Celiac Disease in Children: A Review

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Summary

Celiac disease is a lifelong immune-mediated systemic disorder that may develop in genetically predisposed individuals when exposed to dietary gluten. Its prevalence is estimated to be 1-3% in the European Community; in particular in children studies report a prevalence ranging from 1/500 to 1/93. Awareness of its wide clinical spectrum is mandatory and relevant to all physicians, and in particular pediatricians, to allow a prompt diagnosis and therapy. While the first european guidelines recommended the need of 3 consecutive duodenal biopsies to establish a diagnosis, from 2012 an histological assessment is not considered necessary in certain circumstances in children. Gluten free diet is still the only therapy available in celiac disease but dietary adherence allows control of symptoms and reduces the risk of malignancy. However this diet is challenging due to its costs, quality of life implications, and health consequences such as obesity. Therefore alternative therapies are currently being developed. This review will focus on the current knowledge on celiac disease in children.

Abbreviations

CD: Celiac Disease; GFD: Gluten Free Diet

Definition and Prevalence

Celiac disease (CD) was first described in 1887 and is a lifelong immune-mediated multi-system disease. It may develop in genetically susceptible individuals when exposed to gluten and related prolamins. The diagnosis is based on the presence of gluten induced clinical symptoms, CD-specific antibodies and enteropathy [1-4]. Recent studies have shown that the prevalence of CD is much higher than previously recognised. In Europe 1-3% of the total population is affected [1]. Several paediatric studies have shown similar results in children with a ranging prevalence from 1/500 to 1/93 [5-10] and a higher incidence in the female gender [11]. In the past few decades the average age at diagnosis has risen from <2 years up to 6-9 years in many developed countries [11].

However, CD is still underdiagnosed; for every child with confirmed CD, there are seven other children with unrecognised and therefore untreated disease [1, 5, 12]. Clinicians are hence advised to have a low threshold for investigating symptomatic children or those with associated conditions [13].

Pathogenesis

A complex interplay between genetic, environmental and immunological factors plays a crucial role in the pathogenesis of CD [14].

In the 1940s Dicke identified gluten as the environmental trigger of CD. Gluten is a heterogeneous protein whose toxic fractions are a mixture of alcohol-soluble proteins called gliadins, which are found in cereals such as wheat, barley, rye consumed in most countries [15]. Gut enzymes are not capable of digesting gliadin fractions. Large proline/glutamine peptides therefore accumulate in the small intestinal lumen and may lead to a pathological innate and adaptive immune responses in genetically predisposed subjects [16].

Multiple genes are held responsible for the pathogenesis of CD: 97% of affected individuals carry at least one of the two human leukocyte antigen (HLA) class II genes DQ2 or DQ8 on

chromosome 6p21; more than 90% have the DQ2 gene. These are responsible for the production of surface molecules expressed on the gut antigen presenting cells which bind gliadin peptides which in turn leads to a gliadin specific immune response through activation of CD4+ T cells [17]. The HLA-DQ2 and DQ8 genes are necessary but not sufficient for the development of CD [18, 19]; thirty-nine non-HLA loci have been also found to contribute to the development of the disease, although to a much lesser degree (5% versus 35 %) [18, 19]. The activation of CD4+T cells stimulate the release of proinflammatory cytokines and the production of specific antibodies such as anti-tissue transglutaminase (anti-tTG), endomysial antibodies (EMA) and antibodies agains deaminated forms of gliadin peptides (DGP) [20]. In addition to gluten ingestion, multiple environmental factors have been linked to the development of CD in genetically predisposed children such as infections in early childhood, the gut microbiota in infants, feeding pattern and amount and timing of the initial introduction of gluten into the diet [21]. In particular associations between intestinal dysbiosis and CD has been demonstrated with microbiota imbalances observed not only in untreated CD patients but also in patients on a GFD. Microbiota alterations could play both a primary role by contributing to disease onset and a secondary role by aggravating CD pathogenesis [22].

Clinical Presentation

Since its first description in 1887 the understanding of CD is greatly improved. Atypical symptoms may be much more common than the classical ones. CD is not just a condition limited to the gastrointestinal tract and awareness of its huge clinical spectrum amongst clinicians is essential for a timely diagnosis and initiation of a gluten free diet [23]. In the medical literature 'typical' and 'atypical' CD have become obsolete and are replaced by classical and non classical CD [24]. Silent CD occurs in asymptomatic patients who have CD specific antibodies and duodenal biopsy findings in keeping with CD. Latent CD is seen in individuals with a CD compatible HLA status with a past history of gluten-dependent enteropathy but no current histological changes who may or may not be symptomatic and may be positive or negative for CD specific antibodies. Potential CD refers to patients with CD specific antibodies, compatible HLA type but normal small bowel biopsy in the presence or absence of symptoms. A gluten dependant enteropathy may develop at later stage [1].

In children classical CD is commonly diagnosed in the first 2 years of life. It is characterized by signs and symptoms of malabsorption such as chronic diarrhea, steatorrhea, failure to thrive and weight loss, stunted growth, muscle wasting, poor appetite, nausea and vomiting leading to lethargy and emotional distress. [23, 25, 26]. Other milder abdminal symptoms are currently more often described in CD such as abdominal pain, abdominal distention, flatulence, irregular bowel habits and chronic constipation [1]. In particular the last one is normally not responsive to standard therapy and is described in up to 25-30% of children [27-29].

Celiac crisis, once common, is a potentially life threatening complication of CD that is now rarely seen. It presents with profuse diarrhea leading to eletrolyte imbalances, severe dehydration and shock, abdominal distention, pedal edema, carpopedal spasm due to hypocalcaemia, muscle and buttock wasting, head drop, inability to stand and bleeding diathesis. If left untreated celiac crisis can lead to shock and eventually death [30].

Non classical CD is mostly diagnosed in older children and adolescents presenting with extra-intestinal symptoms associated with the disease, such as puberty delay, unexplained chronic or iron deficient anaemia non responsive to supplementation, decreased bone mineralisation (osteopenia/osteoporosis), dental enamel defects, irritability, chronic fatigue, neuropathy, arthritis/arthralgia, amenorrhea, unexplained increased liver enzymes and recurrent aphthous stomatitis [1, 25, 26]. Moreover CD can present with a well-recognized skin manifestation, named dermatitis herpetiformis, which is characterized by pruritic papular eruption over the extensor surfaces around the elbows, knees, and buttocks, with a characteristic subepithelial deposition of IgA at the histological examination [1, 25, 31]. Signs and symptoms of CD and related frequencies are reported in (**Figure 1**).

The recent advances in serological testing have allowed many patients to be diagnosed when still asymptomatic but at risk of developing CD due to a CD associated condition or first degree relative in the family. According to reports only 1:3 to 1:7 of CD sufferers are symptomatic. [32]. A number of conditions have been associated with CD including type I diabetes (life-time prevalence ≥ 8%), selective IgA deficiency (1.7%–7.7%), Trisomy 21 (5%–12%), Williams (8.2%) and Turner syndrome (4.1%–8.1%), autoimmune thyroiditis (∼ 15%) and autoimmune liver disease (12-13%) [1]. First degree relative of an index case have 10% chance of developing CD at some point in their life, HLA matched siblings 30 to 40% and monozygotic twin 70 % higlighting the strong genetic link [13]. CD should also be ruled out in children with juvenile idiopathic arthritis, epilepsy characterized by intracranial calcification and in those with unexplained neurological problems such as palsies, neuropathies, or migraine [13].

Diagnosis

In 1969 the the European Society of Pediatric Gastroenterology and Nutrition (ESPGHAN) established the first criteria for the diagnosis of CD: Three consecutive biopsies with relapse of the histological changes when the patient was challenged with gluten after a strict gluten free diet were deemed necessary to confirm the diagnosis [32]. Since then the diagnostic criteria have been modified several times, particularly since serological testing has become widely available.

In children the correlation between significantly elevated tTG IgA levels and CD compatible duodenal biopsy results [33-35] and the strong dependence of CD on the HLA DQ2-DQ8 haplotypes, has questionned the diagnostic necessity to perform an upper gastrointestinal endoscopy [36, 37]. In 2012 the ESPGHAN working group on Celiac Disease Diagnosis published new guidelines on which current clinical practice in Europe is based [1]. The diagnostic approach differs quite significantly from the past.

Initial screening of children with both classical or non classical symptoms requires measurement of total IgA and anti-tTG IgA

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Sign/Symptom	Frequency
Iron-deficiency anaemia	3-16
Other anaemia	3-23
Anorexia	8-35
Weight loss	44-60
Abdominal distension/bloating	28-36
Abdominal pain	8-12
Vomiting	26-33
Flatulence	5
Diarrhoea	70–75
Short stature/growth failure	19 -31
Irritability	10–14
Increased level of liver enzymes	5
Chronic fatigue	7
Failure to thrive	48–89
Constipation	4–30
Irregular bowel habits	4–12

Figure 1 Signs and Symptoms of CD and related frequencies. Adapted from the ESPGHAN guidelines 2012.

antibodies [1]. Negative anti-tTG IgA antibodies in the presence of a normal total IgA make a diagnosis of CD unlikely; however false negative anti-tTG IgA must be considered if the child's diet is low in gluten, in the presence of a protein losing enteropathy, concommitant immunosuppressive therapy and in children younger than 2 years of age [1].

When anti-tTG IgA antibodies are ten times or more above the normal range, EMA IgA should be checked and HLADQ2/DQ8 typing performed. A diagnosis of CD without need for duodenal biopsy can be made if both results are positive. Upper GI endoscopy is recommended if one result is not in keeping with CD [1]. A false positive tTG IgA should be considered if both results are negative [1].

Duodenal biopsies are required if anti-tTG IgA antibodies are less then ten times above the normal range [1]. CD may be patchy and four biopsies from the second part of the duodenum or more distally and one or two biopsies from the dudodenal bulb are hence recommended [1]. An adequate gluten intake at the time of duodenal biopsy is essential for reliable results [1].

The histological findings according to the Marsh-Oberhuber classification is based on the degree of villous atrophy, crypt elongation, villus-crypt ratio and the number of intraepithelial lymphocytes. A Marsh-Oberhuber grading of 2–3 is consistent with CD [1].

More challenging clinical situations in symptomatic children are also addressed in the guidelines.

• In the presence of IgA deficiency, at least one additional test using IgG class specific antibodies should be performed (anti tTG or anti EMA or antibodies against DGP) which may help to decide if to proceed to duodenal biopsy or not. However, as IgG antibodies have a lower specificity, a biopsy may be still indicated if the IgG antibodies come back negative [1].

• CD in children with dermatitis herpetiformis can be confirmed by immunofluorescent examination of the skin

showing IgA deposits in the dermis [1]. Approximately 80% of patients with this skin alteration show villous atrophy in the small bowel mucosa at the time of the diagnosis.

• Children younger than 2 years of age should be tested both for IgA and IgG CD specific antibodies after a trial of a cow's milk protein free diet. DGP antibodies may be helpful as they have a potentially higher sensitivity than EMA and anti-tTG although they are less specific. A duodenal biopsy should be performed when there is a strong clinical suspicion of CD [1].

In asymptomatic children with an increased risk to develop CD, HLA typing can be useful. The development of CD is unlikely in the absence of a HLA DQ2 or DQ8 positive genotype and serological screening is only justified in symptomatic children. Surveillance serological screening every three years can be performed in asymptomatic children who are HLA DQ2/DQ8 positive [1].

Gluten Free Diet

A strict gluten-free diet (GFD) for life is currently the only available treatment for CD [38].

Children should be started on a GFD only once the diagnosis has been made in order to avoid unnecessary dietary restrictions and diagnostic uncertainty; however in very symptomatic patients presenting in poor clinical condition or in celiac crisis, when treatment cannot safely be delayed, GFD can be considered prior to a full diagnostic work-up [1].

Gluten free labelled foods, beverages and medication have a gluten content of less than 20 part per million. A gluten intake of less than 10 mg per day is considered safe for patients with CD [39]. All gluten containing grains such as wheat, rye, barley, spelled and kamut have to be avoided. Pure oats are tolerated by the majority of patients [40]

GFD in most cases leads to a rapid clinical improvement depending on symptoms, however it will take months or years to reach complete mucosal healing [41].

Poor dietary compliance may be complicated by osteoporosis, infertility or certain types of cancer such as small bowel adenocarcinoma, enteropathy associated T cell lymphoma [38], other types of non-Hodgkin's lymphoma and Hodgkin's lymphoma; however recent studies have shown that cancer in patients with CD is lower than previously thought [42-44]. Patients who follow a strict GFD have no increased risk of comorbidity or malignancies. [45].

A GFD is often expensive and can negatively impact on quality of life (Makharia), making strict adherence difficult. Compliance is particularly poor amongst adolescents with rates as low as 52% and 81% at best making this a particularly vulnerable group of patients [46]. Adolescent Celiac clinics tailored to the needs of older children and young adults can help to address this problem.

The Canadian Celiac Association Health Survey conducted in 2003 on 168 children with biopsy-confirmed CD hihlighted many problems children face when starting a GFD: 92% reported difficulty in determining whether foods were gluten free, 90% struggled to find foods which were allowed, 95% complained about having to avoid eating out in restaurants, 46% of children

did not travel away from home or abroad and 72% were angry about having to follow a special diet [47]. In addition the avoidance of gluten-containing staple foods can potentially lead to a loss of an important source of energy, proteins, carbohydrates and micronutrients with long term implications on health, nutritional status and growth [48]. Wheat-based refined gluten-free cereal products do not contain the same levels of thiamine, riboflavin, niacin, folate and iron compared to the equivalent gluten containing products and may further impact on a child's nutritional intake [49]. Some studies have demonstrated that a GFD can be unbalanced, rich in fat and protein and poor in carbohydrate, which may contribute to obesity. Up to 15- 20% of patients with CD move from a normal or low BMI centile at diagnosis to a BMI considered overweight and up to 20% of those already overweight at diagnosis gain more weight on the diet [50, 51]. In 2007 Zuccotti et al demonstrated that children on a GFD had significantly higher energy intakes than controls and consumed excessive intakes of simple sugars, fats and protein; however, the body mass index was similar in both groups. [52] This study also highlighted the lack of information on gluten free products' nutritional contents, and therefore the difficulties encountered in a proper estimation of true fat and micronutrient intake of a child on a GFD [52]. Other studies suggest that patients with CD have a good nutritional status and normal BMI despite a diet often low in fiber and iron and high in satured fats, now common in the countries with high socio economic status [53].

Easy access to a dietitian experienced in the management of CD is crucial and children should receive age appropriate information about the implications of CD. The psychological impact of a CFD should not be underestimated and families supported as much as possible.

Novel Therapies

As children and adults with CD continue to report difficulties related to a life long GFD [54] novel therapeutic strategies with the potential to treat or even cure CD are being explored [14]. Current novel concepts involve dietary modification, permeability inhibition and mucosal reconstruction, antigen presentation suppression, cytokine therapy and anti inflammation, adhesion blockade and immunomodulation [55].

Although still in the preclinical stage new wheat variants are being developed either by reproduction of wheat species lacking harmful gluten epitopes or by genetical modification of the immunogenic peptides. It may be hence possible to avoid gluten in the human diet completely, an approach that may not only treat but also prevent CD ; however, commercially available wheat is a very cheap and robust industrial commodity, therefore it is unlikely that modified grains would replace commercial wheat strains [56, 57]. Inhibition of mucosal permeability, an early pathogenic event in the development of CD which allows the passage of immunodominant gluten peptides and other immunostimulatory luminal antigens, has been used in trails. An octapeptide antagonizing Zonulin, a human protein which enhances epithelial permeability, has been used with good results [58]. In vitro studies using reversible and irreversible inhibitors of tissue transglutaminase 2 enzyme to block the deamidation

process of gluten had mixed results and raised concerns about potential interaction with vital biologic pathways [59, 60]. Analogous gliadin peptide, with enhanced affinity for DQ2 and able to inhibit HLADQ2 mediated antigen presentation, have been developed and may be a potential treatment for CD; however celiac-specific HLA inhibition must not interfere with class 2 dependent responses and immunosurveillance. [61, 62] Different strategies targeting the cytokines and chemokines involved in the pathogenesis of CD as well as the associated chemokine receptors (anti IL-10 and IL-15, anti-Interferon-Gamma and TNF Alpha) are beeing explored. However while this approach may be justified in other auto-immune diseases such as inflammatory bowel disease, the potential side effects may not justify its use in CD where dietary elimination of gluten offers complete resolution of symptoms [55]. Tolerance induction has been demonstrated in mouse models, but lacks human studies. Probiotics have been trialled in CD due to their role in maintaining gut barrier function and regulating the response of the innate and adaptive immune system [22]. To date three randomized, double-blind placebo-controlled human intervention trials have been conducted in CD patients: B. infantis NLS was administered to untreated patients with an improvement in some gastrointestinal symptoms, in particular indigestion and constipation, but with no modification in intestinal permeability or in the pro-inflammatory status [63]; B. longum CECT 7347 was trialled in CD children on a GFD leading to a decrease in peripheral CD3+ T lymphocytes and a trend in the reduction of TNF serum levels [64]; B. breve BR03 and B. breve B632 were administered to children on a GFD with a reduction in pro-inflammatory cytokine TNF [65].

Finally a gluten vaccine has also been developed and completed a phase I clinical trial on HLA DQ2 positive volunteers with CD; the vaccine led to well tolerated immunization without any serious adverse events [55].

Although still far from being available in routine clinical practice, non diet-based therapies hold promise and may be available to patients who cannot or choose not to follow a GFD.

Follow-Up

Little is known from the literature how often and in what format children with CD should be monitored despite a consensus that CD is a chronic and potentially serious medical condition which requires long term follow up to guarantee adherence to therapy and prevent complications.

A Paediatrician familiar in the diagnosis and management of CD or a paediatric Gastroenterologist should review a child with CD every 6 months [45]. Older teenagers and young adults form a particularly challenging cohort of patients who may demonstrate poor adherence to therapy and miss clinic appointments and therefore require special attention.

Anti tTG IgA is checked to monitor compliance although data on the reliability of anti tTG IgA in the context is controversial [45]. Levels of anti tTG IgA should decline consistently over time and can take up to 1-1.5 years before being completely back to normal. Mucosal healing occurs generally in 3 to 6 months [45]. Routine surveillance upper endoscopies with intestinal biopsies

are not recommended except in those cases with lack of clinical response or relapse of symptoms despite a correct GFD [66, 67].

In the presence of ongoing weight loss other parameteres such as haemoglobine, total protein count, albumin, iron, vitamin B6, folic acid, vitamin B12, calcium, alkaline phosphatase, vitamin D, parathyroid hormone may be helpful. Routine screening for other autoimmune disorders (Thyroid-stimulating hormone, Thyroid hormone, liver function tests, glucose) is justifiable and can be done from time to time [45].

Anthropometric parameters should be checked at every visit and BMI recorded. Bone density measurement is not routinely suggested in children but can be considered [45].

At diagnosis screening (DQ2/D8 and celiac serology) should be offered to first degree relatives and membership in a celiac support group encouraged.

Conclusion

CD is estimated to affect 1-3% of children in the European community; while typical symptomatic patients are nowadays a minority, several mild or non gastrointestinal symptoms are currently more common and moreover asymptomatic children form a majority of the new diagnosed cases. Awareness on CD's huge clinical spectrum is hence mandatory and a low threshold for investigating symptomatic children or those with associated conditions is recommended. Duodenal biopsy used to be the gold standard to confirm the diagnosis but can now be avoided in a number of cases highlighted in the 2012 guidelines. GFD remains the only therapeutic option to induce remission but novel therapies may offer alternatives in the future for those who struggle with a GFD.

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