The changing face of coeliac disease

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Historical perspective

Coeliac disease is a condition where there is abnormal proximal small bowel mucosa that improves on withdrawal of wheat. The association with wheat was only recognised after the end of WWII, when children who had been deprived of wheat during the war years had this food source made available again.

Previously the diagnosis was only made in patients presenting with significant weight loss and multiple malabsorptive problems. The diagnosis was confirmed by a jejunal biopsy obtained using a Crosby capsule. This was a difficult, cumbersome and often frustrating test. The simple realisation that a duodenal biopsy was as accurate as a jejunal biopsy led to more frequent diagnosis of the condition. There is now widespread use of a duodenal biopsy at the time of gastroscopy if there is any hint of coeliac disease.

Gliadin antibody tests have been available for many years but problems with false positives and negative tests significantly restricted the usefulness of the test. In the last five years accurate antibody tests (endomysial antibody [EMA] and transglutaminase antibody [tTGA]) have become available for routine use. These tests have proven to be very useful in general practice for detecting new cases.

How common is coeliac disease?

Based on clinical detection the frequency of diagnosis had been around 1:2000, however it is now clear that the disease is actually much more common. A population study of 1064 randomly selected adults in Christchurch showed that 1.2% (12) had positive endomysial antibodies. Only two of these subjects were already known to have coeliac disease. All 12 subjects subsequently had villous atrophy confirmed by duodenal biopsy. The gastrointestinal symptoms of the new cases were minimal but four subjects were iron deficient, four were folate deficient and five had sustained bone fractures. In a UK health survey of 7550 participants, aged 45–76 years, 1.2% (87) were found to have positive endomysial antibodies. There was no difference between subjects who were EMA-positive or EMA-negative for a wide range of parameters that were used to measure health and general well-being. The only significant difference was a higher proportion of EMA-positive subjects with anaemia (16% EMA-positive compared with 4% for EMA-negative individuals). There was a non-significant trend towards lower bone density in EMA-positive subjects. This population data is important when considering the increasing rate of new diagnoses for coeliac disease because of the more frequent use of the antibody tests for mild symptoms. It is perhaps helpful to use an 'iceberg' analogy for coeliac disease with overt severe disease at the top and subclinical or silent disease forming the majority below sea level. As we begin to uncover the larger group beneath the surface the rules for management and general advice may need to be modified. The question to ask is how important is it that we identify all of the 1:100 adults with coeliac disease. Will they be grateful for the diagnosis and for the advice to maintain a life-long gluten-free diet?

What is the cause of coeliac disease?

The strong genetic component to the disease (and the close link to HLA markers) has been known for many years. About 8% of first degree relatives will have positive antibodies and abnormal duodenal biopsies. The HLA association is with HLA DQ2 (90%) or DQ8 (10%). Antigen presenting cells (APC) with these HLA receptors become activated by gliadin protein. The resulting tissue damage leads to the release of tissue transglutaminase. This extracellular matrix enzyme alters an important section of the gliadin protein (a reaction called deamination). This change augments

the presentation of a critical epitope (short amino acid sequence) by the APC to gliadin-reactive lymphocytes. Activated lymphocytes are the cause of tissue damage to the duodenum and jejunum (not the antibodies).

Presentation of coeliac disease in adults

The disease often presents in adults – presumably it has been silent during childhood (i.e. present but producing no symptoms). The most common gastrointestinal symptoms are abdominal bloating, abdominal discomfort and diarrhoea (with or without a history of aggravation by wheat/breads). The finding of iron deficiency (particularly in a younger person with no symptoms and no other obvious cause) is supportive. The additional finding of folate deficiency makes the diagnosis highly likely. Up to 5% of patients referred for upper GI endoscopy because of iron deficiency will have coeliac disease. Low calcium and vitamin D absorption may lead to osteopenia and osteoporosis. Some of the problems with calcium relate to reduced milk intake because of a secondary lactose intolerance. The diminished calcium absorption does improve after a gluten-free diet. Osteopenia is found in one-third of patients at diagnosis and does correct in the majority of patients after a few years. The risk of fractures with coeliac disease has probably been over-estimated in some studies. A large population-based study of known patients with coeliac disease showed a 1.3 times risk of fracture (this was only just significant). The absolute risk was an increase in fractures of only 3.2 fractures per 1000 person years.

Population screening using antibody tests has been proposed but has many counter arguments. An effective approach is 'case-finding' – that is the liberal use of the antibody test for a list of clinical criteria. In a UK study, nine general practices in Oxfordshire serving a population of 70 000, were encouraged to request EMA tests for a list of criteria defined as being suggestive of coeliac disease. 1000 blood samples were requested; 729 of those included were female with an average age of 46 years. Only 5% of samples were taken from patients aged less than 10 years. Thirty patients (3%) had positive EMA results (three times that expected by population screening). The criterion that yielded the most positive EMA results was anaemia (15/126 – 12%). By far the biggest clinical indication was fatigue – a finding of no surprise for primary care physicians. Only six EMA-positives were found out of 329 patients with a primary problem of tiredness. None of the 132 patients with symptoms suggestive of irritable bowel syndrome tested positive. This finding is in contrast to another UK study that showed that 5% of patients attending a gastroenterology outpatients clinic with IBS symptoms had coeliac disease. The true figure is likely to be around 2% (perhaps twice that expected of the general population).

Screening of infertile couples has been suggested but the data is inconclusive. EMA antibody testing in early onset or severe osteoporosis is appropriate. Testing is also appropriate for Type 1 diabetes (4% EMA-positive) but there is no association with Type 2 diabetes. There have been some exaggerated claims of other associations – for example with ADD, schizophrenia and autism. The association with some other neurological disorders (epilepsy, ataxia, peripheral neuropathy) is also debated. Screening of relatives is an effective means of case-finding (8% will be positive; the proportion will be higher if there are suggestive symptoms). Currently, up to 25% of cases are identified by this method. The proportion of newly identified patients with gastrointestinal symptoms is falling with the more widespread use of the antibody tests (now less than 50%). A general practice with 2000 patients should have 20 patients with coeliac disease (according to the Christchurch population survey). Using the clinical criteria of diarrhoea and weight loss only two to three patients will be identified. Testing patients who present with anaemia (or with a past history of unexplained anaemia) will identify another five patients. Testing of first degree relatives will identify another two to three new cases.

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Diagnosis and follow-up

The initial diagnostic test will usually be an endomysial antibody and/or tissue transglutaminase antibody depending on availability in the local laboratory. Some patients are diagnosed by duodenal biopsy directly because of a high index of suspicion at the time of the procedure (either because of the history or by the appearances of the duodenal mucosa – see Figures 1 and 2). The endomysial antibody (EMA) was the first accurate antibody test to be developed. It takes more laboratory time as it is based on immunofluorescence findings when EMA binds to the endomysium. The sensitivity of the test is reported to be very high but may be less with milder disease (mild villous atrophy only). EMA is absent with IgA deficiency (found in 2% of coeliacs). Most laboratories will routinely check the IgA level and perform an IgG endomysial Ab test if the IgA concentration is low. The transglutaminase antibody (tTGA) is also an IgA test. This is a simple ELISA test that is cheap, automated and quantitative. The two tests give highly similar but not identical results. Currently most laboratories are able to offer both tests (probably this is preferable as up to 20% will have only one test positive).

An individual with a positive tTG should have a duodenal biopsy to confirm villous atrophy. Although false positives are uncommon the diagnosis needs to be confirmed beyond doubt. Duodenal biopsy is a straightforward procedure performed at the time of a gastroscopy. It is not adequate to use the symptomatic response to a gluten-free diet as evidence of coeliac disease. Patients with irritable bowel syndrome often improve with exclusion of bread

from the diet (perhaps related to a decrease in wind from fermentation of wheat). There is no need for another biopsy after gluten re-exposure if there is a good clinical response to the initial gluten withdrawal. If a repeat biopsy is performed it is difficult to know how to respond to the histology report. This is because studies of coeliac patients established on a gluten-free diet (who have no symptoms) actually show that the majority of patients have persisting histological changes (only 20% normal, 70% partial villous atrophy and 10% actually have persisting total villous atrophy).

In adults, villous atrophy is almost always due to coeliac disease. The rare possibility of common variable immunodeficiency could be considered if there is a history of recurrent sinus or chest infections. The possibility of tropical sprue should be considered if the patient was a resident in a tropical country (particularly in Southeast Asia) for several years. A trial of tetracycline for one month is given with follow-up duodenal biopsies.

The tTGA titre, or the presence of the endomysial antibody, can be used to monitor progress. It is to some extent a surrogate marker of villous atrophy, although villous atrophy may be present with a negative antibody test. In one study 87% of patients established on a gluten-free diet were endomysial negative by 12 months. Patients who remain symptomatic after a gluten-free diet for six months should be referred to a gastroenterologist. The most likely reason is inadvertent gluten exposure but there are several other diagnostic possibilities to consider.

Treatment of coeliac disease

Basically the only treatment is a gluten-free diet. Most patients have an improvement in symptoms over a few weeks but continued improvement can occur over the first six to12 months. Adherence to a gluten-free diet is enhanced when there is a clear correlation between gluten exposure and abdominal symptoms. Adherence to the diet has become easier because of a wide range of commercially available gluten-free foods and the mandatory labeling of foods for gluten content. A list of manufactured foods that are gluten-free is maintained on the website www.mfd.org.nz. Helpful advice is available through dietitians and through the Coeliac Society of New Zealand. There is a lot of good information on websites. See Box 1 for some examples. Dietary supplements are not usually required except in the first six to12 months if significant nutritional

Figure 1. Left: normal villous structure. Right: Villous atrophy with hypertrophy of crypts

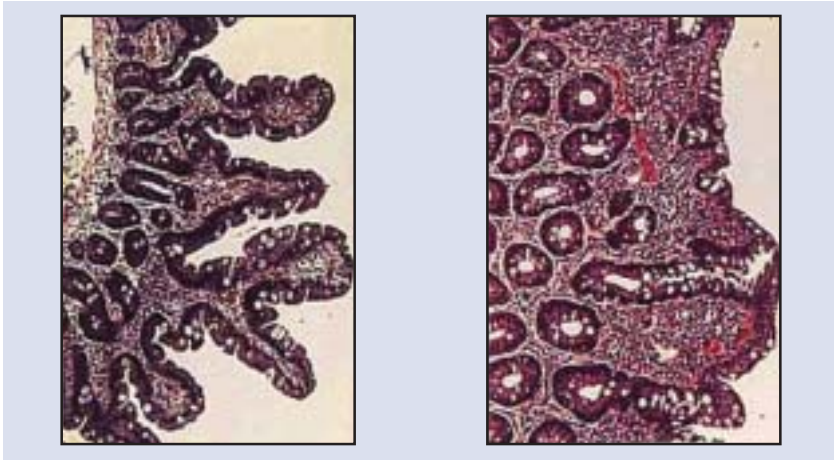
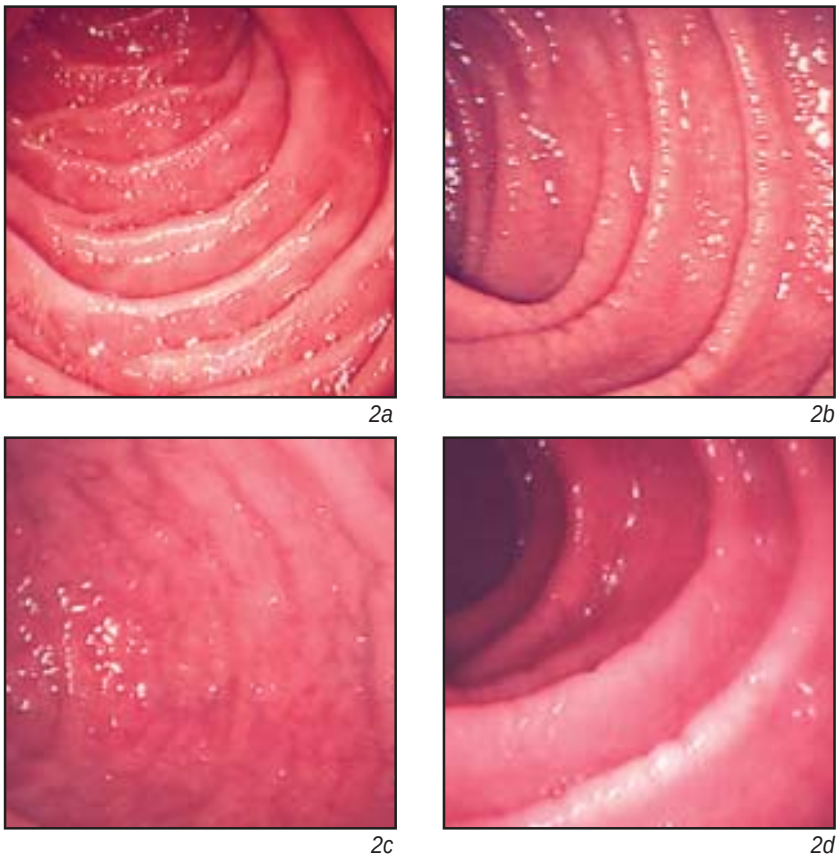


Figure 2a: Normal duodenum showing normal mucosal appearance and normal duodenal folds. Figure 2b–d: These photos illustrate the range of abnormal endoscopic findings with coeliac disease. These include a reduction in number of duodenal folds, scalloping of folds, mucosal fissures, mosaic or nodular appearance. These changes can be subtle and may not recognised if there is no clinical suspicion of the disease.



deficiencies are identified. Prompt replacement of vitamin D (if low serum vitamin D) is appropriate

What are the advantages of a gluten-free diet when there are no or few abdominal symptoms?

This is an increasingly common issue with the more liberal use of antibody tests in primary care. There are three main arguments for a gluten-free diet in this situation. Firstly, the patient may be surprised by how much better they feel – that is, they have been accepting a decreased level of well-being and energy levels as part of normality. It is also common to have accepted abdominal bloating and flatulence as normal. Secondly, osteoporosis is a definite risk with untreated coeliac disease although the absolute fracture risk may not be that large. Bone density does improve significantly on a gluten-free diet. Any nutritional deficiency (iron, folate, B12, calcium, vitamin D) is highly likely to correct on a gluten-free diet without the need for supplements. Thirdly, there is an increased risk of gastro-intestinal cancer with untreated coeliac disease. This includes small bowel lymphoma, a rare cancer, but also includes a slightly increased risk for other more common gastrointestinal malignancies. The risk is most apparent with more clinically overt disease (i.e. significant malabsorption and gastrointestinal symptoms). This risk is virtually eliminated with a gluten-free diet (even though it is known that significant histological changes often persist on a gluten-free diet). Some of the observed increase in mortality in patients with coeliac disease relates to an increased risk of other auto-immune disorders. This risk is not diminished by a gluten-free diet.

What is a gluten-free diet?

It is universally agreed that subjects with coeliac disease have an intolerance to proteins fractions in wheat, rye and barley. The close association of barley and rye to wheat is clear from plant taxonomy. Recent studies of the amino acid sequences of proteins from each of these grains show important areas of homology for the critical epitope (short amino acid sequence) involved in initiating the immune process. It is clear that corn and rice are harmless. There remains a debate about oats. There is much scientific data that is reassuring but there may be problems accessing a pure source of oatmeal. Several other grains such as quinoa, millet, sorghum, buckwheat, amaranth are now more widely available and form the basis for many gluten-free flours. There is not complete data on all these sources but plant taxonomy would suggest that they are safe. There is debate with regard to some processed food items, for example, wheat starch, a common component of processed food, distilled alcohol (made from wheat, barley or rye), distilled white vinegar, malt and malt extract. The policy of 'if in doubt leave it out' is always going to be safe. However it is possible that unnecessary dietary restrictions are being imposed.

The amount of gluten that can be safely taken in coeliac disease is not known. Many patients have ingested small amounts of gluten over the years with no apparent problems. The reaction of a patient on a strict gluten-free diet to inadvertent small amounts of gluten is highly variable. It is important that patients realise that there is some debate and variation in advice (varying from country to country), particularly if the internet is used as a source of information (very common in my experience). The labeling of foods has changed. Previously food containing <0.02% gluten was labeled as gluten-free - now to gain this label there has to be zero gluten. This change may be an advance for patients who develop gastro-intestinal symptoms with inadvertent exposure to very small amounts of gluten, but may impose more dietary limitations on the increasing numbers of patients with no gastrointestinal symptoms prior to starting the gluten-free diet.

Attending doctors, dietitians and support groups need to acknowledge that there are several areas of controversy. Our role is to provide information in an unbiased manner and to support the patient while they are making these important and sometimes difficult dietary and lifestyle adjustments.

Useful websites

www.mfd.org.nz
Very useful list of manufactured foods available in New Zealand that are gluten-free

Gastroenterology Society of Australia / Digestive Diseases Foundation
www.gesa.org.au/consumer/publications/index

Coeliac Society of Australia
www.coeliac.org.au

Suggested reading

1. Seminar: coeliac disease. Lancet 2003; 362:383-91. (best overall review)
2. West J, Logan RFA, Hill PG, et al. Seroprevalence, correlates, and characteristics of undetected celiac disease in England. Gut 2003; 52:960-965 (information of health of screen detected cases with coeliac disease)
3. Hin H, Bird G, Fisher P, et al. Coeliac disease in primary care: a case-finding study. BMJ 1999; 318:164-7. (Oxford study of nine general practices)
4. Cook HB, Burt MJ, Collett JA, Whitehead MR, Frampton CM, Chapman BA. Adult coeliac disease: prevalence and clinical significance. J Gastroenterol Hepatol 2000; 15:1032-6. (Christchurch population screening study)
5. Peters U, Askling J, Gridley G, Ekbom A, Linet M. Causes of death in patients With coeliac disease in a population-based Swedish cohort. Archives Int Med; 2003; 163:1566 (this study show increased overall mortality from a combination of malignancy and auto-immune disorders).