

Coeliac disease

Introduction

Samuel Gee was the first person in late nineteenth century who described coeliac disease (CD). Although in 2nd century AD similar malabsorptive condition was known to Aretaeus from Cappadocchia currently Turkey. It is also known as gluten-sensitive disease and nontropical sprue. The relation between food and symptoms became well known in Second World War when diarrhoea improved due to withdrawn of bread (shortage of food).

Coeliac disease is a chronic enteropathy caused by intolerance to gluten. The principle sources of dietary gluten are wheat, rye, and barley. Although gluten is also found in oats, the toxicity of oats in celiac disease is now in doubt. The true prevalence of this condition is much greater than previously recognized, with increasing numbers of silent cases being diagnosed. Population-based studies, using serologic screening, have indicated that the prevalence of coeliac disease in Caucasian populations is .5%-1%. The pattern of incidence is changing, with a greater proportion of cases diagnosed later in adulthood.

Pathomechanisms in celiac disease.

In spite of well known etiological factor (gluten), CD is considered as autoimmune disease which develops in genetically susceptible individuals. There is a strong genetic association (HLA-DQ2/DQ8), gluten as nutritional etiological factor, and the enzyme tissue transglutaminase as endomysial autoantigen. Deamidation of glutamine residues in gluten to glutamic acid leads to increase binding to HLA-DQ/DQ8 with these peptides and potentiate T cell stimulation. The increase binding of IgA autoantibodies to tTG can be found in patients who are exposed to gluten peptides. Gluten peptides are presented by the disease-associated HLA-DQ2/DQ8 molecules leading to stimulation of gluten-specific T cells. This immune response causes the mucosal transformation characteristic for coeliac disease. This process takes place in lamina propria of small bowel. Increased intestinal expression of tTG in patients with CD appears to play an important role in the pathogenesis of CD. Furthermore, tTG-catalyzed cross-linking and consequent haptenization of gluten with extracellular matrix proteins allows for storage and extended availability of gluten in the mucosa. There is increased risk of refractory celiac disease and enteropathy associated T cell lymphoma in homologous individuals for HLA-DQ2.

Classification

Some authorities have classified into three different categories'

Classical coeliac disease

For the diagnosis of classic disease, there are three cardinal feature; sign and symptoms of malabsorption, microscopic villous atrophy and improvement of above two upon withdrawn of gluten diet.

Latent coeliac disease

In this category either coeliac disease was diagnosed in the past but they are asymptomatic and gut mucosa is normal on gluten diet at the time of presentation or

jejunal mucosa was found to be normal previously on normal diet but developed CD later.

Potential coeliac disease

These are patients who carry few immunological features of CD and some but not all biopsy features correlate with CD. 20% to 50% of these patients can develop the disease later on.

CLINICAL MANIFESTATIONS

With the recent advancement in CD, clinical presentation has changed in the last twenty years; from asymptomatic to classical malabsorptive features. Classic symptoms of coeliac disease include diarrhoea, weight loss (or stunted growth in children) and fatigue, but while coeliac disease is a disease of the bowel, it may present with limited bowel symptoms. Some patients are diagnosed with symptoms related to the decreased absorption of nutrients or with symptoms which, although statistically linked, have no clear relationship with the malfunctioning bowel. Children between 9 and 24 months tend to present with bowel symptoms and growth problems shortly after first exposure to gluten-containing products. Older children may have more malabsorption-related problems and psychosocial problems, while adults generally have malabsorptive problems. Many adults with subtle disease only have fatigue or anemia.

Gastrointestinal symptoms

The diarrhoea characteristic of coeliac disease is pale, voluminous and malodorous. Abdominal pain and cramping, bloatedness and abdominal distention (thought to be due to fermentative production of bowel gas) and mouth ulcers may be present. A degree of lactose intolerance may develop in advanced disease. Constipation is rare, but may be a manifestation of coeliac disease.

Coeliac disease leads to an increased risk of both adenocarcinoma and lymphoma of the small bowel, which returns to baseline with diet. Longstanding disease may lead to other complications, such as *ulcerative jejunitis* and stricturing.

Malabsorption-related symptoms

The changes in the bowel make it less competent in absorbing nutrients, minerals and fat-soluble vitamins. The inability to absorb carbohydrates and fats may cause weight loss or failure to thrive/stunted growth in children and fatigue or lack of energy.

There are different causes of anaemia in CD: iron malabsorption may cause iron deficiency anaemia, and folic acid and vitamin B12 malabsorption may give rise to megaloblastic anaemia. Osteoporosis or osteopenia can be found due to deficiency of calcium/vit D and compensatory secondary hyperparathyroidism. Malabsorption of vitamin D may lead to vitamin D deficiency rickets or even hypocalcemic tetany.

A small proportion has abnormal coagulation due to deficiency of vitamin K, and are slightly at risk for abnormal bleeding.

Coeliac disease is also associated with bacterial overgrowth of the small intestine, which can worsen malabsorption, or cause malabsorption after treatment.

Miscellaneous symptoms

Coeliac disease has been linked with a number of conditions. In many cases it is unclear whether the gluten-induced bowel disease is a causative factor or whether these conditions share a common predisposition.

IgA deficiency is present in 2% of patients with coeliac disease, and in turn this condition features a tenfold increased risk of coeliac disease. Other features of this condition are an increased risk of infections and autoimmune disease.

Dermatitis herpetiformis; features small bowel changes identical to those in coeliac disease and occurs more often (2%) in patients with coeliac disease.

Neurological associations: epilepsy, ataxia, myelopathy and peripheral neuropathy have all been linked with coeliac disease, but the strength of these associations and the causality is still subject of debate.

Growth failure and/or pubertal delay in later childhood can occur even without obvious bowel symptoms or severe malnutrition.

Miscarriage and infertility has been associated with CD

Hyposplenism may be found in coeliacs but not proved it leads in increase incidence of infections.

Strong links have been found with some auto-immune disorders : diabetes mellitus type 1, autoimmune thyroiditis, primary biliary cirrhosis and microscopic colitis.

Diagnosis

Due to recent advances and more awareness among physicians and general publics, CD is diagnosed more often than in the past but still it is frequently misdiagnosed or overlooked as it can exhibit multiple patterns and often the patient or medical staff may not link seemingly unconnected conditions. It is most frequently misdiagnosed when the sufferer complains of diarrhoea, persistent indigestion, an itchy rash (dermatitis herpetiformis), or irritable bowel syndrome.

There are several tests that can be used to assist in diagnosis. No single test can confidently diagnose CD in every individual. The level of symptoms may determine the order of the tests, but *all* tests must be done while the person is on a gluten containing diet although some has already started gluten free diet. Antibodies are reduced and intestinal damage begins to heal immediately upon removing all gluten from the diet, so the risk of misdiagnosis is increased if the person is not eating gluten. For those who have already commenced themselves on a gluten-free diet, professional guidelines recommend a re-challenge of 2-6 weeks with 10 g of gluten (four slices of bread) before repeating the investigations. Those who experience severe symptoms earlier can be regarded as sufficiently challenged and can be tested earlier.

WHO SHOULD BE TESTED

Followings should be consider for investigation of celiac disease

1. Those with malabsorption symptoms.
2. Unexplained symptoms and sign like iron deficiency anaemia, short stature, delayed puberty, raised LFTs, and recurrent fetal loss.
3. All those at high risk like with autoimmune endrinopathies. First and second degree relatives

Blood tests

Serology by blood test has high sensitivity of 98% and high specificity of >95%.

Because of the major implications of a diagnosis of coeliac disease, many recommend that a positive blood test is still followed by an endoscopy. A negative test may still

prompt a biopsy if the suspicion is very high; this would pick up the remaining 2% undiagnosed cases. Due to the few limitations of blood tests, endoscopy and biopsy is still remains the gold standard in the diagnosis of coeliac disease.

Due to its high sensitivity, serology has been proposed as a screening measure, Serology may also be used to monitor adherence to diet.

Four serological blood tests exist for coeliac disease:

IgA and IgG anti-tissue transglutaminase antibody (anti-tTG). This test is sometimes used alone. If this test is positive it is highly likely that the patient has coeliac disease. It is not reliable in children before the age of 2.

IgA and IgG anti-gliadin antibodies (AGA), IgG and IgA. These tests are often useful when testing young symptomatic children, but they are found in fewer coeliacs than anti-tTG, and their presence does not automatically indicate coeliac disease because they are found in some other disorders. Both IgA and IgG anti-gliadin antibodies (AGA) may be detected in sera of patients with coeliac disease. IgA anti-gliadin antibodies are less sensitive but are more specific.

IgA anti-endomysial antibodies (EMA). This test is being replaced by the anti-tTG test because both tests measure the autoantibodies that cause the tissue damage associated with coeliac disease. This test as tTG test is also less reliable in children before the age of 2.

The following is data regarding the sensitivity and specificity of the assay as performed by the testing laboratory before determining the clinical significance of a particular test result.

IgA endomysial antibodies — sensitivity 85% to 98 %; specificity 97% to 100%

IgA tissue transglutaminase antibodies — sensitivity 90% to 98%; specificity 95 to 97 percent

IgA antigliadin antibodies — sensitivity 80% to 90%; specificity 85% to 95%

IgG antigliadin antibodies — sensitivity 75% to 85%; specificity 75% to 90%

For those based on IgA, a total IgA level is checked in parallel, as patients with IgA deficiency may have a normal result while still having coeliac disease ("false negative"). In those patients, IgG antibodies may be diagnostic.

Endoscopy

An upper endoscopy with biopsy of the second and third part of duodenum or jejunum is performed. Multiple biopsies should be obtained although experts recommend at least four biopsies. Not all areas may be equally affected, which is why even upper endoscopy carries a small risk of false negative results. Most patients with coeliac disease have a small bowel that appears normal on endoscopy; however, five endoscopic findings have been associated with a high specificity for coeliac disease when all are found: scalloping of the small bowel folds, paucity in the folds, a mosaic pattern to the mucosa (described as a *cracked-mud* appearance), prominence of the submucosal blood vessels and a nodular pattern to the mucosa.

Pathology

The classic pathology changes of coeliac disease in the small bowel are categorized by the "Marsh classification":

Marsh stage 0: normal mucosa

Marsh stage 1: increased number of intra-epithelial lymphocytes, usually exceeding 20 per 100 enterocytes

Marsh stage 2: proliferation of the crypts of Lieberkuhn

Marsh stage 3: partial or complete villous atrophy

Marsh stage 4: hypoplasia of the small bowel architecture

The changes classically improve or reverse after gluten is removed from the diet; so many official guidelines recommend a repeat biopsy several months after commencement of gluten exclusion.

Other diagnostic tests

These tests help to find out manifestations of CD on other systems. These blood tests are a full blood count, electrolytes, calcium, renal function and liver enzymes.

Coagulation testing may be useful to identify deficiency of vitamin K. These tests should be repeated on follow-up, as well as anti-tTG titres.

Some professional guidelines recommend screening of all patients for osteoporosis by DXA/DEXA scanning.

Screening and case finding

There is ongoing debate as to the benefits of screening. Some studies suggest that early detection would decrease the risk of osteoporosis and anaemia. In contrast, a cohort studied in Cambridge suggested that people with undetected coeliac disease had a beneficial risk profile for cardiovascular disease (less overweight, lower cholesterol levels).

Clinical scenarios in which screening may be justified include type 1 diabetes, unexplained iron-deficiency anemia, Down's syndrome, Turner's syndrome, irritable bowel syndrome, lupus, and autoimmune thyroid disease.

Management of celiac disease

There are six key elements in the management of patients with celiac disease, which can be summarized with the following acronym.

- 1; Consultation with a skilled dietician
- 2; Education about the disease
- 3; Lifelong adherence to a gluten-free diet
- 4; Identification and treatment of nutritional deficiencies
- 5; Access to an advocacy group
- 6; Continuous long-term follow-up by a multidisciplinary team

The only treatment is a life-long gluten-free diet. There is no drug which will prevent damage, nor prevent the body from attacking the gut when gluten is present. The disease is controlled by strict adherence to a gluten-free diet, which allows the intestines to heal and resolves all symptoms in the vast majority of cases and, depending on how soon the diet is begun, can also eliminate the heightened risk of osteoporosis and intestinal cancer. Dietician is very important to ensure the patient is aware which foods contain gluten, which foods are safe, and how to have a balanced diet despite the limitations.

Health-related quality of life (HRQOL) is decreased in people with coeliac disease even on very strict gluten free diet. Some still suffer from persisting digestive symptoms or dermatitis herpetiformis, mouth ulcers, osteoporosis and fractures and other complications. Symptoms suggestive of irritable bowel syndrome may be present, and there is an increased rate of anxiety, fatigue, dyspeptic and musculoskeletal pain.

Refractory disease

A very small number of patients suffer from *refractory* disease i.e. they do not improve on a gluten-free diet. This can be due to two reasons either disease present for a long time and now mucosa is unable to heal or adherence to diet is not maintained. If alternative causes have been eliminated, steroids or immunomodulators (such as azathioprine) may be considered in this scenario.

Experimental treatments

A number of approaches are being evaluated that would reduce the need of dieting. All are still under development, and are not expected to be available to the general public for a while:

Genetically engineered wheat species, or wheat species that have been selectively bred to be minimally immunogenic. This, however, could interfere with the effects that gliadin has on the quality of dough.

A combination of enzymes (prolyl endopeptidase and a barley glutamine-specific cysteine endopeptidase (EP-B2)) that degrade the putative 33-mer peptide in the duodenum. This combination would enable coeliac disease patients to consume gluten-containing products.

Inhibition of zonulin, a substance linked to increased permeability of the bowel wall and hence increased presentation of gliadin to the immune system.

Other treatments aimed at other well-understood steps in the pathogenesis of coeliac disease, such as the action of HLA-DQ2 or tissue transglutaminase and the MICA/NKG2D interaction that may be involved in the killing of enterocytes.

Follow-up

It is generally recommended that yearly weight, full blood count, ferritin, folate, calcium, and alkaline phosphatase should be checked. Follow-up is life-long, and this permits reinforcement of the continuing need for strict adherence to the gluten-free diet. Follow up with dietician is single most step in the long term management of celiac disease.

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