

Making sense of your diagnosis – what your doctor should know

Dr Jason Tye-Din* writes about what you and your doctor should know about the diagnosis and management of coeliac disease.

IMPROVING THE DIAGNOSIS OF COELIAC DISEASE

Many people with coeliac disease know the pain and frustration of a delayed diagnosis all too well. Unresolved, long-standing symptoms, despite multiple visits to doctors and specialists, is a common story. In some instances it takes a serious medical complication to alert the clinician to the possibility of coeliac disease. In the USA, people suffer an average of 11 years before their coeliac disease is diagnosed. Fortunately, this dire situation is better in Australia, and continues to improve. There is still much work to be done, as about 75% of Australians with coeliac disease remain undiagnosed. A key goal of The Coeliac Research Fund Ltd (CRF) [formerly known as the Australian New Zealand Coeliac Research Fund (ANZCRF)] is to improve coeliac disease awareness, diagnosis and treatment through the education of medical practitioners. Following on from last year's CRF release of an educational CD-ROM designed to educate GPs about coeliac disease, a "Coeliac Postcard" has been recently developed that will be distributed to all GPs around Australia (a complimentary copy was provided in the June 2008 edition of *The Australian Coeliac*). This postcard draws together the views of several opinion-leading medical professionals and outlines current "best-practice" for diagnosing coeliac disease. Hopefully Australian doctors will adopt the principles outlined in this postcard to ensure optimal and timely diagnosis of their patients with coeliac disease. This "best-practice" diagnostic process will be discussed in this article.

COELIAC DISEASE REALLY IS COMMON!

In stark contrast to a decade ago when coeliac disease was considered rare, with prevalence rates of 1 in 1000, or lower, quoted, we now know coeliac disease affects around 1% of Australian, European, North American, and Middle Eastern populations¹. Undiagnosed or poorly controlled coeliac disease can be associated with a diverse range of clinical presentations and significant medical complications². In line with increased medical and community awareness, diagnosis of coeliac disease has improved substantially. In the last 6 to 7 years, total membership of the Coeliac Societies in Australia has more than doubled (G. Price, Technical Officer, The Coeliac Society), with more than 20,000 members Australia wide. However gratifying, it remains a sobering fact that only 25% of the 200-250,000 Australians with coeliac disease have been diagnosed to date.

HOW IS THE DIAGNOSIS MADE?

Is it possibly coeliac disease?

Before a diagnosis of coeliac disease can be made a doctor must first think of it! Appreciating the diverse range of clinical presentations is important. Some people suffer long-standing prominent symptoms, while others are completely symptom free. Doctors should have a high-index of suspicion for coeliac disease whenever certain features are present, and this should prompt further investigation. These features include high risk symptoms, such as iron deficiency anaemia, gastrointestinal symptoms that can mimic irritable bowel syndrome (eg. bloating, flatulence, abdominal pain, diarrhoea, constipation or erratic bowel habits), osteoporosis, autoimmune disease (eg. type 1 diabetes or thyroid disease), weight loss, infertility, or having a first-degree relative with coeliac disease (risk for coeliac disease if one affected family member is 10%).

Is adequate gluten being consumed?

When a doctor suspects coeliac disease the first thing he/she should ask is if the person is consuming a normal gluten containing diet. If a



Dr Jason Tye-Din

gluten free diet has already been adopted, the tests used to diagnose coeliac disease are unreliable, and may be falsely negative. This is particularly the case the longer the gluten free diet has been followed. Therefore a person must be willing to resume a normal diet for at least 6 weeks to enable meaningful test results (this is called a "gluten challenge"). Adequate consumption of gluten should be achieved by consuming 4 slices of bread a day for 6 weeks in adults (or 2 slices of bread a day in children). Understandably, many people view the prospect of a gluten challenge extremely daunting, and are particularly anxious about the symptoms they may experience upon reintroducing gluten into their diet. Many people find that symptoms are most prominent for the first few days of a gluten challenge, but that they abate substantially after then. It is important to note that a gluten challenge will be the only way to ensure reliable test results for people who have removed gluten from their diet before testing. Coeliac disease is an important diagnosis with significant health implications, so a definitive diagnosis is paramount. Notably, the development of symptoms is not sufficient to make a diagnosis of coeliac disease. For people who wish to avoid a gluten challenge, the coeliac gene test offers the possibility of excluding coeliac disease without having to consume gluten (the gene test is not dependent on gluten intake) – but if, and only if, the gene test result comes back negative (this is discussed over).

Coeliac serology is used for initial screening

Once the doctor has confirmed the person has been consuming gluten, the initial screening investigation is a blood test (“coeliac serology”). Coeliac serology measures specific immune system responses (as indicated by antibody levels), which are typically elevated (abnormal) in people with untreated coeliac disease. The tests measure antibodies to transglutaminase (transglutaminase antibodies or “tTG”), and gliadin (anti-gliadin antibodies or “AGA”). The endomysial antibody test (“EMA”), similar to the tTG, is less frequently used nowadays. A normal total immunoglobulin level (specifically, “IgA”) should be confirmed to exclude the 3% of people with coeliac disease who cannot produce antibodies – these people with IgA deficiency require definitive investigation with small bowel biopsy as their serology results are unreliable.

If any of the coeliac serology blood tests are abnormal (positive) this suggests coeliac disease is present - the next step is to confirm the diagnosis with a small bowel biopsy. A diagnosis of coeliac disease is never made on the basis of the blood tests alone, as these can be occasionally wrong (either falsely positive or falsely negative). It would be bad practice to commence a lifelong gluten free diet without a small bowel biopsy confirming coeliac disease. In children under the age of 4 years the transglutaminase antibody test is less reliable, so the anti-gliadin antibody test should also be performed. Since levels can fluctuate in children it is suggested the antibody tests be performed on two occasions 3 months apart.

When the screening blood tests are negative (normal) then the diagnosis of coeliac disease is unlikely, particularly if there are no risk-factors for coeliac disease present. However we know that coeliac serology only detects 85-90% of true cases of coeliac disease, even when the patient is consuming adequate gluten. Therefore, if coeliac serology is normal but the doctor still suspects coeliac disease on the basis of certain risk-factors (eg. patient has a history of autoimmune disease, iron deficiency, or a family history of coeliac disease), then consideration and discussion about testing with small bowel biopsy should be made.

Definitive diagnosis requires small bowel biopsy

The diagnosis of coeliac disease is based on the small bowel biopsy. Specifically, it is how tiny samples (or “biopsies”) of the small bowel lining look under a microscope that determines the diagnosis. In coeliac disease the small bowel is damaged, with inflammation that obliterates the usual finger-like villi causing a flat appearance (this is called “villous atrophy”). The small bowel biopsies are taken by a day procedure called a gastroscopy, where a flexible instrument is inserted via the mouth into the stomach and then the small bowel. The patient has short-acting anaesthetic sedation to make them comfortable. It is a straightforward procedure, taking about 10 minutes. Biopsy results (and hence a diagnosis) are available within a few days. Once again, a person must be consuming gluten for the biopsy result to be reliable. Expert opinion recommends at least 4 biopsies are taken from the small bowel in different areas to ensure it has been adequately sampled so that the diagnosis is not missed. If classic small bowel changes are present to confirm a diagnosis of coeliac disease then definitive management – a strict, lifelong gluten free diet can commence.

How can the coeliac gene test help?

In the last few years the coeliac gene test (also known as “HLA gene testing”) has emerged as a very useful tool to determine a person’s risk of coeliac disease. It is based on the understanding that 99.6% of all people with coeliac disease have at least one of two genes, called HLA DQ2 and HLA DQ8. It is important to note that these genes do not cause coeliac disease, but having either one appears necessary for coeliac disease to develop. The test is a simple blood test, but can also be performed on a cheek (buccal) scrape which provides a DNA sample. If a person does not have either gene then their risk of coeliac disease is extremely low (< 1%), and effectively avoids the need for further investigations for coeliac disease. However, if one or both genes are present, then it means the person is susceptible to coeliac disease but not necessarily that they have it. Only 1 in 30 people with either of these genes will develop or have coeliac disease. Thus gastroscopy with small bowel biopsy is still essential to make the diagnosis of coeliac

disease. For people (over the age of 10 years) with HLA DQ2 or HLA DQ8, if coeliac disease has been definitively excluded on biopsy, the risk of developing coeliac disease in the future is thought to be very low.

There are a number of situations where gene testing is useful. The gene test is not dependent on gluten intake, so can be used when people are already following a gluten free diet. In this setting, a negative gene test avoids the need for further coeliac investigations. However a positive gene test means the traditional tests

There is still much work to be done...

75% of Australians with coeliac disease remain undiagnosed

The Coeliac Postcard

Copies of this card can be obtained from your State Society.

still need to be performed, following a gluten challenge as discussed above. The other situation when gene testing is useful is when test results are inconsistent or difficult to interpret – this may occur when coeliac serology does not match the small bowel biopsy appearance. The gene test can also be used in family members of people with coeliac disease to provide additional information to measure coeliac disease risk.

MANAGEMENT AND FOLLOW-UP

A strict, lifelong gluten free diet remains the cornerstone of treatment for coeliac disease. Unfortunately, as little as 50 mg of gluten (equivalent to 1/100th of a slice of standard wheat bread, essentially a bread crumb), damages the small intestine in coeliac disease³. This makes the requirements for the diet extremely strict. Deliberate or inadvertent intake of gluten is the most common cause of incomplete intestinal healing (i.e. ongoing damage). Concerningly, ongoing small bowel damage is associated with a fourfold increased long-term risk of osteoporosis and cancer⁴, and this is irrespective of symptom improvement on the gluten free diet.

The complexities and stringent requirements of the gluten free diet make expert education by a specialist dietitian essential. This will encompass the knowledge and practical skills required to follow a gluten free diet – such as shopping gluten free, interpreting food labels, food preparation, eating out, and having a healthy, balanced diet. Membership of The Coeliac Society is an important source of ongoing information and support. New research and new understanding about coeliac disease is constantly emerging, and one of the best ways of keeping informed is to remain involved with the Society.

Baseline medical investigations should be performed at diagnosis and include screening for nutritional deficiencies and autoimmune disease, and checking bone density. Nutritional deficiencies (such as low iron, folate or Vitamin D) are common in newly diagnosed coeliac disease. Supplementation is often recommended for the first 3 months (eg. iron tablets), followed by repeat assessment by the local doctor. With a strict gluten free diet and healing of the small bowel lining (allowing it to properly absorb nutrients), long-term supplementation is usually not

necessary. An optimal Vitamin D level ensures maximal calcium absorption and bone health. Family screening for coeliac disease should be advised.

A diagnosis of coeliac disease is *never* made on the basis of the blood tests alone, as these can be occasionally wrong

A repeat gastroscopy to obtain small bowel biopsies at 12 months after diagnosis and following a gluten free diet is important to confirm small bowel healing and is the best way of confirming adequate compliance to the gluten free diet. Blood tests (coeliac serology) can be used to follow compliance to diet, but while more convenient, are less accurate than biopsy. Results from coeliac serology and small bowel biopsy are occasionally conflicting, and many studies show that serology does not always accurately reflect the state of the small bowel. For instance serology can be elevated, even when the small bowel is fully healed, or conversely, it can be normal, while the small bowel remains damaged. Therefore, if the serology results are unexpected, then consideration for small bowel biopsy should be given.

Ongoing medical follow-up enables assessment of treatment adequacy and screening for complications, such as osteoporosis and emergence of autoimmune disease.

CONCLUSION - THE KEY POINTS:

- Coeliac disease is common, and can present in a multitude of ways, in adults and children of all ages.
- Diagnosis requires vigilance by the doctor. An awareness of high-risk conditions associated with coeliac disease is important. Family members of coeliac disease patients should be screened.
- Screening blood tests and small bowel biopsies for coeliac disease are only useful if the patient is consuming gluten (for at least 6 weeks prior).
- If there are high-risk symptoms or features present, small bowel

biopsy may be indicated even if screening coeliac serology is negative.

- Definitive diagnosis of coeliac disease necessitates a small bowel biopsy showing typical changes (“villous atrophy”).
- The gene test never diagnoses coeliac disease, but can be useful to exclude a diagnosis in particular situations e.g. where traditional testing has not resulted in a clear-cut diagnosis. Gastroscopy with small bowel biopsy still remains essential to make the diagnosis of coeliac disease.
- The only treatment for coeliac disease is a strict, lifelong gluten free diet. The prime reason to adhere strictly to the diet is to enable small bowel healing (and therefore avoid long-term complications). Avoidance of symptoms (if symptoms are present) is a secondary benefit.
- Given the potential complexities of the diet, appropriate dietary education and membership of The Coeliac Society are important.
- After a biopsy confirms coeliac disease, improvement on gluten free diet (measured by small bowel appearance, coeliac serology, and clinical symptoms) helps confirm the diagnosis.
- Ongoing medical follow-up is important to assess progress on gluten free diet, normalisation of small bowel damage, and allow for screening of complications.

References

1. Dube C, Rostom A, Sy R, Cranney A, Saloojee N, Garrity C, Sampson M, Zhang L, Yazdi F, Mamaladze V *et al*: **The prevalence of coeliac disease in average-risk and at-risk Western European populations: a systematic review.** *Gastroenterology* 2005, **128**(4 Suppl 1):S57-67.
2. Anderson RP: **Coeliac disease.** *Australian Family Physician* 2005, **34**(4):239-242.
3. Catassi C, Fabiani E, Iacono G, D'Agate C, Francavilla R, Biagi F, Volta U, Accomando S, Picarelli A, De Vitis I *et al*: **A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with coeliac disease.** *Am J Clin Nutr* 2007, **85**(1):160-166.
4. Kaukinen K, Peraaho M, Lindfors K, Partanen J, Woolley N, Pikkarainen P, Karvonen AL, Laasanen T, Sievanen H, Maki M *et al*: **Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease.** *Aliment Pharmacol Ther* 2007, **25**(10):1237-1245.

*Dr Jason Tye-Din MBBS, FRACP. Consultant Gastroenterologist, Coeliac Clinic, The Royal Melbourne Hospital. Postgraduate Scientist, Autoimmunity and Transplantation Division, The Walter and Eliza Hall Institute of Medical Research. Consultant and Assistant Chief Medical Officer, Nexpep P/L.