

Review Article

Celiac Disease: A Pediatric Perspective

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Abstract

Celiac disease (CD) is a disease of the small intestine characterized by villous atrophy that impairs with nutrient absorption and improves upon withdrawal from wheat gliadin barley, rye and oat prolamines of the diet. Susceptibility to celiac disease is determined significantly by genetic factors. Extraintestinal manifestations have been increasingly recognized and the strict association with diseases, characterized as autoimmune, is well established. Although a diagnostic and subsequent follow-up jejunal biopsy are necessary in children in order to confirm diagnosis, anti-gliadin IgA and IgG, anti-reticulin and anti-endomysium antibodies, are now reliable in identifying children with celiac disease and are valuable in monitoring the adequacy of gluten withdrawal. A lifelong strict gluten free diet is essential to reduce the chance of developing late gastrointestinal malignancy. Celiac disease is important for both clinicians and scientists because it represents a valuable model for comprehension of diseases in which environmental, genetic and immunologic factors interplay. *Int Pediatr.* 2003;18(3):141-148.

Key words: celiac disease (CD)

Introduction

Celiac disease (CD) is a chronic enteropathy, related with permanent intolerance to wheat gliadins and other similar proteins (prolamines) contained in barley, rye and oats. The disease is characterized by small bowel villous atrophy resulting in malabsorption of food nutrients. Celiac disease today has achieved significant clinical and scientific importance, because it represents “a model disease” concerning the general understanding of diseases in which environmental, genetic and immunologic factors interplay.¹⁻³

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Precipitating Factor

Gluten can be defined as the rubbery mass that remains when wheat dough is washed to remove starch granules and other water-soluble constituents. It mainly contains glutamine (35%), proline (15%) and hydrophobic amino acid (19%). Gluten's major protein fractions are gliadin and glutenin, which can be distinguished by their different solubility in aqueous alcohol. Gliadin, which is readily soluble in alcohols, is believed to be the principal toxic peptide fraction of gluten for patients with celiac disease.

In 1961, the components of gliadin were classified on the basis of mobility at low PH in gel electrophoresis into four subgroups (α , β , γ , and ω -gliadins in order of decreasing mobility) rich in glutamine and prolamines. Initially α -gliadins were suspected as toxic in patients with celiac disease. Later (1984), it was demonstrated that all the subgroups of gliadin could induce lesions on the intestinal mucosa of patients with genetic predisposition. In addition, studies on N-terminal sequences have shown that electrophoretic mobility does not always reflect the protein relationships and that α and β gliadins fall into one group (a-type). So, in 1986 gluten protein components were classified based on their molecular weight into three groups: a) high molecular weight group, HMW b) medium molecular-weight group, MMW and c) low molecular-weight group, LMW. Low molecular weight subunits are thought to be the important toxic gluten's proteins of celiac disease.^{3,4}

Incidence

The average incidence of celiac disease in 22 European countries is 1 case every 1000 live births. In Denmark, the incidence is 0.025:1000 and in Italy 0.63:1000. In Sweden is observed the highest incidence of celiac disease in Europe (3.52:1000). Comparable rates of disease have been found in North African countries and in South America. In the United States, the incidence of celiac disease is very low, even in those

populations that have the same genetic background as European populations with a high rate of CD. Slightly higher incidence is observed in girls, 57%. The prevalence of sub clinical or silent celiac disease is higher.^{1,5,6}

Following the 1950's, a rise in incidence of celiac disease was observed from epidemiological studies, which was attributed to the establishment and broad use of intestinal mucosa biopsy. However, following the 1970's a sudden and important decrease in incidence of celiac disease was reported in Great Britain and in other areas in Europe. It is not clear, if the declining incidence of primarily symptomatic celiac disease, was representative of a real reduction in prevalence of the disease or if it was due to a shift of the disease to an older age group. This declining incidence of CD was associated with changing infant feeding practices, characterized by the later introduction of dietary gluten, an increased use of baby rice and gluten free foods for weaning and an increased incidence of initial breast feeding.^{3,7,8}

The association of celiac disease with adenovirus (serotype 12) is particular interesting. One of the virus's proteins, Elb protein, demonstrates similar antigenic sequencing of amino acids to that of gluten peptides. Infection with adenovirus and subsequent exposure to gliadin could trigger the development of CD resulting from cross-reacting immune reactions. This observation is only experimental and far from providing a substantial conclusion.^{1,9}

Genetics

Studies from small intestine - biopsy specimens from first degree relatives of patients with celiac disease provided compelling evidence that genetic factors may influence susceptibility to this disease. In a large polycentric study the incidence of celiac disease, in first degree relatives with celiac disease reaches 8.7%, while 75% of monozygotic twins suffer from celiac disease.^{1,3}

Celiac disease is most probably an immunologic disease and shows a well defined HLA association. The disease shows a strong human HLA association predominantly to the *cis* or *trans* encoded HLA -DQ (a1* 0501, b1* 0201) heterodimer (heterodimer DQ - α/β) (Fig 1).¹⁰⁻¹²

The DQ- α/β heterodimer is found in 95% of patients with celiac disease in Southern Europe, while

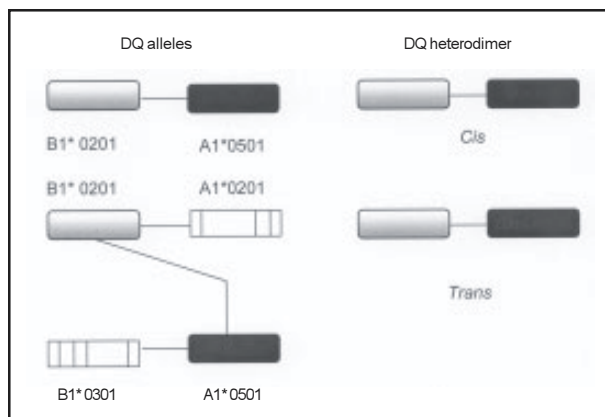


Fig 1 - Association of celiac disease with HLA-DQ heterodimer (DQ α/β). DQ molecule is encoded by DQ A1*0501 and DQB1*0201 genes in *cis* or in *trans*. The DQ heterodimer binds gliadin which is presented to CD4 lymphocytes.

it also exists in 20-30% of healthy controls. A gene dosage effect has been suggested because subjects carrying a double dose of DQ* B1 0201 have been found to have a greater risk of having CD.^{1,13}

The most probable mechanism explaining the association with HLA class II genes is that the DQ heterodimer binds a peptide fragment of an antigen (gliadin) implicated in the pathogenesis of celiac disease, which is then presented to CD4 lymphocytes. CD4 lymphocytes present in the intestinal mucosa of patients recognize gliadin peptides only when they are presented by the DQ heterodimer.^{3,10,14}

However, the presence of other non-HLA genes, concerning T-cell immune response seem to be associated with celiac disease. These genes are linked with the expression of T-cell receptors (TCR). In healthy individuals, all mature lymphocytes hold TCR receptors on their surface and are responsible for the identification of foreign antigens. The T-cell receptor is a disulfide heterodimer composed of α and β glycoprotein chains. A small percentage of T-cells showed receptors having chains other than α - or β - but γ - and δ - chains. It is determined that patients with celiac disease have an important increase (2-6 fold) of CD8 lymphocytes which express γ -, δ -TCR. Although the function of cells expressing the γ/δ receptor has not been clarified, it is possible that these intraepithelial lymphocytes play an important role in the mechanism of intestinal damage. They probably evoke late and not immediate damage to intestinal mucosa. This

hypothesis is reinforced by the discovery of a greater number of T lymphocytes positive for γ - and δ - TCR in patients with latent celiac disease, several years before the appearance of intestinal mucosa atrophy. The cluttered distribution of these cells in the intestinal mucosa may possibly cause disorder of focal immune mechanisms that control tolerance to antigens in the diet.^{1,3,14}

Immunology

Lamina propria lymphocytes are mainly CD4 lymphocytes. These are stimulated by MHC II molecules, which present gliadin proteins. The main antigen - presenting molecule was established to be the CD - associated DQ($\alpha 1^*0501, \beta 1^* 0201$) heterodimer. A trimolecular complex is formed that transmits a signal to the CD4 lymphocyte. The signal initiates a series of biochemical reactions within the cell resulting in subsequent biologic responses. There are data to suggest that cytokines associated with both TH1 (IL-2, interferon γ) the TH2 cells (involved in promotion of B-cell growth, differentiation and immunoglobulin secretion: IL-4, IL-5, IL-6 and IL-10) are produced by lamina propria CD4 cells.^{3,10,14,15}

The other important feature of celiac mucosa is lymphocytic infiltration of epithelial cells. Extensive immunophenotypic studies have shown that intraepithelial lymphocytes are predominantly CD8 TCR $\alpha\beta$ + cells. In celiac disease there is an increase in the number of CD 8 TCR $\gamma\delta$ + types. The relative absence of CD 8 TCR $\alpha\beta$ + types is thought to disrupt immune mechanisms that control tolerance to gluten.^{14,15}

Regarding humoral immunity, in children with celiac disease a large increase in plasmacytes in the basal membrane of the intestinal mucosa is observed, an up to six fold increase compared to healthy individuals, resulting in the production of IgA, IgG and IgM antibodies. Particular interesting is the gliadin-triggering production of autoantibodies directed to noncollagenous proteins of the extracellular matrix (antireticulin or antendomysial). The action of these antibodies is mainly indirect, forming immune complexes, complement activation and aggregation of infectious mediators and cells in the intestinal mucosa.^{1,3}

Clinical Manifestations

Symptoms depend on the age of onset of the disease and the extent of intestinal involvement. The genetic disorders aforementioned determine the age of onset as well as the extent of intestinal involvement.²

Although the classic picture of an unhappy blond child with slender limbs, wasted buttocks and prominent abdomen is well known, gastrointestinal symptoms predominate in children diagnosed within the first two years of life. Therefore, young children primarily display diarrhea, vomiting, abdominal pain and abdominal distention. Failure to thrive, anorexia, and irritability often are present. The clinical history reveals that growth has been normal during the first few months of life, and a few weeks or months since the introduction of cereals into the diet, stools become malodorous, bulky and greasy. Some children may display severe symptoms with profuse diarrhea, leading to severe dehydration (celiac crisis). Contrarily, in a small number of patients no abnormal stools are observed although constipation may appear occasionally.^{2,3,16}

In children diagnosed later in childhood (>2 years) extraintestinal symptoms often predominate, such as short stature or arthritis, which cannot be attributed to usual causes. Approximately 10% of children with short stature who undergo jejunal biopsy were found to have villous atrophy with hyperplasia of the crypts and abnormal surface epithelium.^{1,2,16}

Symptoms and clinical signs observed in children with active celiac disease, are shown in Table 1.

Characteristically, many authors maintain that short stature and failure to thrive are the main features in children with celiac disease. In fact weight and height over the 50th percentile are strong evidence against the diagnosis of celiac disease in childhood.²

Apart from the typical picture of an unhappy child with diarrhea and failure to thrive, celiac disease may occur with atypical manifestations. Therefore, some children with celiac disease display symptoms such as recurrent aphthous ulceration. Different degrees of dental abnormalities have also been described in children with celiac disease. Permanent characteristic dental enamel lesions are present in as many as 30% of untreated children with celiac disease. Recurrent aphthous stomatitis is contributed to immune disorders of the buccal mucosa, similar to the immune disorders described concerning the intestinal mucosa. Dental enamel defects are frequent in children and adolescents

Table 1 - Frequency of symptoms & signs in children with CD

Symptoms	
Failure to thrive	81-86%
Diarrhoea	68-76%
Irritability	40-72%
Vomiting	52-57%
Abdominal pain	15-19%
Constipation	12-15%
Signs	
Weight <25 th percentile	72-86%
Height <25 th percentile	72-74%
Abdominal distention	78-82%
Edema	5-30%
Finger clubbing	6-26%

with celiac disease and are associated with HLA-DR3 in the genetic makeup of these patients. Enamel hypoplasia is the most common type of defect.^{2,18}

Few children display CNS symptoms such as peripheral neuropathy, demyelination of the spinal cord, hypotonia and cerebellar atrophy. Intractable seizures and occipital calcifications have been described in association with celiac disease in childhood. Many of these children had behavioral disorders, which often improve within days of starting a gluten-free diet.^{12,19} The possibility of celiac disease should also always be considered in patients with iron-deficiency anemia without demonstrable bleeding, unexplained folate deficiency, or unexplained osteopenic bone disease. Vitamin D deficient rickets occurs occasionally in active celiac disease and is particularly common in Asian children. Pancreatic insufficiency is present in about 30% of children with active celiac disease. Pancreatic insufficiency is usually reversible with treatment. Isolated idiopathic transaminasemia without other hepatic symptoms may be also an early manifestation of celiac disease in childhood.^{2,3,16}

Recently, it was proven, mainly through studies of patients' family members, that celiac disease may occur with mild symptoms or even may be asymptomatic or silent (latent celiac disease). In these patients on small bowel biopsy severe mucosal damage consistent with celiac disease is apparent.^{1,20}

High Risk Groups

A number of conditions are associated with celiac disease more often than by chance. First-degree relatives of patients with known celiac disease are considered "high risk group" for celiac disease and must be examined for the disease. The reported

prevalence of celiac disease among first-degree relatives varies from 8 to 12 percent in most studies.^{1-3,16}

Various diseases, autoimmune endocrinopathies, connective tissue and collagen disorders have been reported in association with celiac disease. (Table 2)^{2,15}

A high proportion of patients with autoimmune diseases such as Sjogren's syndrome, Hashimoto's thyroiditis, autoimmune thrombopenia and insulin dependent diabetes mellitus, have abnormal intestinal mucosa consistent with celiac disease. Patients with diabetes mellitus type I have an increased incidence of celiac disease, with a prevalence of 1.1- 3% in Swiss and German patients. In Finland, 2.3% of 43 diabetic children had celiac disease. The reported prevalence in recent studies in Greece varies from 2-3.5%. These associations may be consequences of the shared identical HLA aptotypes (B8, DR3)^{3,6}

IgA deficiency affects 1:400-1:700 children. Those affected have a tenfold risk of celiac disease compared with the general population. IgA deficiency has practical implication when interpreting serum IgA antibody tests, but IgG anti-gliadin and endomysium antibody test are usually positive.²¹

It is clearly established that a high proportion of patients (60%) with dermatitis herpetiformis have celiac disease. The prevalence of HLA-DR3, HLA -DQw2, and circulating antigliadin antibodies in this group parallels that in celiac disease.^{2,22}

There is also a relationship between celiac disease and Down syndrome. The reported prevalence of celiac disease among patients with Down syndrome varies from 4-4.5%.⁴

Patients with cystic fibrosis have a 5-fold risk of celiac disease compared with the general population (5:1000). A sweat test to exclude cystic fibrosis is

Table 2 - High risk groups for CD

First degree relative of patients with celiac disease
Patients with autoimmune disease
Patients with diabetes mellitus type
Patients with IgA deficiency
Patients with herpetic dermatitis
Patients with Down syndrome
Patients with cystic fibrosis

mandatory in all children with celiac disease at the time of diagnosis, while every child with cystic fibrosis who displays protracted symptoms of malabsorption, despite pancreatic enzyme supplementation, should undergo jejunal biopsy.^{1,2}

Diagnosis

Although the diagnosis of celiac disease may be obvious by clinical picture, non-invasive tests of intestinal absorption (e.g. D-xylose) and even gliadin antibody studies, a jejunal biopsy is still required to establish the diagnosis.^{1,15,23}

Over the past decades the use of celiac antibody tests (anti-gliadin IgA and IgG, anti-endomysium and antireticulin IgA antibodies) has found great application and has modified the use of jejunal biopsy to selected cases.^{1,2,4,24-26}

At risk for celiac disease and therefore should be tested are all of the children presented in Table 3.

Immunological Tests

The measurement of serum "celiac antibodies" (anti-gliadin IgA and IgG, anti-endomysium and antireticulin IgA antibodies) is non-invasive for the patient and relatively inexpensive.

Tests detecting circulating antibodies to gliadin, reticulin or endomysium, using immunofluorescence

or the enzyme linked immunosorbent assay (ELISA) have been considered potential screening tests for celiac disease. The sensitivity and specificity of these tests varies in different studies but is generally high.²⁴⁻²⁶

Upon diagnosis anti-gliadin antibodies (AGA) are positive in almost all patients. Antibodies belonging to the IgG class are of limited diagnostic value in patients with celiac disease, whereas IgA antibodies show high sensitivity and specificity for the diagnosis of celiac disease.^{2,27-29}

Anti-reticulin antibody (ARA) test is highly specific (96-100%) and gives an almost 90% sensitivity for celiac disease.^{1,2,27}

IgA class anti-endomysial antibodies (AEA) were reported as very specific and sensitive tests for celiac disease (sensitivity and specificity 90-100%). The application of the AEA is however limited by its higher cost and the absence of AEA (an IgA class antibody) in celiac disease patients also affected by IgA deficiency.²⁷⁻²⁹

Recently tissue transglutaminase (tTG) is believed to be the major autoantigen recognized by endomysial antibodies patients with celiac disease. Tissue transglutaminase belongs to the family of enzymes that catalyze protein cross-linking reactions and is consistently expressed in many tissues as well as being activated during apoptosis. The anti-tTG antibody ELISA represents a cost effective strategy for identifying both symptomatic and atypical forms of celiac disease.³⁰⁻³⁴

The combined determination of IgA-AGA and IgA-EMA, taking advantage of the high sensitivity of AGA and high specificity of EMA, gives an excellent prediction of the condition of the intestinal mucosa.^{2,24,33} In a large study of patients with positive both IgA and IgG-AGA and IgA-EMA mucosal damage consistent with celiac disease was observed in 99.6%.²

After starting a gluten free diet there is a gradual fall in the antibody levels (IgA-AGA and IgA-ARA) over 3-9 months. Persistently positive antibody levels are valuable in indicating continuing gluten ingestion. To verify a gluten challenge test the most reliable marker is IgA-ARA, IgA-AGA and EMA, in which a rise in titer is observed following the introduction of gluten (within 3-6 months). The "re-appearance" of antibodies has been used as an indication to perform the diagnostic biopsy.^{27,29}

Table 3 - Possibilities of CD should be investigated

Failure to thrive
Unexplained recurrent abdominal pain
Short stature and/or pubertal delay
Recurrent aphthous stomatitis or dental enamel defects
Juvenile diabetes mellitus
IgA deficiency
Down syndrome
Cystic fibrosis
Dermatitis herpetiformis
Vitamin D deficiency
First -degree relatives with celiac disease

In conclusion positive “celiac antibodies” are important diagnostic tools for celiac disease in children. Although the demonstration of “celiac antibodies” is not confirmative, it has very high predictability for celiac disease. Serologic screening tests have also been used to assess the prevalence of celiac disease on groups at high risk and for follow-up of these patients. Intestinal permeability tests based on intestinal permeability to sugars (e.g. D-xylose) have a sufficient sensitivity for abnormalities of jejunal mucosa but they are characterized by a low specificity for celiac disease.^{5,16,27,29}

Biopsy

Tests based on the detection of “celiac antibodies” may be useful at the time of the diagnosis of celiac disease. However the diagnosis is still based on the finding of a severe histologic lesion of the jejunum (hypertrophic crypts and characteristically flattened, or cyboidal enterocytes that lie on the mucosal surface between the widened crypt cells) while the patient is receiving a free diet.^{1-3,20,27}

In 1969, the European Society of Gastroenterology and Nutrition (ESPAGAN) recommended three intestinal biopsies in order to confirm celiac disease, one performed at the time of presentation, another after the patient has been on a gluten – free diet when the mucosa is expected to have returned to normal and the final biopsy after the patient has been rechallenged with gluten, when villous atrophy is expected to have recurred. Although these guidelines were later revised, they were believed to be satisfactory.² However only approximately 2/3 of ESPAGAN members followed these guidelines, which demanded a challenge test and a repeat biopsy for all patients.³⁵⁻³⁷

Twenty years later (1989), diagnostic guidelines for celiac disease were revised by ESPAGAN. The two requirements mandatory for the diagnosis of celiac disease remain: (1) the finding of characteristic intestinal mucosa while the patient is eating an adequate amount of gluten (2) a full clinical remission after gluten is withdrawn from the diet.^{9, 27, 37}

However a second biopsy, after beginning the gluten free diet is recommended only in asymptomatic patients (ex. first degree relative) to demonstrate the histological recovery of the mucosa.^{1,37}

The third biopsy following the challenge test (according to initial guidelines) is recommended in all children, in children diagnosed of less than 2 years of

age. The gluten challenge test is necessary to exclude other causes that could be responsible for flat mucosa in children such as cow’s milk allergy.^{36,37}

A gluten challenge test should not be undertaken for at least two years and preferably not before the age of 6 years because it can damage the dentition if performed earlier. The gluten challenge is usually delayed until catch – up growth has been completed, which may be some years after starting the gluten free diet. When carrying out a gluten provocation test it is important to ensure adequate gluten intake. The test is carried out by adding 5-15 gr of gluten powder daily, depending on age. An alternative method is to permit 2-4 slices of bread daily (one slice of bread contains 2.5-3 gr gluten) to be added to the gluten free diet. A jejunal biopsy is performed at least 3-6 months following the reintroduction of gluten to the diet. The “celiac antibodies” are now recognized as valuable adjuncts to evaluation of gluten challenge test and they have been used to indicate the appropriate time to perform the biopsy.^{27,37} Although 5% of children with celiac disease will eventually become “gliadin tolerant” returning to a completely normal diet is unwise as the majority of children will need to continue on a life-long gluten-free diet.^{2,27,37}

If following the challenge test the biopsy shows normal mucosa, long term follow up is essential, with further biopsies taken if symptoms recur or if antibody tests becomes abnormal.^{1,27,37}

Jejunal biopsy is performed using modifications of the Crosby capsule to obtain specimens for histological purposes. The child is sedated and the tube of the capsule is introduced and passed through the stomach into the duodenum under fluoroscopy.²

The characteristic histological lesions encountered in patients with celiac disease are a) partial to total villous atrophy b) hyperplasia of the crypts c) Increased lymphocytes, plasma cells, mast cells and eosinophils in lamina propria d) absence of identifiable brush border and flattened or cyboidal epithelial cells. These lesions are not however pathognomonic for celiac disease.^{1-3,37}

Therapy

The children diagnosed as having celiac disease require a permanent gluten free diet to maintain a normal jejuna mucosa. Their diet should exclude wheat, oats, rye and barley. Rice, potatoes and corn are used

as wheat substitutes. The gluten free diet reduce the risk of developing focal and general complications. It is particularly important that gluten is permanently excluded from the diet. In children ingesting a normal diet the risk of subsequent gastrointestinal malignancy (lymphoma) is increased (25 to 120 fold). Other neoplasms appear to occur with increase frequency in patients with celiac disease (carcinomas of the oropharynx, esophagus, small intestine and breast). For children ingesting gluten free diet for at least 5 years the risk of developing malignancies is not increased compared with the general population. Parents of patients with celiac disease should be informed of this threat as well as the benefits of a gluten free diet.^{23,27}

At the time of the diagnosis most children are not in a dehydrated condition and it is reasonable to start a gluten free diet. In severely ill and debilitated children it is reasonable to start with gluten and cows milk free diet. A protein hydrolysed milk substitute will be required. In these infants a gluten free diet should precede the biopsy at least 2-3 weeks, so the infants will have improved clinically. The histological lesions will still be present weeks or even months after starting the gluten free diet. In severely ill children in so-called "celiac crisis" the use of corticosteroids may cause dramatic improvement.^{2,16,27}

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