Coeliac disease

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Abstract

Coeliac disease is an autoimmune enteropathy triggered by the ingestion of gluten-containing cereals, such as wheat, rye and barley. It is estimated to occur in one per cent of people of European ancestry, and in 0.3% of black Africans. Coeliac disease has a strong genetic component as nearly all patients with the disease share the same genetic predisposition in the form of the presence of either the human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 alleles. The spectrum of symptoms ranges from asymptomatic to chronic diarrhoea, flatulence, abdominal pain and weight loss. Although serological testing for tissue transglutaminase antibodies is both sensitive and specific for the disease, and reflects disease activity, small bowel biopsy is considered to be the standard when diagnosing the disease. The therapy for coeliac disease is a gluten-free diet, which may be difficult and expensive to follow. Nonadherence to a gluten-free diet is the main cause of persistent or recurrent symptoms. Coeliac disease increases the risk of malignancies, such as small bowel adenocarcinoma and enteropathy-associated T-cell lymphoma; pathologies which should be excluded in patients who are compliant with the diet but who are either persistently symptomatic or have a reoccurrence of symptoms. Because coeliac disease is an important cause of common gastrointestinal symptoms and may have significant long-term complications if left untreated, it is paramount that the family practitioner should consider it in the differential diagnosis of patients who present with suspected symptoms. The perception of coeliac disease has changed in recent years from an uncommon enteropathy to a common multisystem disease with a strong genetic predisposition.

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Introduction

Coeliac disease, often called coeliac sprue, is an autoimmune disorder of the small intestine which occurs in genetically predisposed people. Coeliac disease is not an allergy or intolerance to gluten. It can present at all ages, from infancy to middle age. Symptoms include chronic diarrhoea, failure to thrive in children and fatigue. Patients may also be asymptomatic. Treatment involves the removal of gluten proteins from the diet which improves and often eliminates small intestine pathology.[1]

Epidemiology

Coeliac disease occurs in approximately one per cent of the population in Western countries. The shared genetic predisposition is reflected in the high rates of coeliac disease in regions that share a common European ancestry, such as North America, South America and Australia. Although very little information in available on the prevalence of coeliac disease in Africa, modelled estimates place the population prevalence at 0.33%.[2]

Pathophysiology

Two factors are involved in the development of coeliac disease, namely the consumption of gluten proteins and a genetic predisposition.[3]

Gluten, the protein component of wheat, barley and rye, is found in many commonly consumed food items. Gliadin is the alcohol-soluble part of gluten which contains the bulk of the toxic components.[4] Gliadin is relatively resistant to degradation by gastric, pancreatic and intestinal brush border membrane digestive enzymes, and so remains in the intestinal lumen after gluten ingestion. These peptide derivatives are highly immunogenic to patients with coeliac disease. They pass through the epithelial barrier of the intestine where they interact with the antigen-presenting cells in the lamina propria.[1] Tissue transglutaminase is an intestinal enzyme which deaminates gliadin, and so increases its immunogenicity. Gliadin particles promote an inflammatory response in the upper intestine, characterised by the infiltration of the lamina propria and intestinal epithelial layer with chronic inflammatory cells in patients with coeliac disease.[5] The inflammation that results induces

changes in the intestine that lead to crypt hyperplasia and villous atrophy.

The genetic influence in the development of coeliac disease is indicated not only because it occurs in families, but also because the the disease does not develop unless a person expresses human leukocyte antigen (HLA)-DQ2 or HLA-DQ8.[6] However, many people who carry these alleles do not develop the disease. Their presence is necessary, but not sufficient, to influence the development of the disease.

Epidemiological studies have suggested that environmental factors may also play an important contributory role to the development of coeliac disease. Breastfeeding may have a protective effect,[7] while the introduction of gluten in the diet before the age of four months is associated with a higher risk of developing the disease.[8]

Clinical diagnosis

The classic symptom of coeliac disease in adults is diarrhoea, which may be accompanied by abdominal pain or discomfort. Other symptoms include bloating, constipation, weight loss and fatigue. As a result of these sometimes non-specific symptoms, up to 36% of patients are diagnosed with irritable bowel syndrome prior to the diagnosis of coeliac disease.[9] Strikingly, symptoms have often been present for up to 11 years before the diagnosis is made. The disease often presents with diarrhoea, abdominal distension and failure to thrive in children. Other symptoms which are common in the younger age group include vomiting, anorexia and constipation. Older children and adolescents may present with short stature, neurological symptoms and anaemia.[10] Although the majority (45-85%)[9,11] of patients display gastrointestinal symptoms, coelic disease can also present with non-gastrointestinal complications, and may be diagnosed after investigations for conditions such as iron deficiency anaemia and decreased bone density (osteopenia and osteoporosis.) It may also be diagnosed after an endoscopic evaluation for symptoms not typically associated with the disease, such as dyspepsia, upper abdominal pain and gastroesophageal reflux.[9]

Dermatitis herpitiformis, a pathognomonic rash which occurs in 10-20% of patients with coeliac disease is a well recognised extraintestinal complication.[12] It is characterised by intensely pruritic, chronic papulovesicular eruptions, usually distributed symmetrically on extensor surfaces and areas, such as the buttocks, back of neck, scalp, hairline, groin or face.

Another rare atypical presentation of coeliac disease is neurological disease which can manifest as a symmetrical distal sensory neuropathy, cerebellar ataxia or migraine.[13] Abnormalities in blood chemistry, such as elevated serum amylase, hypoalbuminaemia and an elevated sedimentation rate above 100, have also been reported.[9]

Diagnostic tests

Although no single test has universally been accepted as a diagnostic standard for coeliac disease, the diagnosis is easily established in most patients. It remains difficult to make the diagnosis in only 10% or less of cases because of lack of concordance between clinical, serological and histological findings.[4] Serological testing and histology from small bowel biopsy samples are highly sensitive and specific for diagnosing coeliac disease, especially in symptomatic patients and in those at increased risk, owing to a positive family history. Patients who should be investigated for coeliac disease include those with persistent gastrointestinal symptoms such as diarrhoea, malabsorption, weight loss, abdominal pain, flatulence and bloating. Because of the association of coeliac disease with other conditions, symptomatic patients with autoimmune hepatitis, Down's syndrome, the premature onset of osteoporosis, unexplained elevations of liver transaminase levels and unexplained iron deficiency anemia should also be tested.[14]

Serology

Antigliadin antibodies were one of the first serological markers for coeliac disease, and in the past were used to test for the disease. However, testing for antigliadin antibodies is no longer recommended because of the low sensitivity and specificity for coeliac disease.[15] The most sensitive antibody tests for the diagnosis of coeliac disease are of the immunoglobulin (IgA) class, namely antiendomysial antibodies and antibodies directed against tissue transglutaminase (tTG), the enzyme that is responsible for the deamidation of gliadin in the lamina propria. Most studies have found the sensitivity and specificity of testing for IgA endomysial and tTG antibodies to be greater than 95%.[16] However, the sensitivity of the tests depends on the degree of mucosal involvement, to which the titres of the endomysial antibodies and anti-tTG correlate with the degree of mucosal damage.[17] Because tTG is the autoantigen that is recognised by the endomysial antibody, there is rarely a need to perform both tests. It is recommended that the tTG antibody test should be the single serological test for coeliac disease screening in the primary care setting.

However, approximately three per cent of patients in some studies have an IgA deficiency, which may cause a false-negative serological test result.[18] Total IgA levels should only be measured if an IgA deficiency is suspected, or if serum tTG is negative, but coeliac disease still suspected.

Additional diagnostic testing can be performed by testing for the presence of the HLA-DQ2 or HLA-DQ8 alleles in selected patients. The HLA-DQ2 allele is present in 90-95% of patients with coeliac disease, while the HLA-DQ8 allele

is present in the remainder. As these alleles occur in 30-40% of the general population, their absence has a high negative predictive value for coeliac disease.[19] Testing for these alleles can be particularly useful when needing to exclude coeliac disease in patients who are already on a gluten-free diet and in whom serological testing for tTG can be expected to be negative.

Because serological markers may have false-positive or false-negative results, they cannot be relied upon solely for the diagnosis of coeliac disease. A positive test for serological markers should be an indication of further evaluation with a small bowel biopsy in most patients. Conversely, negative serological markers in low-risk patients without an IgA deficiency have a high negative predictive value, and generally a small bowel biopsy is not needed. However, negative markers should never prevent a small bowel biopsy if the index of suspicion for coeliac disease is high.[3] Coeliac disease may be diagnosed on the basis of serology and symptoms in a few cases only. Patients with highly suggestive symptoms and signs and high anti-tTG titres (more than 10 times the upper limit of normal), can be diagnosed with coeliac disease if the antiendomesial antibodies are also positive on a separate testing occasion. A positive anti-tTG result should be followed-up with confirmatory histology in most other cases. Small bowel biospies and HLA-DQ testing is recommended for patients who are seronegative for anti-tTG and antiendmomesial antibodies, but with severe symptoms and a strong clinical suspicion for coeliac disease. If testing for HLA-DQ2 and HLA-DQ8 alleles is negative despite positive histological lesions, coeliac disease is unlikely to be the cause of the enteropathy. An alternative diagnosis should be sought.[20]

Small bowel biopsy

A small bowel biopsy should always be performed when there is a high clinical suspicion of coeliac disease, even when serological testing is negative. A biopsy of the small intestine remains the standard for diagnosing the disease. Histological confirmation should be obtained for most patients with positive serological tests.[21] Because of the patchy nature of the disease, and the difficulty in orienting the small pieces of tissue taken during the biopsy for villous morphology assessment, the endoscopist should obtain at least four duodenal biopsy specimens to increase the sensitivity of the test.[4] The histological findings in coeliac disease can range from near normal to the typical findings of total villous atrophy and lymphocytic infiltration. It should be noted that poorly orientated tissue samples may lead to an over-interpretation of villous atrophy.[22] Also, although the histological findings in coeliac disease are characteristic, they are not specific, as many other diseases such as giardiasis, tropical sprue, bacterial overgrowth and Crohn's disease can cause villous atrophy.

Treatment

Treatment of coeliac disease involves the lifelong elimination of products containing gluten protein. This entails the avoidance of wheat, rye and barley products, specifically. It is essential that a diagnosis of coeliac disease is confirmed before patients are started on diet therapy because of the cost and social impact of a gluten-free diet. While oats are normally well tolerated by patients and are used as a substitute to improve nutritional content and fibre in the diet, most commercially available oats may be contaminated with other grains. Only a purified source should be used. Grains which may serve as substitutes to provide flour for cooking and baking include buckwheat, polenta, millet and sorghum. Any rice, such as white, brown, basmati or jasmine, is safe to use. Because many substitute flours are not fortified with B vitamins, vitamin supplementation is advised. Once gluten has been eliminated from the diet, clinical improvement occurs within days or weeks, while a histological recovery may take months. However, despite providing significant symptomatic relief, adhering to a gluten-free diet can be very difficult for patients and may cause considerable psychological, emotional and financial stress.[23,24] Whereas governments in some developed countries subsidise certain gluten-free products, these products are usually expensive and are hard to find in developing countries, such as South Africa. A change to a completely gluten-free diet is difficult to maintain. Consultation with an experienced dietitian is invaluable. The dietitian plays a vital role in helping the patient to successfully adapt to the necessary behavioural and dietary changes, and may assist with much of the required follow-up.[23] National coeliac disease support organisations can provide patients with valuable resources in respect of information and support.

Complications

Patients with coeliac disease have increased mortality, mostly because of the added risk of developing certain associated malignancies.[25] Reported cancers include non-Hodgkin's lymphomas (enteropathy-associated T-cell lymphoma), and also oropharyngeal and oesophageal adenocarcinomas, as well as other malignancies of the small and large intestine. Malignancy should always be ruled out as an underlying cause in patients with refractory disease or those who develop new symptoms during treatment (approximately five per cent of patients).

Follow-up

Patients with coeliac disease should receive long-term follow-up because of the associated complications and chronic nature of the disease. Serological markers can be used to assess disease activity and to monitor compliance with a gluten-free diet. Typically, antibody levels will return

to normal within 3-12 months of starting a gluten-free diet.[26] Follow-up visits should be viewed as opportunities to carry out nutritional education, to screen for the need for nutritional supplementation and to assess clinical response to treatment. If symptoms do not improve despite compliance with a gluten-free diet, alternative diagnoses and further diagnostic testing should be considered. However, noncompliance remains the most common cause of refractory coeliac disease. Studies have shown that less than half of patients still strictly adhere to the diet a year after diagnosis.[27]

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