Case report

Celiac disease in children

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Abstract

Celiac disease (CD) is an autoimmune enteropathy triggered by ingestion of the gluten fraction of wheat proteins and similar alcohol-soluble proteins of barley and rye in genetically susceptible subjects. For many years, celiac disease has been under diagnosed. However, because of today's greater knowledge of its presentations and the availability of new more accurate serologic tests, it is now known that CD is relatively common. Although CD can occur at any age, with a broad clinical spectrum affecting any organ, typical cases often manifest in infancy. This review aims to bring together the most significant current knowledge about this disease.

Key words

Celiac disease, gluten, autoimmunity, tissue transglutaminase, intraepithelial lymphocytes.

INTRODUCTION

Celiac disease (CD), also known as celiac sprue and gluten sensitive enteropathy, is an autoimmune disease triggered by the ingestion of gliadin fractions present in gluten and similar proteins of rye and barley by genetically predisposed individuals (1). Gluten is the major protein component of wheat, rye and barley. In CD, it triggers an immune reaction that leads to bowel inflammation mediated by T lymphocytes. Hyperplastic crypts, intraepithelial lymphocytes (IELs) and atrophy of the villi develop causing chronic enteropathy with a broad range of manifestations. The result is a systemic disease of varying severity (2). Adherence to a gluten-free diet by these patients leads to clinical and histological improvement, with long-term normalization of intestinal architecture. Symptoms recur if gluten is reintroduced into the diet (3).

There have been descriptions of CD since the first century BC, but its association with the ingestion of gluten was only found in 1940. During the World War II pediatricians Dicke and Dutch observed clinical improvement in patients when they replaced bread with food that did not contain grain. Patients suffered relapses after cereals were returned to their diets (4).

A series of studies carried out after the Second World War by Dicke, Wingers and van de Kamer administered different diets to children suffering from CD. By measuring variations in the weight of the feces and degree of steatorrhea they were able to measured the degree of malabsorption clearly showing that wheat, barley and rye aggravated the disease, whereas exclusion of these grains from the diet led to improvement of the patients (5). These studies allowed identification of gliadin (wheat gluten fraction soluble in alcohol) as the toxic agent in this disease (6).

EPIDEMIOLOGY

The epidemiology of CD has changed dramatically in the last decade. In the past it was considered a rare disorder with a prevalence estimated at 1:500 to 1:8,000 people in the general population (7). But large increases in the use of techniques that look for endomysial antibodies (EMA)

and anti-tissue transglutaminase (tTG) in circulation have shown that this disease occurs much more frequently than was previously estimated. In addition it is now know that there are incomplete or atypical clinical presentations. Recent studies show that the CD has been under-diagnosed (8), and it is in fact one of the most common disorders worldwide. It affects 0.5-1% of the general population of the United States and other developed countries. Previously, CD geographical distribution was restricted to Europe and other developed countries such as the USA, Canada and Australia. New epidemiological studies show that this disorder is also common in other parts of the world including the Asian continent (9).

In Latin America little epidemiological data exists. In Argentina a prevalence of 1 in 167 adults has been reported (10), but no statistics exist for the pediatric population. In Colombia there are no data about CD. The under-diagnosis can be explained by the celiac iceberg model (Figure 1) which is related to the frequency of predisposing haplotypes in each population and of gluten consumption habits. The tip of the iceberg is the symptomatic patients, but the submerged part of the iceberg contains the majority of the cases who have not been diagnosed. They may have atypical symptoms or may not even have symptoms. For every case diagnosed, it is estimated that there are 5 to 10 undiagnosed cases (11).

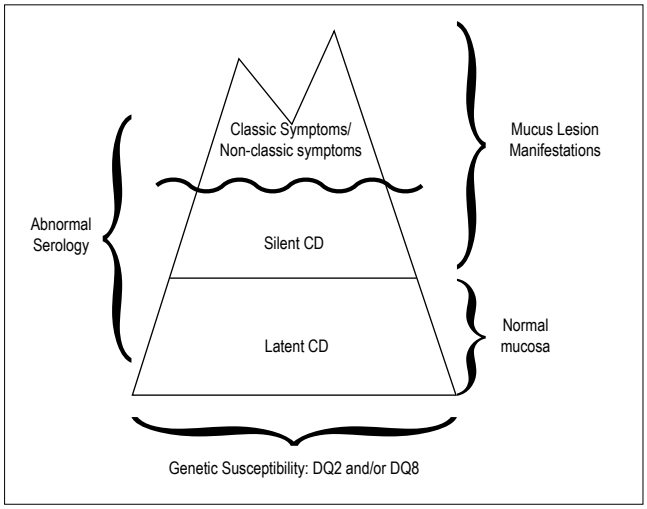

Figure 1. Iceberg model of Celiac Disease. Modified from de: Fasano A. Celiac disease in children. Best Practice & Research Clinical Gastroenterology 2005; 19:467-478.

GENETICS

Progress in genetic studies has shown that genetic predisposition plays a key role in CD. It is well known that CD is strongly associated with human leukocyte antigen (HLA) class II, HLA-DQ2 and HLA-DQ8 which are located on chromosome 6p21. About 95% of CD patients express HLA-DQ2 while the remaining patients are usually HLA-DQ8 positive (12). Although having antigens to DQ2 or DQ8 is necessary for development of CD, it is not sufficient. The risk for development of CD among patients with these haplotypes is 36% to 53%. The presence of the HLA-DQ2 allele is common in the general population, and it is present in approximately 30% of Caucasian individuals (9).

Different studies have found several loci associated with this disease. They show significant heterogeneity across different populations and have smaller impact than HLA DQ2 and DQ8. Among the predisposing loci for CD are CELIAC1 on chromosome 6 (HLA-DQ2 and HLA-DQ8), CELIAC2 on chromosome 5q31-33, CELIAC3 on chromosome 2q33 (includes T-lymphocyte regulatory genes CD28, CTLA4, and ICOS), and CELIAC4 (the myosin IXB gene, MYO9XB) on chromosome 19p13.1.ls.

The MYO9B gene encodes an unconventional myosin molecule involved in actin remodeling of epithelial enterocytes. It is believed that this genetic variant may lead to an alteration in the intestinal barrier which allows the passage of immunogenic gluten peptides (13). Also this genetic variation has been found in patients with systemic lupus erythematosus and rheumatoid arthritis suggesting that the gene MYO9B is an autoimmune risk factor (14).

In general, genetic predisposition to CD depends on genes with large effects on adaptive immune response to gluten peptides (HLA-DQ2/DQ8). This is influenced by many other genes involved in different aspects of adaptive or innate immune reactions, intestinal permeability and general autoimmune predispositions (9).

ETIOPATHOGENESIS

CD is the only autoimmune disease in which there is a clearly identified environmental trigger. 95% of CD patients have autoantibodies against tTG enzyme (1). CD is characterized by three key components. CD is triggered by gluten proteins. Antibodies against tTG are present in CD patients, and the expression of certain HLA phenotypes is required (8).

Multiple pathways are involved in the pathogenesis of CD which finally lead to the destruction of the enterocyte and subsequent atrophy of intestinal villi. Gluten, the non soluble water protein fraction of wheat flour, plays the leading role. Proteins in wheat flour can be separated into glutens which are insoluble in ethanol, and gliadins which are soluble in ethanol. Both have high glutamine and proline contents. Gliadin is a prolamin. Two other similar prolamins, secalins, and hordein have been isolated in rye and barley.

Innate and adaptive immune responses are involved in CD (15). Tissue transglutaminase (tTG), an intestinal enzyme, deaminates gliadin peptides, increasing immune power. In the adaptive immune response $CD4^+$ T cells recognize deaminated gliadin peptides in the lamina propia through HLA class II molecules DQ2 or DQ8 on antigen-presenting cells. This promotes the release of proinflammatory cytokines and metalloproteinases with consequent intestinal damage. Regarding innate immunity, the ingestion of gliadin causes direct toxicity to enterocytes by overexpression of IL-15 in the intestine (16, 17). Subsequent positive regulation of stress molecules MIC-A on the surface of the enterocyte causes activation of intraepithelial lymphocytes (18) and their differentiation in the presence of IL-15 into NK (Natural Killer cells). This expresses the activated receptor NKG2D which is cytolytic for the enterocyte through the NK- G2D and MIC-A interaction.

HISTOLOGY

The histology of CD studies the mucosa of the small intestine, especially the submucosa, muscularis and serosa. A flat mucosa with villus shortening can be observed which is compensated for by hyperplasia and elongation of intestinal crypts. These changes reduce the amount of epithelial surface available for absorption. There is increased permeability of the intestinal mucosa because of alterations in intercellular tight junctions between injured absorptive cells and because of increases of zonulin, a protein responsible for providing intestinal mucosal permeability. Increased permeability allows passage of large molecules. The disaccharidases, peptidases, alkaline phosphatases, adenosine triphosphatases and esterases are reduced. The amount of intraepithelial lymphocytes (IELs)/mm increases, although with no real increase in absolute numbers because the absorptive surface is greatly reduced (19). The proximal intestine most affected, with severity decreasing towards the distal small intestine. Exclusive compromise of the distal segment is not a feature of celiac disease.

The IELs occupy a particular place in the immune system and play an important role in intestinal homeostasis. The normal ration of IELs to epithelial cells in the small intestine is 1:10. Since the intestinal absorption surface is approximately 300 mt^2, IELs are an important lymphoid compartment (20, 21).

The intestine is the organ with the highest antigen load in the body. Their first contacts are with the IELs which have a regulatory function involved in oral tolerance. Usually TcRαβ lymphocytes predominate with γδ TcR T cells accounting for less than 10% of the lymphocytes. However, the number of γδ TcR T cells steadily increases in CD. These cells, which are involved in autoimmune phenomena, have a great capacity for antigen recognition and demonstrated cytotoxic power (20).

CLINICAL MANIFESTATIONS

The clinical presentation of CD is very diverse, and is closely related to age (19). There is a wide spectrum of clinical manifestations (Table 1).

Table 1. Clinical characteristics of Celiac Disease.

Symptoms	Extraintestinal Manifestations	Associated conditions
Gastrointestinal:	Arthritis	Diabetes type 1
• Diarrhea	Aphthous Stomatitis	Autoimmune Thyroid Disease Down Syndrome
• Abdominal Pain	Dermatitis herpetiformis	Turner Syndrome
• Distension	Osteoporosis/Osteopenia	IgA Deficiency
• Constipation	Elevated levels of hepatic transaminases	IgA Nephropathy
Nutritional Deficiencies:	Infertility	
• Anemia	Recurrent miscarriages	
• Iron Deficiency	Neurological	
• Folate Deficiency	• Ataxia	
• Vitamin D Deficiency	• Epilepsy	
• Rickets	Psychiatric	
• Hypocalcemia	• Anxiety	
• Vitamin K Deficiency	• Depression	
• Coagulopathy		
• Small size		
• Delayed puberty		

Modified from: Barker JM, Liu E. Celiac Disease: Pathophysiology, Clinical Manifestations, and Associated Autoimmune Conditions. Advances in Pediatrics 2008; 55: 349–365.

CD with classic symptoms

CD with classic symptoms is characterized by gastrointestinal manifestations which start between the ages of 6 and 24 months after gluten is introduced to the diet (22). Symptoms which typically present include diarrhea, disturbed growth, malnutrition, pain, abdominal distension, muscle weakness and hypotonia. Weeks to months after the start gluten ingestion there is a clear decrease in the rate of weight gain. In severe forms intestinal malabsorption of vitamins and micronutrient deficiency may present (23), leading to long term severe vitamin D deficiency, hypocalcaemia or rickets, coagulopathy secondary to vitamin K deficiency or anemia due to iron and folate deficiencies (24). The celiac crisis, which is characterized by the presence of explosive watery diarrhea, marked abdominal distention, dehydration and electrolyte disturbance, is not seen often.

CD with non-classic symptoms

There is a delay in the beginning of symptoms to between the ages of 5 and 7 years old. Intestinal manifestations are unusual, with recurrent abdominal pain, nausea, vomiting and constipation, or extra intestinal manifestations may occur.

Children and adolescents with CD often have short stature and delayed puberty. A diagnosis of CD should be considered in these patients. Serological screening tests for CD are recommended (25).

Acute non-erosive arthritis has been reported in 25% of CD patients (26). However, more recent data have shown a much smaller proportion (9). Other symptoms that are frequently found among CD patients are tooth disorders, recurrent aphthous stomatitis (27) and elevated liver transaminases (28). All have the special feature of being completely resolved after a gluten-free diet is adopted. Osteoporosis is a well-known complication of untreated CD (29). Persistent atrophy of intestinal villi is associated with low bone mineral density and deficiencies of calcium and vitamin D due to intestinal malabsorption.

Neurological and psychiatric disorders described include depression, anxiety, irritability, peripheral neuropathy, cerebellar ataxia and migraines (See Table 1) (30).

In adults diarrhea is the main manifestation. It is found in 50% of cases (19) and is often confused with irritable bowel syndrome. They are usually diagnosed after multiple appointments within a study of anemia or osteoporosis.

Silent CD

Silent CD is defined when they are incidental findings of a typical gluten-sensitive enteropathy in an apparently healthy person. There have been many cases reported after screening programs in studies that were looking for the presence of EMA and tTG antibodies in the general population in at risk populations (22). Thorough evaluations including detailed anamneses revealed that many of these patients had low intensity symptoms.

Latent CD

These patients have normal intestinal mucosae even though their diets contain gluten, but they have had CD in the past or will have it in the future. This subgroup represents is the most difficult to diagnose.

Potential CD

Patients are diagnosed with the potential form of CD when they test positive for endomysial antibodies (EMA) and/or tTG antibodies in addition to the typical HLA predisposing genotype (DQ2 or DQ8). Although they have normal or only minimally altered intestinal mucosa, these patients typically risk developing CD later.

ASSOCIATED CONDITIONS

One of the biggest controversies about CD in children regards its association with autoimmune disorders. One proposition in the theories is that this association is secondary to an imbalance between genes which predispose for both CD and autoimmune diseases. Another is that CD stimulates the onset an autoimmune diseases in genetically predisposed patients. This is evidenced by tTG which is one of the auto antigens involved in gluten-dependent autoimmune reaction (22).

A strong association with autoimmune thyroiditis has been found in autoimmune diseases. Larizza et al found a CD prevalence of 7.8% in children with autoimmune thyroiditis or Graves' disease (31). Also there is a CD prevalence of 4.5% in patients with type 1 diabetes mellitus (32).

Special mention goes to children with Down syndrome in whom CD can occur at any age. Their CD, which ranges from 5% to 15%, higher than that in the general population (33). Among Down syndrome patients silent CD is most commonly manifested. Symptoms tend to be vague and include constipation, dyspepsia, abdominal pain and flatulence. Usually the diagnosis is much more delayed than in the general population because these nonspecific symptoms are attributed to the Down syndrome.

Currently, in United States a complete CD screening for IgA and IgA TGT is recommended for all children with Down syndrome who are two years and older (33). Down syndrome children under 2 years of age who have

suggestive symptoms should be tested for gliadin antibodies (AGA) IgA in addition to the two serological tests mentioned above (34). Identification of CD and its proper treatment has been shown to improve the quality of life of these patients (35).

SEROLOGICAL TESTS

The measurement of IgA anti-tTG serological test is recommended in the initial evaluation of patients suspected of having CD. This test's sensitivity and specificity are greater than 95% (1). Although the dosage of IgA anti-endomysial antibodies is highly specific for celiac disease, approaching 100%, it has the problem of being observer-dependent and is subject to misinterpretation which can increase costs by repeating the test. Because of its lower precision, AGA is not recommended for use in CD detection of CD except for those under 18 months of age (36).

Selective IgA deficiency is more common in patients with celiac disease than in the general population. These patients have elevated levels of Ac Ac tTG IgA or EMA IgA, therefore it is recommended that they be tested for Ac tTG IgG (37). In addition to their uses in screening, these serological tests have proved useful for monitoring patients' responses to treatment (Table 2).

Table 2. Serological tests for Celiac Disease.

Antibody	Sensitivity %	Specificity %
Antigliadin	79-90	82-95
Anti-endomysium	85-98	97-100
Anti-tissular transglutaminase antibodies (tTGA)	95-98	94-95
Anti- deamidated Gliadin	95-98	94-98

From: Barker JM, Liu E. Celiac Disease: Pathophysiology, Clinical Manifestations, and Associated Autoimmune Conditions. Advances in Pediatrics 2008; 55: 349-365.

SCREENING

Because of diverse presentation of CD diagnosis is often difficult, incorrect or delayed. The consequences of untreated CD include anemia, delayed puberty, stunted growth and low bone density, among others. They are related to time of exposure to a diet containing gluten (38).

Current international consensus recommends using serological screening tests on members of those groups which have been shown to have oligosymptomatic or monosymptomatic forms most frequently (36, 39). These groups include patients who have dermatitis herpetiformis, insulin dependent diabetes mellitus, Down syndrome, Turner syndrome, IgA deficiency, short stature, delayed puberty, infertility, severe enamel hypoplasia, more than 3 episodes of stomatitis per year, hypertransaminasemia of unknown etiology, epilepsy in which the CT shows bilateral occipital calcifications, autoimmune diseases of poorly defined etiology (hepatitis, thyroiditis, arthritis, etc.), irritable bowel syndrome, low response to treatment, and close relatives of celiac patients.

CASE 1

Male patient with a history of prematurity, pathological short stature and pubertal delay, who at 11 years old showed a year-long, self-limiting thrombocytopenia and for which no etiology was found. The following year he debuted with autoimmune hepatitis and hemolytic anemia, which were resolved with immunosuppressive therapy (prednisone, azathioprine and cyclosporine) and also found hypothyroidism and diarrheal stools. Simultaneously, he showed edema, local pain in joints of large and medium size, which were resolved with NSAIDs. The ANAS, anti-native DNA, anticardiolipin and lupus anticoagulant were negative. Within the inmunological study was found diminished IgG and IgE total serum, and in the subpopulation of lymphocytes was observed deficiency in memory B cells, especially in those who had made isotype change. Common variable immunodeficiency diagnosis was made and was treated with monthly immunoglobulin, with a good clinical response and improvement of polyglandular commitment, but with persistent diarrheal stools for prolonged periods. Six months later there was a significant deterioration in his gastrointestinal profile, with abundant and persistent loose stools, which caused severe electrolyte and acid base problems, and were associated with significant abdominal distension and weight loss. Upper gastrointestinal endoscopy was performed without pathological findings, but the histology study showed marked villous atrophy in the duodenum. CD was suspected and it was started a gluten-free diet. The result of antibodies for CD would not be interpretable if they receive gamma globulin, so they were not realized. Gluten-free diet was the only intervention, after multiple treatment options used that led to a significant improvement in his gastrointestinal and histological profile. Currently, immunological studies and molecular biology are completed in this patient with polyglandular commitment, enteropathy and immunodeficiency.

CASE 2

Female patient, 7 years old, with a history of recurrent sinus-lung infections, intestinal malabsorption and delay pondostatural since her 6 months of life. At 16 months began with recurrent episodes of diarrheal stools, sometimes dysenteric and for which there was not germ isola-

tion. Showed an average of six pneumonia and five acute otitis media per year. At 3 years was diagnosed selective IgA deficiency. She was referred to our hospital at age 7 for presenting oral papillomatosis. It was also found hepatosplenomegaly and infection by Epstein Barr virus. The serological tests for HIV, hepatitis B and C were negative. The tomography in her lung showed widespread bronchiectasis. Within the study of chronic diarrhea were made IgG anti-tTG which were positive. Endoscopy showed nodular hyperplasia in the duodenum. In the histology was observed severe atrophy of the villi in the duodenum with increased intraepithelial lymphocytes. It started gluten-free diet wich presented normalization of stool and subsequent recovery of intestinal histology (Figures 2A and B).

Although the patient presents recurrent infectious processes by her immunodeficiency, her gastrointestinal symptoms were resolved after the therapy for CD.

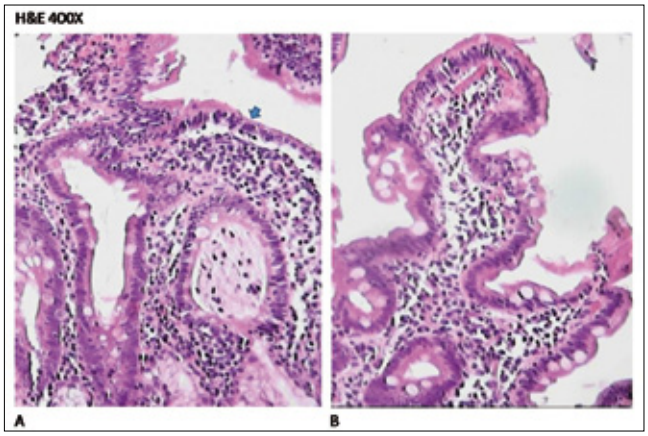

Figure 2. Duodenal biopsy for upper gastrointestinal endoscopy. Duodenum before (A) and after (B) the introduction of gluten-free diet. A. Villous atrophy and infiltration of the epithelium by lymphocytes. There are accumulations of lymphocytes in the lamina propria. B. Recovery of villous architecture and epithelial reparative changes.

DIAGNOSIS

A diagnosis of requires CD confirmation by intestinal biopsy in all cases (40). Because histological changes in CD can be patchy, obtaining multiple samples from the second portion of the duodenum, or a more distal part, is recommended. Marsh type3 villous atrophy is usually the histopathology presentation characteristic of CD. However there are cases where the intestinal biopsy is compatible with CD, although the evidence is less clear. In these cases the diagnosis should be reinforced by the presence of positive serology (tTG or EMA) for CD (36).

The diagnostic criteria of celiac disease currently used are those established by the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) (41). The presence of two criteria is required: characteristic abnormalities of the intestinal mucosa while the patient's diet contains a significant quantity of gluten, and resolution of histological changes or symptoms with a strict gluten-free diet. The presence of auto-immune antibodies is hugely important additional evidence for diagnosis and management of these patients (Figure 3). In symptomatic patients, the presence of anti-EMA or anti TGT is highly predictive (97% to100%) of histological changes compatible with CD (42).

The decision to diagnose CD in a patient is important since the disease is life-long and people with CD have a higher risk of malignancy in adulthood if their adherence to a gluten-free diet is poor (43).

TREATMENT

The only scientifically proven treatment to date is a gluten-free diet (No wheat, barley or rye). This must be strictly adhered to for life, independent of the person's clinical status (39).

With respect to oats, their exclusion from the CD patient's diet is also recommended. Even though we know that oats are not harmful to the vast majority of celiacs, oats may contain trace amounts of gluten from cross-contamination in mills where wheat, barley and rye are also processed. The patient's diet should be supplemented with multivitamins, calcium and vitamin D, and the iron and folate deficiency should be repaired.

Treatment should begin only after diagnostic confirmation by biopsy. (36) 70% of patients' symptoms improve after two weeks of a gluten-free diet (44). If there is no improvement after in the following weeks, the most common cause is incomplete removal of gluten from the diet. Histological resolution is not as immediate, and may be observed later.

Treatment options focused on the pathophysiological targets of CD are now being developed on the basis of the improved understanding of the molecular and cellular basis of CD that has been achieved in the last decade (9). These include enzyme therapy designed to promote complete digestion of gliadin peptides and preventing the immune response to them. Another method under study is identification of antigenic epitopes and the development of immunomodulators against them. One possibility would be selective inhibition of TGT (autoantigens CHD) (45). One pharmacological target for development of drugs against celiac disease is zonulin inhibitors. This protein is elevated in patients with CD. It increases intestinal mucosa permeability, facilitating the passage of gluten through the mucosa.

Another therapeutic alternative that is being studied is the use of gluten digesting enzymes such as prolyl-endopeptidase which is derived from the Aspergillus Niger fun-

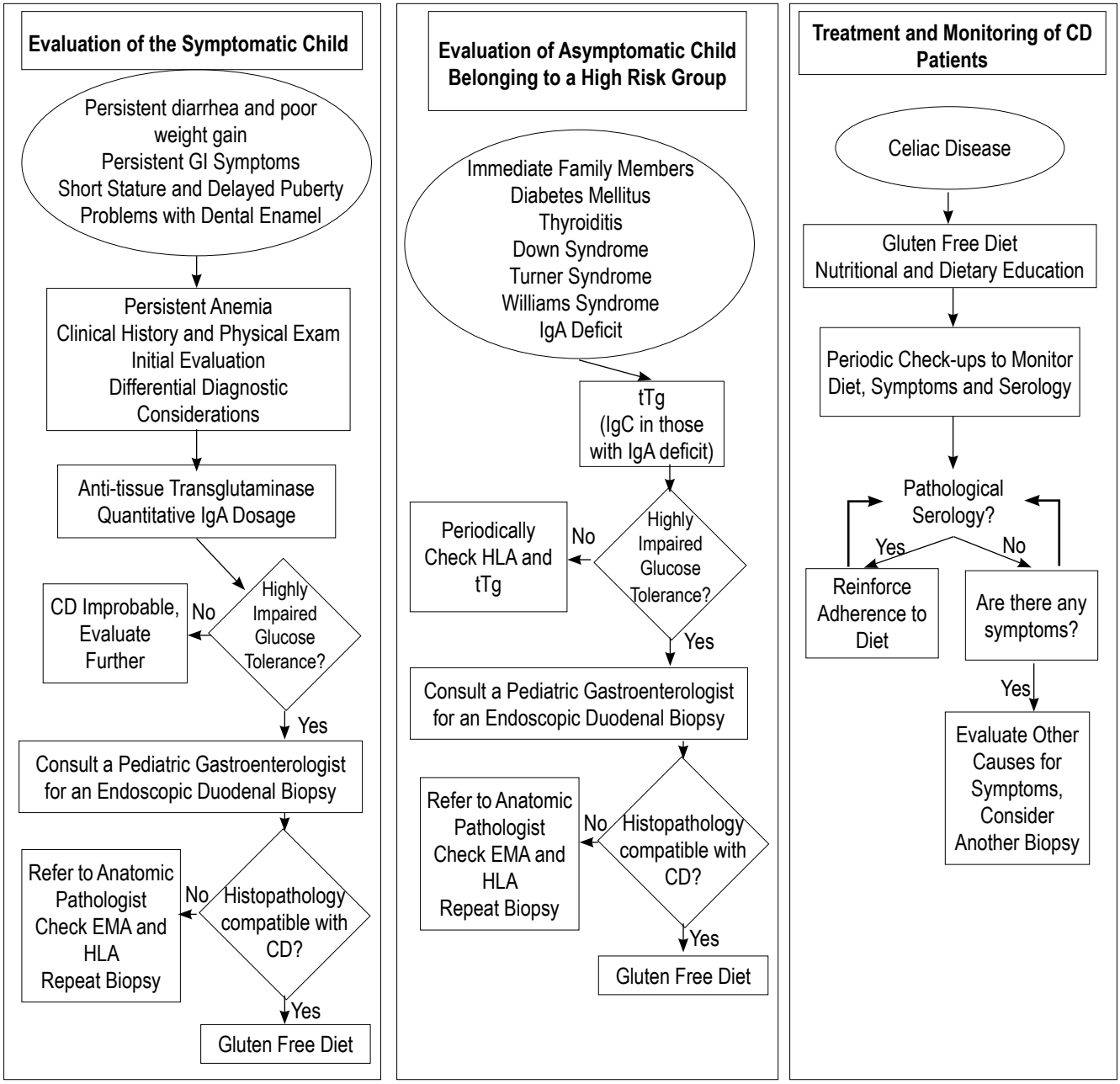

Figure 2. Algorithms for evaluation and management of infants and children suspected of having Celiac Disease. Modified from: J Pediatr Gastroenterol Nutr 2005; 40: 1-19.

gus. It is said to be capable of degrading gluten protein into fragments safe for celiac patients. Studies are also underway on the therapies using with IL10 to promote antigenic tolerance, and against IL15 to decrease inflammatory activity.

Correction of defects in the intestinal barrier basically requires restoration of the balance of gut-associated lymphoid tissue and neuroendocrine tissue and between tolerance and immunity to foreign antigens. Despite future therapeutic possibilities for CD, adequate education for CD patients, families and health professionals should be included as a mainstay.

A prospective study conducted in Denver, Colorado provides information in regard to the moment of introduction of gluten in infant feeding. The study of 1,560 children who were at risk of CD or type 1 myotonic dystrophy was conducted over a 10 year period. It concluded that children with risk factors for CD who were exposed to gluten during the first 3 months of life have 5 times more risk of develo-

ping CD than those exposed between 4 and 6 months of life (46).

However, it has also been found that this risk increased when the exposure was delayed until after the seventh month of life compared with exposure between 4-6 months. Unfortunately, this article does not refer to data on the amount of gluten consumed since this is important in connection with the hypothesis that CD risk increases more if gluten is introduced rapidly at 6 months than if it is introduced slowly from 4 months and if breastfeeding is not discontinued (47).

Several studies have also concluded that breastfeeding and the continuation of breast feeding after gluten is introduced to the diet are associated with reduced risks of CD development (48, 49).

COMPLICATIONS

Death is still the most feared complication of CD. The study by West et al of group of 4,732 CD patients that they had a 30% higher risk of developing malignancies (50). Among the possible malignancies the most closely associated with CD was enteropathy-associated T cell lymphoma (8). Other related neoplasms are adenocarcinoma of the small intestine, and oropharyngeal and esophageal carcinomas (43). Refractory celiac disease can occur through primary resistance to the gluten-free diet, called primary refractory celiac disease, or it can occur when a patient who initially responds well to the gluten-free diet frequently breaks the diet. This is called secondary refractory celiac disease. These diagnoses are made after causes of enteropathy similar to celiac disease and the possibility of inadvertent gluten intake have been ruled out. Severe cases may require complete intravenous nutrition. Immunosuppressive medications such as corticosteroids are the first-line drug in treatment of refractory celiac disease, while cyclosporine has been used successfully in severe cases (51).

Other complications include jejunoileitis and colitis. These are rare, but often fatal complications in adults between 60 and- 70 years of age. Another complication is collagen CD in which there is no response to the elimination of gluten from the diet. Over time collagen deposits develop in the lamina propia.

If the disease is not recognized and treated appropriately, patients can develop malnutrition and dye from complications. The prognosis for correctly diagnosed and treated CD patients is excellent.

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