .0001$ for both groups) and weight ($P < .001$ for both groups). No change was found in BMI z-score ($P = .1335$ for Italian celiac children and $P = .0646$ for American ones). However, the GFD resulted in an increase of underweight in Italy while overweight prevalence increased in the US.

A recent study [19] reported that up to 20% of CD children would not show healing of the small intestinal mucosa 1 year or more after beginning the GFD and thus claimed the need for a repeat biopsy. However, the study was biased as the sample of the studied children was a small fraction of CD children, selected mostly (about 70%) for the persistence of symptoms, largely due to ongoing ingestion of gluten. In addition, numerous previous observations had conclusively shown that almost 100% of CD children actually do show complete normalization of their damaged mucosa by 1 year into the diet. In fact, an immediate reply by the European working group on CD [20] strongly rebuked such findings and recommended against the need for repeat biopsy.

What follow-up is currently recommended for celiac children after diagnosis? Recent papers addressed this issue, in the lack of specific recommendations by academic societies such as ESPGHAN or NASPGHAN. In 2016, a panel of experts produced an evidence-based document [21] advising to perform in all cases the tests reported in Table 3, and of course adding any specific laboratory tests that the individual cases may require.

While the GFD is, as we have seen, an effective treatment for CD especially in children, there is clearly the need to offer to celiac

patients an alternative form of therapy and even a cure. In recent years major efforts have been made in this directions. Alternate pharmacological therapies being evaluated for the treatment of CD include enzymes to inactivate immunogenic gluten peptides in the human gastrointestinal tract, agents that sequester gluten in the lumen, modulators of gut permeability and of antigen presentation and immune responses including those that block tTG and HLA, IL-15 inhibitors, and finally the development of vaccines able to restore the lost oral tolerance to gluten [22].

To investigate the attitude of celiac patients toward possible new treatment options, we have recently completed and published a survey [23]. Two scenarios were presented to CD patients following a GFD: a novel therapy that protects against cross contamination while on a GFD and one that allows intentional gluten consumption. The survey also included the Celiac Dietary Adherence Test and the CD Quality of Life (QOL) questionnaire. A total of 182 CD patients completed the survey. Significantly more respondents would take a novel therapy to protect against cross contamination compared with one that allows intentional gluten consumption (87% vs. 65%; $P < .001$). This difference was significant among women but not men. In both scenarios, protection against bowel inflammation was significantly more important than symptom control, and side effects were more important than cost. For a novel therapy that would allow intentional gluten consumption, a one-time injection was preferred over a daily pill, and patients willing to take this therapy had significantly lower QOL scores.

2. Conclusions

Celiac disease affects an increasing number of children around the world, for as yet unclear reasons: the role of contributing environmental factors, such as Reovirus infections, is being actively looked at. Clinical presentations can vary considerably, challenging the pediatrician; and in some cases CD can even be asymptomatic. Its diagnosis is currently facilitated by the availability of accurate screening tests based on the detection of CD-specific antibodies and typical findings at the biopsy of the duodenal mucosa. In addition, in well selected and quite frequent cases, the endoscopic procedure needed to obtain the biopsy can now be skipped. A well conducted gluten-free diet has been shown to be very effective in healing completely the small intestinal mucosa in almost every child in a rather short time, and in obtaining the regression of both, intestinal as well as extra-intestinal manifestations. A careful yearly follow-up is however strongly recommended. New forms of treatment are currently under study and show some promise.

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