

Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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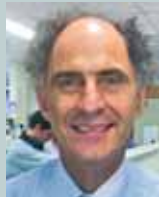
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Coeliac disease

Adverse reactions to wheat

Adverse reactions to wheat are not uncommon presentations to the GP. Given the high profile of wheat and wheat products as a cause of disease, many patients will attribute their gastrointestinal symptoms to wheat. Additionally, some patients will attribute other, more general symptoms, to wheat.

It is important to make sure there are not other causes for these GI and other more general symptoms, especially if the symptoms are of more recent onset and the timing between ingestion of wheat products and onset of symptoms is not close. Upper and lower GI endoscopy may be needed to exclude other causes for GI disease.

Coeliac disease

Coeliac disease is a common cause of adverse reactions to wheat. It is a disease caused by an immune reaction to gliadin, which is one of the protein components of gluten that is present in many foods. Gluten is a set of proteins found in wheat and related species, including barley and rye. A major property of gluten is that it is insoluble in water and so can be separated from starch in flour.

Gliadin gives flour the property of elasticity, which makes wheat ideal for making bread. However, it is not well broken down by proteolytic enzymes in the gut and therefore, in certain circumstances, it can become immunogenic.

Coeliac disease has probably existed for as long as wheat has been used as food and has spread with the advance of wheat across the world, with a prevalence of about 1% in all racial groups. Wheat was originally grown in the Middle East and bread was developed in ancient Egypt. Roman civilisation led to the almost universal use of bread as a staple food (the Romans regarded the races that did not eat bread as barbarians!). Across the world, the consumption of wheat has risen sharply since the mid 19th century, in parallel with the development of high-producing strains and the automation of virtually all aspects of wheat-growing and bread-making.

The presenting symptoms of coeliac disease are bloating, abdominal pain, intermittent diarrhoea, failure to thrive and weight loss.¹ It may occur at

any age. Patients frequently have a family history of coeliac disease and may have a history of other autoimmune disease. Other presenting features include the consequences of malabsorption, such as osteoporosis and iron deficiency, and non-specific features such as fatigue and malaise.

Recent advances in coeliac disease testing, and in particular the measurement of IgA antibodies to transglutaminase, have revolutionised the diagnosis of coeliac disease.

Serological testing for coeliac disease

The measurement of anti-gliadin antibodies has been used for the serological diagnosis of coeliac disease. Unfortunately, both IgG and IgA anti-gliadin ELISA tests lack adequate specificity for coeliac disease. Positive results may occur in patients with other GI diseases and even in normal populations.

Until recently, the serological diagnosis of coeliac disease was performed by measuring anti-endomysial antibody. With the production of transglutaminase by cloning, ELISA (Enzyme-

‘Assays of IgA antibodies to transglutaminase are the serological test of choice for coeliac disease’

Linked ImmunoSorbent Assay) testing against human tissue transglutaminase (TTG) has become the serological test of choice.

Detection of IgA to tissue transglutaminase has both a relatively high specificity and sensitivity for the diagnosis of coeliac disease. However, problems remain with testing as there is a large variation in test performance among the commercially available kits. False-negative results remain a problem in the case of IgA-deficient patients and there remain questions as to the usefulness of this test in patients under two years of age.

Recently, a new anti-gliadin ELISA that measures IgG antibodies against deaminated gliadin has become available. This test may have a role in the diagnosis of those patients with coeliac disease who are IgA-deficient.





CASE 1

A 36-year-old woman with a long history of systemic lupus erythematosus manifest by rash and polyarthritis presents with a six-month history of abdominal bloating and constipation. Upper GI endoscopy and colonoscopy were reported as normal. On history, the woman mentions she has an aunt with coeliac disease and wishes to have testing for the disease.

Discussion

The most expeditious test for coeliac disease is IgA TTG antibody. In this case, the level of IgA to TTG was greater than 100u/ml (normal is less than 5u/ml). The high result, in the clinical context, indicates a high probability for coeliac disease but this should always be followed up by a small-bowel biopsy. The rate of positive serology for coeliac disease in this situation still remains at 50-75%. A small-bowel biopsy subsequently confirmed the diagnosis of coeliac disease in this case, showing subtotal villous atrophy: a biopsy should have been done at the first upper GI endoscopy.

HLA typing in the diagnosis of coeliac disease

HLA testing (“tissue typing”) in patients with coeliac disease has a role in ruling out (not ruling in) coeliac disease. Only certain HLA types have the ability to present the putative antigen, deaminated gliadin, to the immune system and hence trigger coeliac disease. More than 90% of coeliac patients express DQ2; the remaining 2-10% express HLA-DQ8.

The absence of DQ2 and DQ8 in patients essentially rules out the diagnosis of coeliac disease (although very occasionally cases of coeliac disease

‘The absence of DQ2 and DQ8 essentially rules out the diagnosis of coeliac disease’

without these HLA types have been recorded). As about 60% of the Australian population is positive for either DQ2 or DQ8, a positive result does not

necessarily mean the patient has coeliac disease.

Patients with the DQ2 gene have an 8% post-test

‘The presence of DQ2 or DQ8 does not necessarily indicate coeliac disease since up to 60% of the Australian population has one or both of these genes’

probability of having coeliac disease while the presence of DQ8 alone does not increase the risk at all.

The role of HLA testing is to rule out the possibility of coeliac disease in patients who have a high life-long propensity to coeliac disease. This includes first-degree relatives of people with coeliac disease, insulin dependent diabetics, those with Down or Turner’s syndrome and IgA deficiency. It may be of use in patients where there is a high clinical suspicion of coeliac disease but who are TTG antibody-negative and cannot undergo a small-bowel biopsy.

CASE 2

A five-year-old patient with insulin-dependent diabetes is screened for coeliac disease using IgA against TTG on a yearly basis in view of the high prevalence of coeliac disease associated with this condition. Venepuncture is difficult to carry out in this patient and his mother asked for an alternative approach to exclude coeliac disease.

Discussion

HLA testing is helpful in this situation. If the patient is negative for the HLA DQ2 and HLA DQ8 then he is not at risk of coeliac disease. Such was proven to be the case and he no longer needs further screening for coeliac disease.

Screening for coeliac disease in the general population

Serological testing for coeliac disease cannot be justified in populations with a low prevalence of the disease (that is, in populations with a low pre-test probability of the disease). Serological screening of the normal population for coeliac disease will lead to many false-positive results and unnecessary small-bowel biopsies.

Although coeliac disease may present with

fatigue, the results of testing for TTG antibody in this population have to be regarded with caution. There are many other, more common causes of fatigue besides coeliac disease. As with all autoantibody testing, a positive result that is close to the laboratory's normal cut-off value is likely to be less significant than is a test result that is well above the cut-off value.

‘Only 8% of asymptomatic individuals with a positive IgA to transglutaminase will have coeliac disease’

Among patients whose clinical presentation is suggestive of coeliac disease, the probability of having coeliac disease if the IgA to TTG is positive is about 56%. If patients with no symptoms are screened, the probability of people with a positive test having coeliac disease is only 8%.

Common causes of false-negative IgA antibodies to transglutaminase

One of the most common causes of a false-negative result when IgA antibodies against TTG are measured is that the patient has already commenced a gluten-free diet. This has become more common with increased community awareness of coeliac disease. Consequently, patients should

have a gluten-rich diet for six weeks before undergoing testing. If the patient claims to have followed the gluten-free diet, testing before six weeks may be able to be done if the patient's diet still contains gluten. Critical review of the patient's self-reported intake will often help here.

The other important cause of a false-negative for IgA against transglutaminase is IgA deficiency. Serum IgA should be measured in all patients where there is a clinical suspicion of coeliac disease and who have negative IgA antibodies to transglutaminase. Under these circumstances, ELISA testing for IgG to deaminated gliadin may be helpful (see previous section, ‘Serological testing for coeliac disease’).

CASE 3

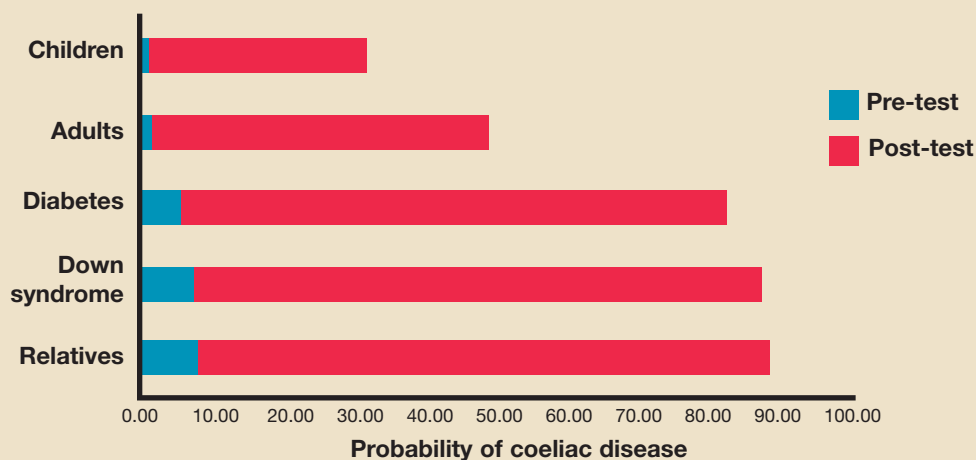
A 10-year-old boy presents with weight loss, diarrhoea and abdominal bloating.

Radiological examinations revealed no abnormalities. His IgA to TTG is undetectable.

Discussion

This result does not exclude coeliac disease. He may still have coeliac disease, since a positive IgA to TTG does not occur in all patients with coeliac disease. Of great importance to consider is whether or not the patient is IgA deficient. In this case, he had no detectable serum IgA, making the IgA antibody against TTG unreliable.

Probability of coeliac disease if positive IgA to transglutaminase





This patient underwent further testing of IgG to deaminated gliadin, which was found to be highly positive. He then had subtotal villous atrophy confirmed on a small-bowel biopsy.

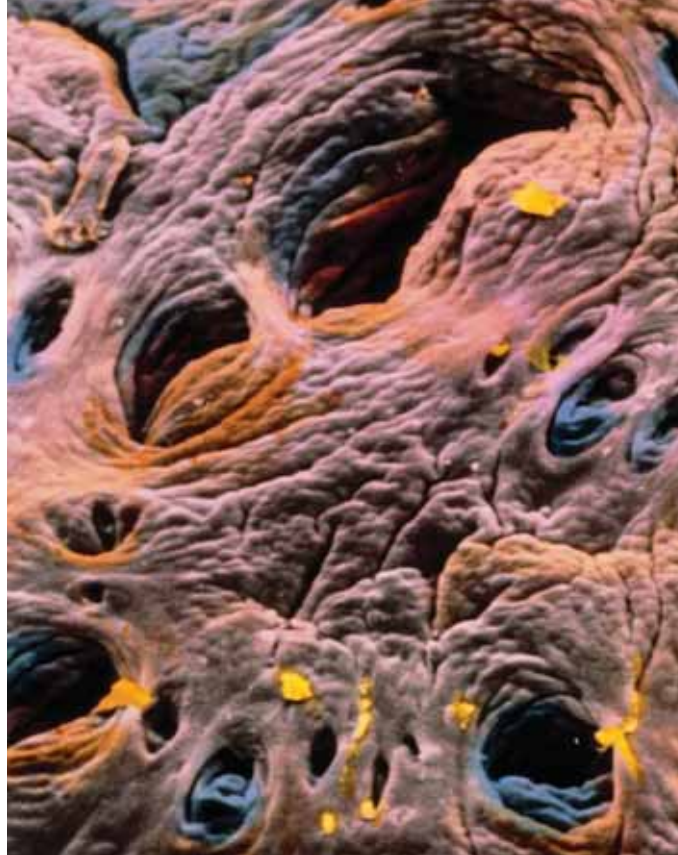
Serological testing in patients without villous atrophy

In the past, the gold standard for the diagnosis of coeliac disease was the presence of villous atrophy on small bowel biopsy. However, some patients with coeliac disease, who have been identified by positive serology, have only minor histological lesions, such as increased intra-epithelial lymphocytes but with no villous atrophy.

The natural history of patients who have positive serology and minor findings on biopsy is unclear. These patients may be at greater risk of developing full-blown coeliac disease in the future. At the very least, close follow-up of these patients is warranted.

Monitoring of coeliac disease

The use of coeliac serology is of limited value for monitoring dietary compliance. Measurement of anti-deaminated gliadin antibodies is probably more useful for monitoring than TTG antibodies, despite the paucity of studies directly comparing the two tests for monitoring. An initial fall in the titre of either serological test may sug-



gest that the patient has been avoiding gluten to an adequate degree. These antibodies frequently disappear in children but not adults. It is important to be aware that the disappearance of these antibodies does not necessarily predict the resolution of duodenal mucosal damage – a repeat small-bowel biopsy is better to verify an adequate response to a gluten-free diet.

Children aged under two years

The measurement of IgG antibodies to deaminated gliadin is probably a more sensitive test in children younger than two years of age for the diagnosis of coeliac disease than the measurement of IgA antibodies to TTG. Children of this age

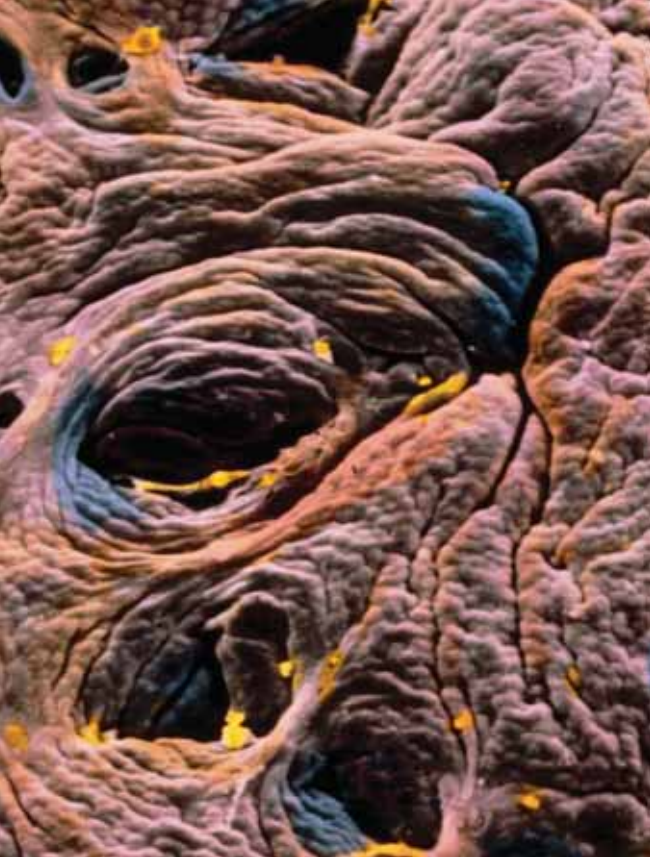
Tests that have been superseded

IgA antiendomysial antibodies

IgA and IgG antigliadin antibodies

Antireticulin antibodies

IgG to transglutaminase antibodies



Coloured SEM of intestine, showing coeliac disease.



cated but in patients who test positive for DQ2 or DQ8, repeat testing may be indicated if there is an ongoing clinical suspicion of coeliac disease despite negative antibody results.

Follow-up of patients with a positive IgA to tissue transglutaminase

Repeat testing should be carried out in all patients with a positive antibody results to confirm the result. If still positive, the patient should undergo small-bowel biopsy to confirm the diagnosis of coeliac disease. Patients should not be started on a gluten-free diet solely on the basis of serological testing, since such a diet is meant to be a life-long commitment.

“Patients should not be started on a gluten-free diet solely on the basis of serological testing”

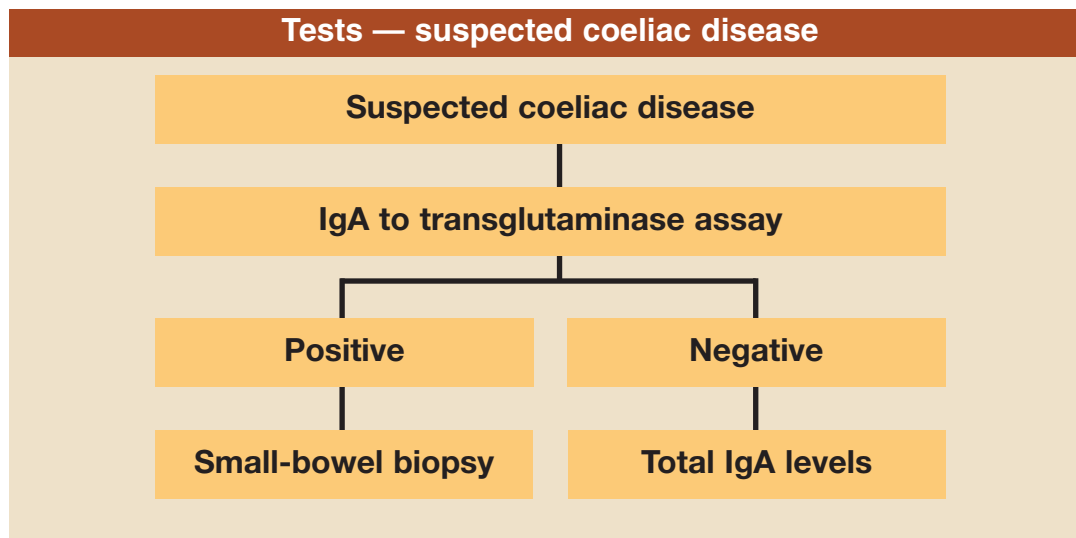
have low IgA levels that slowly rise to adult levels. Only about 20% of children attain an adult IgA level by the age of one. One should always proceed to duodenal biopsy in this age group if there is a high clinical suspicion of coeliac disease.

Repeat antibody testing

Coeliac disease may present at any age, and groups who are at high risk of coeliac disease may need repeated serological testing for coeliac disease. Genetic testing helps reduce the number of patients in these risk groups who need repeated serological testing. In patients who test negative for DQ2 or DQ8, repeat testing is not indi-

Summary

Despite the advances in serological and genetic testing, confirmation of coeliac disease requires collection of biopsies from the first, second and third part of the duodenum before patients commence a gluten-free diet.² Even with negative serology, duodenal biopsy should be considered where suspicion is high.





Other adverse reactions to wheat

Irritable bowel syndrome

Wheat may cause adverse reactions in a number of different ways, perhaps the most common being the exacerbation of symptoms of irritable bowel disease. Typically, symptoms of bloating, diarrhoea and abdominal pain are present for many years and cereals, such as wheat, are one of a number of food groups that cause or exacerbate the symptoms. Gibson *et al* have shown abnormalities in the breakdown of short-chain poorly absorbed carbohydrates in patients with these symptoms; dietary restriction can lead to reduction of symptoms of irritable bowel syndrome.³

CASE 4

A 60-year-old man attends his local doctor with a 25-year history of loose bowel motions and abdominal pain about one hour after meals. He identifies fruit as one of the precipitants but, on further questioning, his symptoms also follow eating cereal-based foods including bread. He avoids wheat-based products, other cereals and fruit, and has had an 80% reduction of symptoms since restricting his diet.

Discussion

The long history of GI symptoms is suggestive of irritable bowel syndrome, although it is important to exclude other causes. In some cases of irritable bowel syndrome, restriction of wheat products can lead to an improvement of symptoms.

Type I hypersensitivity

Wheat can also cause classical Type 1 hypersensitivity, which is mediated by specific IgE to wheat. In such cases, symptoms occur within one hour of ingestion of wheat and may consist of rash, bronchospasm or occasionally full-blown anaphylaxis. Such a reaction can be confirmed by the demonstration of specific IgE to wheat, either serologically or by skin-testing.

CASE 5

A five-year-old child with previous eczema presents with wheeze and flushing following meals. Specific IgE testing to wheat is positive and restriction of wheat in the diet leads to amelioration of symptoms.

Discussion

The clinical picture is the more common form of Type 1 IgE-mediated hypersensitivity to wheat. The specific IgE result confirms clinical suspicion and the amelioration of symptoms is consistent with Type I IgE-mediated hypersensitivity to wheat.

Wheat may be implicated in exercise-induced anaphylaxis whereby patients develop symptoms of anaphylaxis only when they exercise after ingestion of wheat. Testing for such a reaction involves the measurement of IgE to a component of wheat – omega-5 gliadin.⁴

CASE 6

A 45-year-old man presents with generalised rash and bronchospasm following exercise. It is recorded that he had a pizza 30 minutes prior to exercise. On history, it is noted that he has had previous episodes of anaphylaxis following exercise on ingestion of toast and sandwiches prior to exercise. Specific IgE to omega-5 gliadin is positive.

Discussion

The clinical picture is that of a Type 1 IgE-mediated hypersensitivity reaction following exercise. Exercise-induced anaphylaxis is commonly associated with ingestion of wheat followed by exercise. The specific IgE testing result confirms the clinical suspicion of exercise-induced anaphylaxis following ingestion of wheat. He now avoids eating prior to exercise and has had no further attacks.

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