Review Article

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Coeliac Disease

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Abstract: Coeliac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. It occurs in children and adolescents with gastrointestinal symptoms, dermatitis herpetiformis, dental enamel defects, osteoporosis, short stature, delayed puberty and persistent iron deficiency anaemia and in asymptomatic individuals with type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, selective immunoglobulin (Ig)A deficiency and first degree relatives of individuals with coeliac disease. The Coeliac Disease Guideline Committee of the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition has formulated a clinical practice guideline for the diagnosis and treatment of paediatric coeliac disease based on an integration of a systematic review of the medical literature combined with expert opinion.

The Committee examined the indications for testing, the value of serological tests, human leukocyte antigen (HLA) typing and histopathology and the treatment and monitoring of children with coeliac disease. It is recommended that children and adolescents with symptoms of coeliac disease or an increased risk for coeliac disease have a blood test for antibody to tissue transglutaminase (TTG), that those with an elevated TTG be referred to a paediatric gastroenterologist for an intestinal biopsy and that those with the characteristics of coeliac disease on intestinal histopathology be treated with a strict gluten-free diet (GFD).

Keywords: Coeliac disease (CD); Gluten free diet (GFD).

Introduction

Coeliac disease is an autoimmune disorder of the small intestine that occurs in genetically predisposed people of all ages from middle infancy onward. This condition has several other names, including coeliac sprue, non tropical sprue, endemic sprue, gluten enteropathy or gluten-sensitive enteropathy, and gluten intolerance. The term coeliac was derived from the Greek (koiliakos, "abdominal") and was introduced in the 19th century in a translation of what is generally regarded as an ancient Greek description of the disease by Aretaeus of Cappadocia.[1,2]

Symptoms include pain and discomfort in the digestive tract, chronic constipation and diarrhoea, failure to thrive (in children), and fatigue, but these may be absent, and symptoms in other organ systems have been described. Vitamin deficiencies are often noted in people with coeliac disease due to the reduced ability of the small intestine to properly absorb nutrients from food. Increasingly, diagnoses are being made in asymptomatic persons as a result of increased screening.[3]

The condition is thought to affect between 1 in 1,750 and 1 in 105 people in the United

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States.[4] Coeliac disease is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in the crops of the tribe Triticeae (which includes other common grains such as barley and rye).[5] Upon exposure to gliadin, and specifically to three peptides found in prolamins, the enzyme tissue trans glutaminase modifies the protein, and the immune system cross-reacts with the small-bowel tissue, causing an inflammatory reaction. This leads to a truncating of the villi lining the small intestine (called villous atrophy). It interferes with the absor-ption of nutrients because the intestinal villi are responsible for absorption. The only known effective treatment is a lifelong gluten-free diet.[5] While the disease is caused by a reaction to wheat proteins, it is not the same as wheat allergy.

Pathogenesis

Susceptibility to CD, and its activation and perpetuation, involve a combination of environmental and genetic factors, and immunological mechanisms. A number of important factors and mechanisms underlying disease pathogenesis are well defined, whereas others are only now coming into focus.

A) The role of dietary proteins in disease pathogenesis

CD is activated by proteins in the dietary cereal grains wheat, rye, and barley. The disease-activating proteins in these grains are widely termed "gluten". Gluten includes 2 major protein types, the gliadins and glutenins, both of which contain disease-activating peptides.[6] The closely related proteins in barley and rye that activate CD are the hordeins and secalins, respectively.[7] Oats are thought to activate CD only rarely[8], and, consistent with this, oat avenins are more distantly related to the analogous proteins in wheat, rye, and barley and have a substantially lower proline content.[9] Gliadins, glutenins, hordeins, and secalins have a high proline and glutamine content. The high proline content renders these proteins resistant to complete proteolytic digestion by gastric, pancreatic, and brush border enzymes in the human intestine, since those enzymes are deficient in prolyl endopeptidase activity. This can result in the accumulation of relatively large peptide fragments (as many as 50 amino acids in length) with a high proline and glutamine content in the small intestine. Nonetheless, the relatively poor digestion of these proteins alone is not sufficient to cause CD. However, failure to digest these and other proteins might be exaggerated in the small intestine of individuals with active disease who manifest epithelial cell brush border injury and accompanying pancreatic dysfunction.[10]

B) Genetic factors

MHC class II HLA-DQ alleles. The pathogenesis of CD is firmly rooted in host genetic factors. It is known that CD is associated with specific MHC class II alleles that map to the HLA-DQ locus. The presence of speci-fic HLA-DQ alleles is necessary, although not sufficient, for the phenotypic expression of CD in virtually all affected individuals, irrespective of geographic location.[11] Indeed, almost all individuals with biopsy-confirmed CD express HLA-DQ alleles that encode specific HLA-DQ2 heterodimers or specific HLA-DQ8 heterodimers, and the alleles that encode these heterodimers are relatively common in the white population.CD is substantially more prevalent in those in whom 100% or approximately 50% of the HLA-DQ heterodimers are HLA-DQ2 than in those in whom only approximately 25% of the HLA-DQ heterodimers are HLA-DQ2. In this regard, the approximately 2% of the population who are homozygous for the HLA-DQ2 heterodimer account for approximately 25% of all patients with CD. Notably, an increased abundance of HLA-DQ2 heterodimers on APCs has correlated with an increased magnitude of in vitro gluten-specific T cell responses, which, if paralleled in vivo, might contribute to the increased risk of developing clinically apparent CD in individuals homozygous for HLA-DQ2. Once

CD develops, the clinical course seems generally similar whether or not 100%, 50%, or 25% of the HLA-DQ molecules form the HLA-DQ2 heterodimer. Most recently with the use of genome-wide screening approaches Candidate genetic regions that possibly increase CD susceptibility have been noted in some populations on chromosomes 2, 3, 4, 5, 6 (telomeric of the HLA locus), 9, 11, 18, and 19.[12]

HLA-DQ2 and HLA-DQ8 heterodimers on APCs can bind and subsequently present "gluten" peptides to populations of CD_4^+ T cells in the lamina propria of the small intestine. Tissue TGase, which is released in the intestinal mucosa during tissue injury, has a role in tissue repair and cross-links proteins by forming isopeptide bonds between glutamine and lysine residues. However, tissue TGase also has a high avidity for "gluten" peptides and, under certain conditions (for example, low p^H) and in the absence of lysine residues, can deamidate glutamine, which converts neutral glutamine to negatively charged glutamic acid. Some, but not all, of the deamidated "gluten" peptides, by virtue of having negatively charged glutamic acid residues, manifest an increased binding affinity for the disease-relevant HLA-DQ2 or HLA-DQ8 molecules. Once bound to HLA-DQ2 and HLA-DQ8, the "gluten"-peptide–HLA-DQ complexes can activate T cells in the mucosa of the small intestine that recognize these complexes. Glutamine deamidation is not an absolute requirement for T cell activation early in the course of disease in children. It is now known that T cells in adults with CD also are reactive to multiple peptides from α- and γ-gliadins.[13]

'The production of IFN-γ is a signature of "gluten" peptide–specific HLA-DQ2– and HLA-DQ8–restricted T cells and it is considered to have a key role in the downstream initiation of mucosal damage. Neutralization of IFN-γ has been shown to prevent "gluten"-induced mucosal damage, at least in biopsies of CD mucosa maintained in organ culture. Recent studies suggest that activation of the innate immune system is important in the pathogenesis of CD and in some of the complications of this disease, namely in refractory CD (that is, severe villous atrophy and malabsorption that either does not respond or no longer responds to a GFD). In particular, an increase in the number of IELs in the mucosa of the small intestine is a characteristic feature of CD, and those cells are likely to be important for the ongoing pathogenesis of CD. Following activation, IELs from patients with CD change from being typical antigen-specific T cells to being NK-like cells able to mediate epithelial cell damage through the recognition of stress-induced molecules on intestinal epithelial cells. The cytokine IL-15 takes center stage in this process. Up regulation of IL-15 expression by epithelial cells in CD seems to contribute to altered signalling properties of the CD_8^+ IEL population.[14]

Clinical features

The clinical manifestations of CD vary markedly with the age of the patient, the duration and extent of disease, and the presence of extra intestinal pathology. Depending on the features at the time of presentation, together with the histologic and immunologic abnormalities at the time of diagnosis, CD can be subdivided into the following clinical forms.

a) Classical (typical) form

The onset of symptoms in the classical form generally occurs between 6 and 18 months of age. This form is typically characterized by chronic diarrhea, failure to thrive, anorexia, abdominal distention, and muscle wasting. Growth is usually normal during the first months of life. Symptoms begin within weeks to a few months after the introduction of weaning foods containing prolamines, and soon there is a progressive decrease in weight gain with a decline in the child's percentile for weight and weight for height. On examination, the children are often pale and noticeably thin with a protuberant abdomen, decreased subcutaneous fat, and reduction in

muscle mass. The stools are characteristically pale, loose, bulky, and highly offensive because of fat malabsorption. A small number of these infants also have severe hypoproteinemia and edema and may present in a shock like state that has been termed "coeliac crisis".[15]

b) Atypical forms

In recent years there has been a noticeable change in the age of onset of symptoms and the clinical presentation of CD. Ma¨ki *et al*[16] first reported an up-shift of age at diagnosis in Finland to 5–6 years, with fewer than 50% of new cases presenting with typical gastrointestinal symptoms. Reports from Scotland, England, Canada, and the United States have also shown that almost 50% of patients with newly diagnosed CD do not present with gastrointestinal symptoms.

c) Dermatitis herpetiformis

Dermatitis herpetiformis is currently regarded as a variant of CD ("skin CD"). It is a blistering skin disease characterized by pathognomonic granular immunoglobulin (Ig) A deposits in uninvolved skin. The most typical sites of the rash are the elbows, knees, and buttocks. Intestinal symptoms are not common, but a varying degree of enteropathy, ranging from the infiltrative-type lesion to flat mucosa, can be found on small intestinal biopsy in almost 100% of cases. Both the enteropathy and the rash slowly clear with a gluten-free diet (GFD) and relapse when patients return to a regular diet.[17]

d) Iron-deficiency anaemia

Iron deficiency with or without anaemia, typically refractory to oral iron supplementation, can be the only presenting sign of CD.[18]

e) Short stature

Short stature is well described as the only symptom of CD in some older children and adolescents, and it is believed that as many as 9%–10% of those with "idiopathic" short stature have CD. In these patients, both the bone age and growth velocity are significantly impaired. Some patients have also demonstrated impaired growth hormone production after provocative stimulation testing. This value returns to normal after introduction of a GFD.[19]

f) Dental enamel Hypoplasia

It has been found in up to 30% of untreated patients with CD.[20]

g) Arthritis and Arthralgia

CD has been described in 1.5%–7.5% of patients with rheumatoid arthritis. These symptoms were reported by Ma¨ki *et al* as the only presentation of CD in 7 adolescent patients. In each case, the symptoms resolved on introduction of a GFD and all other anti-inflammatory medications could be discontinued.[21]

h) Chronic hepatitis and Hypertransaminasemia

Idiopathic chronic hepatitis as the initial presentation of CD has been reported occasionally.[22] Vajro *et al* described 3 children with cryptogenetic chronic hepatitis secondary to CD. In all cases, GFD induced complete remission with normalization of the biochemical and histologic changes of hepatitis. Resolution of the biochemical abnormalities associated with hepatic damage has been reported in a high percentage of paediatric patients with CD who adhered to a strict GFD.[23]

i) Osteoporosis

Patients with CD are at high risk for developing low bone mineral density and bone turnover impairment. Persistent villous atrophy is associated with low bone mineral density. In adult patients responsive to diet, the bone density seems comparable to that of healthy individuals. Children who followed a

GFD for at least 5 years had normal bone mineralization and bone turnover.[24]

j) Neurologic problems

Gluten sensitivity is common in patients with neurological diseases of unknown cause and may have etiologic significance.

k) Other extra-gastrointestinal symptoms

A delay in onset of puberty secondary to CD has been described in a number of adolescent patients. Recurrent abortions and reduced fertility caused by CD have also been reported in this age group.[25,26]

l) Asymptomatic (silent) form

This form is characterized by the presence of histologic changes, probably limited to the proximal intestine, that occur in individuals who are apparently asymptomatic. Most cases in this category have been identified through screening programs involving apparently healthy subjects. However, a more careful clinical anamnesis typically reveals that many of these "silent" cases are indeed affected by low-intensity illness often associated with decreased psychophysical well-being. Common problems behavioral disturbances, such as tendency to depression, irritability, or impaired school performance in children; impaired physical fitness, feeling always tired, and easy fatigue during exercise. Current evidence suggests that subjects with "silent" CD are at risk to develop the same long-term complications experienced by individuals with typical symptoms.[27,28]

Associated conditions

Conditions associated with coeliac disease are IDDM, autoimmune hepatitis, autoimmune thyroiditis, Sjogren syndrome, Addison disease, autoimmune atrophic gastritis. Gluten independent conditions are Down syndrome, Turner syndrome, Williams syndrome, congenital heart disease, IgA deficiency.

Complications Associated With Unrecognized CD

1) Malignancies

The persistence of mucosal injury with or without typical symptoms can lead to serious complications, and gastrointestinal malignancies (particularly lymphoma) have been reported in 10%–15% of adult patients with known CD who do not strictly comply with a GFD. It has been reported that the mortality rate in CD patients is almost double (1.93) the rate calculated for the general population, mainly because of the occurrence of neoplasms.[29]

2) Autoimmune diseases

CD seems to meet the criteria of a true autoimmune disease for which the genetic predisposition (HLA), exogenous trigger (gluten), and auto antigen (tTG) are known. It seems that tTG is only one of the auto antigens involved in gluten dependent autoimmune reactions. Other auto antigens that are normally "cryptic" can be unmasked and cause a self-aggressive immunologic response following the gliadin-initiated inflammatory process. Recent data suggest that the prevalence of autoimmune diseases among patients with CD is proportional to the time of exposure to gluten.[30]

Diagnosis

Testing for CD should be offered to the following groups:

Group 1: Children and adolescents with the otherwise unexplained symptoms and signs of chronic or intermittent diarrhoea, failure to thrive, weight loss, stunted growth, delayed puberty, amenorrhoea, iron-deficiency anaemia, nausea or vomiting, chronic abdominal pain, cramping or distension, chronic constipation, chronic fatigue, recurrent aphthous stomatitis (mouth ulcers), dermatitis herpetiformis–like rash, fracture with inadequate traumas/osteopenia/osteoporosis, and abnormal liver biochemistry.

Group 2: Asymptomatic children and adolescents with an increased risk for CD such as type 1 diabetes mellitus (T1DM), Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective immunoglobulin A (IgA) deficiency, autoimmune liver disease, and first-degree relatives with CD.

Diagnostic tools

CD-specific antibody tests

CD-specific antibody tests measure anti-Tissue transglutaminase2 or endomyecial antibody in blood.

It is not sufficient to state only positivity or negativity. Reports on EMA results should contain the specification of the investigated immunoglobulin class, cut-off dilution, interpretation (positive or negative), highest dilution still positive, and specification of the substrate tissue. For the interpretation of antibody results, total IgA levels in serum, age of the patient, pattern of gluten consumption, and intake of immunosuppressive drugs should be taken into account. If gluten exposure was short or gluten had been withdrawn for a longer period of time (several weeks to years) the negative result is not reliable. For IgA-competent subjects, the conclusions should be drawn primarily from the results of IgA class antibody tests. For subjects with low serum IgA levels (total serum IgA < 0.2 g/L), the conclusions should be drawn from the results of the IgG class CD-specific antibody tests.

HLA testing for HLA-DQ2 and HLA-DQ8

Typing for HLA-DQ2 and HLA-DQ8 is a useful tool to exclude CD or to make the diagnosis unlikely in the case of a negative test result for both markers. HLA testing should be performed in patients with an uncertain diagnosis of CD, for example, in patients with negative CD-specific antibodies and mild infiltrative changes in proximal small intestinal biopsy specimens. If CD is considered in children in whom there is a strong clinical suspicion of CD, high specific CD antibodies are present, and small-bowel biopsies are not going to be performed, then the working group recommends performing HLA-DQ2 and HLA-DQ8 typing to add strength to the diagnosis.

Histological analysis of duodenal biopsies

The histological features of the small intestinal enteropathy in CD have a variable severity, may be patchy, and in a small proportion of patients with CD appear only in the duodenal bulb. The alterations are not specific for CD and may be found in enteropathies other than CD. Biopsies should be taken preferably during upper endoscopy from the bulb (at least 1 biopsy) and from the second or third portion of duodenum (at least 4 biopsies). The pathology report should include a description of the orientation, the presence or not of normal villi or degree of atrophy and crypt elongation, the villus-crypt ratio, the number of intraepithelial lymphocytes (IELs), and grading according to the Marsh-Oberhuber classification.[31,32]

Diagnostic approach for a child or adolescent with symptoms or signs suggestive of CD

A test for CD-specific antibodies is the first tool that is used to identify individuals for further investigation to diagnose or to rule out CD. Patients who are consuming a gluten-containing diet should be tested for CD-specific antibodies. It is recommended that the initial test be IgA class anti-TG2 from a blood sample. Tests measuring antibodies against DGP may be used as additional tests in patients who are negative for other CD-specific antibodies but in whom clinical symptoms raise a strong suspicion of CD, especially if they are younger than 2 years.

Tests for the detection of IgG or IgA antibodies against native gliadin peptides (conventional gliadin antibody test) should not be used for CD diagnosis. Tests for the detection of antibodies of any type (IgG, IgA, secretory IgA) in faecal samples should not be used.

If IgA class CD antibodies are negative in an IgA-competent symptomatic patient, then it is unlikely that CD is causing the symptom at the given time point. Further testing for CD is not recommended unless special medical circumstances (e.g., younger than 2 years, restricted gluten consumption, severe symptoms, family predisposition or other predis-posing disease, immunosuppressive medication) are present.

In seronegative cases for anti-TG2, EMA, and anti-DGP but with severe symptoms and a strong clinical suspicion of CD, small intestinal biopsies and HLA-DQ testing are recommended. If histology shows lesions are compatible with CD but HLA-DQ2/HLA-DQ8 heterodimers are negative, then CD is not likely and an enteropathy caused by a diagnosis other than CD should be considered. In these patients, the diagnosis of CD can be made only after a positive challenge procedure with repeated biopsies.

When duodenal biopsies, taken during routine diagnostic workup for gastrointestinal symptoms, disclose a histological pattern indicative of CD (Marsh 1–3 lesions), antibody determinations (anti-TG2 and, in children younger than 2 years, anti-DGP) and HLA typing should be performed. In the absence of CD-specific antibodies and/or HLA-DQ2 or HLA-DQ8 heterodimers, other causes of enteropathy (e.g., food allergy, autoimmune enteropathy) should be considered.

In children and adolescents with signs or symptoms suggestive of CD and high anti-TG2 titers with levels >10 times ULN, the likelihood for villous atrophy (Marsh 3) is high. In this situation, the paediatric gastroenterologist may discuss with the parents and patient (as appropriate for age) the option of performing further laboratory testing (EMA, HLA) to make the diagnosis of CD without biopsies. Antibody positivity should be verified by EMA from a blood sample drawn at an occasion separate from the initial If EMA testing confirms specific CD antibody positivity in this second blood sample, then the diagnosis of CD can be made and the child can be started on a GFD. It is advisable to check for HLA types in patients who are diagnosed without having a small intestinal biopsy to reinforce the diagnosis of CD.

Diagnostic approach for an asymptomatic child or adolescent with CD-associated conditions

If it is available, HLA testing should be offered as the first-line test. The absence of DQ2 and DQ8 render CD highly unlikely and no further follow-up with serological tests is needed. If the patient is DQ8 and/or DQ2 positive or HLA testing is not done, then an anti-TG2 IgA test and total IgA determination should be performed, but preferably not before the child is 2 years old. If antibodies are negative, then repeated testing for CD-specific antibodies is recommended.

Individuals with an increased genetic risk for CD may have fluctuating (or transient) positive serum levels of CD-specific antibodies, particularly anti-TG2 and anti-DGP. Therefore, in this group of individuals (group 2) without clinical signs and symptoms, duodenal biopsies with the demonstration of an enteropathy should always be part of the CD diagnosis

To avoid unnecessary biopsies in individuals

Table 1: Sensitivity, Specificity, and Positive and Negative Predictive Values of Serologic Screening Tests Reported in the Literature for the Diagnosis of CD[33]

Test	Sensitivity	Specificity	PPV	NPD
AGA IgG	57–100	42–98	20–95	41–88
AGA IgA	53–100	65–100	28–100	65–100
AEA IgAa	75–98	96–100	98–100	80–95
Guinea pig tTGb	90.2	95		
Human tTGb	98.5	98		

PPV, positive predictive value; NPD, negative predictive value

with low CD-specific antibody levels (i.e., <3 times ULN), it is recommended that the more specific test for EMA be performed. If the EMA test is positive, then the child should be referred for duodenal biopsies. If the EMA test is negative, then repeated serological testing on a normal gluten-containing diet in 3 to 6 monthly intervals is recommended.

Treatment

The only treatment available for CD is gluten free diet(GFD) for life. It is recommended that treatment for CD be started only after the diagnosis has been confirmed by intestinal biopsy. Wheat, rye and barley are the predominant grains containing the peptides known to cause CD. Triticale (a combination of wheat and rye), kamut and spelt (sometimes called farro) are also known to be harmful. Other forms of wheat are semolina (durum wheat), farina, einkorn, bulgur and couscous. The harmful potential of rendered gluten-reduced wheat starch is controversial. Many coeliac societies in southern Europe exclude wheat starch; however, there is some evidence that it does not cause villous damage.[34] Malt is also harmful because it is a partial hydrolysate of barley prolamins. It may contain 100-200 mg of barley prolamins per 100 g of malt.[35] In general, any ingredient with malt in its name (barley malt, malt syrup, malt extract, malt flavorings) is made from barley.

Previously, oats were implicated in the development of the villous damage in CD. More recently this has been questioned as both in vivo and in vitro immunologic studies suggest oats are safe.[36] Despite the accumulating evidence that oats are safe for individuals with CD, there remains some concern about recommending consumption of this grain to CD patients. Contamination of oats with gluten during the harvesting and milling process is known to occur, so unless the purity of the oats can be guaranteed, their safety remains questionable.

There is evidence to demonstrate that even small amounts of gluten ingested on a regular basis can lead to mucosal changes on intestinal biopsy. However, the strict definition of a GFD remains contentious. Products containing less than 200 ppm (<200 mg/kg) were previously regarded as effectively gluten free. Currently, <20 ppm (<20 mg/kg) is being considered in the proposed Codex Alimentarius Guidelines to define "gluten free." The National Food Authority has recently redefined their term for "gluten free." By their definition "gluten free" now refers to no gluten, and <200 ppm is regarded as low gluten.

The American Dietetic Association (ADA) recently published guidelines for the dietary treatment of CD.[37] However, given the dynamics of this field, the diet requires ongoing collaboration between patients, health care professionals and dieticians, and the recommendations require periodic review and modification in the light of new scientific evidence. At this time, a GFD for life remains the only scientifically proven treatment available for symptomatic individuals with CD.

Most children with newly diagnosed CD will tolerate ingestion of lactose, particularly in moderate amounts; therefore dietary lactose restriction is not usually necessary. Young children with more severe disease may benefit from a lactose-free diet initially.[38]

How to monitor?

It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination and adherence to the GFD . The range of adherence to a strict GFD as reported by patients is 45% to 81%. These may be overestimates, as some patients reporting strict adherence have abnormal intestinal histopathology.[39] The range of reported complete lack of adherence is 6% to 37%. These may be underestimates, as patients are reluctant to admit they are not following physician advice. The rate of adherence in patients who were detected as part of a population screening may be comparable to that of patients who had symptoms that led

to detection of coeliac disease.[40]

There is little evidence on the most effective means of monitoring patients with CD. The Coeliac Disease Guideline Committee recommends measurement of TTG after 6 months of treatment with a GFD to demonstrate a decrease in antibody titer as an indirect indicator of dietary adherence and recovery. Measurement of TTG is also recommended in individuals with persistent or recurrent symptoms at any time after starting a GFD, as a rise in antibody levels suggests dietary non adherence. In the asymptomatic patient measurement of TTG at intervals of 1 year or longer may serve as a monitor of adherence to the GFD

Conclusion

Coeliac disease is a unique autoimmune disease in which some of the genes involved, the target auto antigen, and, most importantly, the environmental trigger, are all known. Therefore, coeliac disease represents a superb model to study the genetic, immunological, epidemiological, and clinical aspects of multifactorial diseases. Given the undisputable role of gluten in inducing the autoimmune intestinal insult typical of coeliac disease, the GFD is considered the only effective treatment for individuals with coeliac disease. However, the implementation of a GFD is challenging and most of the time suboptimal. A better understanding of the complexity of the genetic/environmental interaction responsible for coeliac disease development opens the way to explore alternative therapeutic strategies.

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