DIAGNOSTIC TESTS

# Gluten enteropathy

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## SYNOPSIS

**The presentation of coeliac disease is changing, and typical malabsorption is now uncommon. Patients are more likely to present with non-specific symptoms or with iron and/or folate deficiency. The diagnosis still depends upon finding villous atrophy in the small intestine by endoscopic biopsy of the distal duodenum. The mucosal changes should improve after the patient has followed a gluten-free diet for at least six months.**

**IgA antibodies to gliadin, endomysium and/or tissue transglutaminase are detectable in most untreated patients. Antibody testing should not be used alone to make the diagnosis, because of the possibility of false positive results. This testing is used in patients where the clinical index of suspicion is low, in those with one of the disorders associated with coeliac disease or for screening relatives. Everyone with detectable antibodies requires a small bowel biopsy. Patients in whom the clinical index of suspicion of the disease is high should undergo biopsy regardless of the results of antibody testing. There is no place for an empirical trial of a gluten-free diet if coeliac disease is suspected.**


**Index words: coeliac disease.**

*(Aust Prescr 2001;24:38–40)*

## Introduction

Gluten enteropathy, or coeliac disease, results from an abnormal immune response to gliadin, a component of dietary gluten, found in wheat, barley, rye and possibly oats. This causes villous atrophy of the small bowel mucosa, which in turn leads to malabsorption and a predisposition to gastrointestinal malignancy, particularly carcinoma of the oropharynx and oesophagus, and small bowel lymphoma. The disease may present in either children or adults, but it is uncommon in adolescence and its manifestations may disappear at this age.

Coeliac disease is largely a disorder of Caucasians. In Australia it affects approximately 1 in 2000 people. Subclinical, or 'silent', coeliac disease, detected by antibody screening, may be up to ten times more frequent.

## Pathogenesis

Patients with coeliac disease typically have the HLA-B8, DR3, DQ2 or DQ8 haplotype. This genetic background explains the occurrence of coeliac disease in 10% of first-degree relatives, 30% of HLA-identical siblings and 70% of monozygotic twins. However, approximately 20% of the general population have the same HLA alleles but do not develop coeliac disease.

When gliadin enters the small bowel mucosa, it undergoes enzymatic deamidation by tissue transglutaminase (tTG), an extracellular enzyme found in the connective tissue of the small bowel. In susceptible people, the gliadin-tTG complex becomes antigenic, producing a local immune response. This leads to the characteristic villous atrophy of coeliac disease. As part of this immune reaction antibodies to tTG are produced and are recognised as endomysial antibodies.

## Clinical features

The classic presentation of a patient with abdominal distension, steatorrhoea, weight loss, bruising and other obvious features of malabsorption is now uncommon. Adults are more likely to seek help for milder, non-specific symptoms such as diarrhoea, flatulence and bloating, or fatigue.[1] Isolated iron and/or folate deficiency anaemia are also common forms of presentation.[2]

The clinical features have also changed in children. Coeliac disease should be suspected in children with growth or pubertal failure, recurrent abdominal pain, iron and/or folate deficiency or malaise. It can also lead to irritability and poor school performance.

Coeliac disease can also present with non-gastrointestinal problems. Apart from anaemia, it can cause recurrent mouth ulcers and, in women, delayed menarche, infertility or repeated miscarriage. Most adults with coeliac disease will have significant osteopaenia at the time of presentation. Conversely, approximately 5% of adults diagnosed with osteoporosis will be found to have underlying coeliac disease as the cause.

A number of other disorders are associated with underlying coeliac disease (Table 1).[3] At least 75% of patients with dermatitis herpetiformis have the typical villous atrophy on small bowel biopsy. Most of the others have more subtle mucosal changes. Coeliac disease is significantly more common in patients with type 1 diabetes, autoimmune thyroid disease, IgA deficiency and Down's syndrome. More unusual associations are with hyposplenism, and cryptogenic neurological illness, in particular epilepsy and ataxia (leading to the term 'gluten ataxia').

## Diagnostic tests (Table 2)

The most important factor for the early diagnosis of coeliac disease is a high index of suspicion, keeping in mind the variable clinical features and known associated disorders.

*Table 1*

**Disorders associated with coeliac disease**

| |
|---|
| Dermatitis herpetiformis |
| IgA deficiency |
| Hyposplenism |
| Type 1 diabetes mellitus |
| Autoimmune thyroiditis |
| Atrophic gastritis |
| Down's syndrome |
| Epilepsy |
| Ataxia |
| Peripheral neuropathy |
| Autoimmune liver disease |
| Primary biliary cirrhosis |
| Alopecia areata |

### *Histology*

The definitive diagnosis in adults and children is the finding of villous atrophy in a biopsy of the small bowel mucosa. Nowadays, biopsies are generally taken from the distal duodenum during upper gastrointestinal endoscopy. At least three, and preferably more, samples should be taken because of the patchiness of the changes seen in some patients. Characteristic changes include flattening or loss of villi, hyperplasia of mucosal crypts and increased numbers of lymphocytes in the epithelium.

If coeliac disease is a possibility, duodenal biopsies should be taken in patients undergoing endoscopy for unexplained iron deficiency anaemia.

### *Antibody testing*

Serological testing can aid in the diagnosis of coeliac disease. However, it is less sensitive and specific than small bowel biopsy and cannot be relied on alone to make the diagnosis. The role of serological testing is in screening relatives and selecting which patients to biopsy when the clinical suspicion is low, for example patients with irritable bowel syndrome, chronic fatigue syndrome, or one of the disorders associated with coeliac disease. If the clinical suspicion of coeliac disease is high, for example in patients with malabsorption or iron deficiency, then biopsy should be done in all cases so antibody testing is unnecessary for diagnosis. All patients with dermatitis herpetiformis should also have a small bowel biopsy.

The two most commonly used investigations test for antigliadin antibody (AGA) and endomysial antibody (EMA). These are IgA antibodies. Testing for IgG antibodies is of little value since the sensitivity and specificity are only approximately 50%. More specific tests for antibody to tTG have also been developed and are likely to replace the other tests when they become more widely available.[4]

Over 90% of patients with coeliac disease will have detectable IgA AGA before diagnosis, while on a normal diet. Conversely, 80–90% of people with IgA AGA will have coeliac disease; the other 10–20% have a false positive result and a normal small bowel biopsy. Some will have other gastrointestinal disorders, such as Crohn's disease.

Endomysial and tTG antibodies have the greatest sensitivity and specificity for coeliac disease. IgA EMA is found in 95–100% of patients. False positives are much less common than with IgA AGA, being found in only 1% of subjects tested. EMA is detected by means of immunohistochemistry, using tissues which contain large amounts of tTG.

Tissue transglutaminase is now recognised as the antigen of endomysial antibody. Direct measurement of antibody to tTG can now be done by immunoassay without the need for animal tissue. As expected, the sensitivity and specificity of anti-tTG are the same as those of EMA.

Three to five percent of patients with coeliac disease have IgA deficiency. In these patients the IgA antibody tests will be negative. The total serum IgA concentration should therefore also be measured at the same time as antibody tests.

## The need for biopsy

Antibody testing alone is still not recommended for the diagnosis of coeliac disease even though the combination of IgA AGA and EMA/tTG antibody will detect most patients. This is because at least 1 in 100 subjects with detectable antibody will be committed to a strict lifelong gluten-free diet without having the disorder. Moreover, if a patient starts a gluten-free diet without having a biopsy the diagnosis may subsequently be very difficult to confirm if there is any doubt. Finally, biopsy confirms the diagnosis for each patient and

*Table 2*

**Diagnostic tests for coeliac disease**

| *Test* | *Indication* | *Comment* |
|---|---|---|
| Small bowel biopsy | • Essential for diagnosis in all patients | • Repeat biopsy after at least six months on gluten-free diet |
| Antibody testing | • Low index of suspicion<br>• Associated disorder<br>• Screening relatives<br>• Dietary compliance | • Antibody tests alone not sufficient for diagnosis<br>• Endomysial and/or transglutaminase antibodies most sensitive and specific<br>• IgA antigliadin antibody of less value<br>• IgG antigliadin antibody not specific for coeliac disease |
| Tests for malabsorption | • Raise suspicion of coeliac disease | • Not sufficient for diagnosis |
| HLA-phenotype | • No value in diagnosis | • Found in 20% of general population |
| Trial of gluten-free diet | • NO PLACE IN DIAGNOSIS OR TREATMENT | • Diet needs to be lifelong<br>• Non-coeliac gluten intolerance |

aids in ensuring the compliance that is required to avoid the nutritional consequences and the risk of malignancy.

### *Diagnosis by diet*

There is absolutely no place for giving patients with suspected coeliac disease an empirical therapeutic trial of a gluten-free diet. Some people with a normal small bowel develop symptoms such as bloating and diarrhoea from the fermentation of wheat starch. This is referred to as non-coeliac gluten intolerance. They will improve after removal of gluten. Their symptoms recur if they are rechallenged but most are unwilling to do this if it is decided to rule out coeliac disease. The time to investigate someone for coeliac disease is at the time when the suspicion is first raised, and before prescribing a gluten-free diet.

### *Diagnosis of coeliac disease in children*

The principles of diagnosis in children are the same as in adults. A general anaesthetic may be required for endoscopic biopsy. Children have a high frequency of transient IgA deficiency, meaning that IgA antibody tests are less reliable and measurement of total IgA is important. The serological and histological changes of coeliac disease might not occur until children have had gluten in their diet for at least two years. It is therefore important to ask about the amount and duration of gluten intake and whether this has been normal or restricted. Negative serological or other investigations done before two years of age should be repeated at a later time if coeliac disease is still suspected.

## Confirmation of diagnosis

In children and adults the diagnosis of coeliac disease should be confirmed by a repeat small bowel biopsy after at least six months on a gluten-free diet. Symptom resolution alone is not a reliable guide to histological improvement. In the majority, the mucosa will have returned to normal. In some there may be persistent villous atrophy, although this is usually mild and improved compared with the pre-treatment appearance.

In the past, it was recommended that all children with coeliac disease undergo gluten challenge and biopsy as final confirmation of the diagnosis. However, recent guidelines recommend that this only be done in selected children where there is doubt about the initial diagnosis on clinical or histological grounds.[5]

## Additional investigations

The determination of HLA phenotype is of little value in diagnosis or screening because of its frequency in the general population, despite the strong association of the HLA-B8, DR3, DQ2/DQ8 haplotype with coeliac disease.

Tests for nutritional deficiencies, such as iron, folate, calcium and vitamin D, may give a clue as to the possibility of malabsorption and the need for diagnostic testing but do not help in the diagnosis. They also give a guide to nutritional therapy. The same is true of measurement of bone mineral density. Specific tests for malabsorption, such as the d-xylose test, are no longer used.

## Conclusion

Coeliac disease is more common than previously thought.[1] A high index of suspicion is important. Diagnosis still depends on the demonstration of villous atrophy on small bowel biopsy, with repeat biopsy after at least six months on a gluten-free diet. Antibody tests alone are not sufficient for diagnosis, but are useful in screening. All patients with detectable antibodies should undergo biopsy.

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## Self-test questions

*The following statements are either true or false (answers on page 47)*

3. Before children with suspected coeliac disease are subjected to endoscopy, they should be given a trial of a gluten-free diet.
4. Coeliac disease can be excluded if the patient has no IgG antigliadin antibodies.

# Patient support organisations

## The Coeliac Society of Australia

The Coeliac Society of Australia supports people who have been diagnosed with coeliac disease, and their families. It also supports sufferers of dermatitis herpetiformis and those medically diagnosed as requiring a gluten-free diet.

The State and Territory societies (see opposite) give advice and information about the gluten-free diet, ingredients and where to buy them, recipes and cooking, overseas travel, educational material, and research into coeliac disease. The Society works with food authorities and manufacturers to promote standards and labelling of food products.

Support groups have been set up throughout the States and Territories. Coeliac Awareness Week is held each year in March.