Coeliac disease

BACKGROUND Coeliac disease (CD) probably affects one in 100 Australians, but is greatly underdiagnosed. Heightened media interest in the negative effects of dietary gluten has led many patients to request testing for CD or follow inappropriate diets. Doctors have had little education in CD because of its perceived rarity.

OBJECTIVE This article summarises current knowledge of clinical presentations, optimal screening and diagnostic tests, and how the general practitioner can best assist patients in adopting a successful gluten free diet.

DISCUSSION Coeliac disease is associated with a range of conditions including type 1 diabetes, thyroid disease, osteoporosis, and iron deficiency with or without anaemia. Gastrointestinal symptoms may not be present. The GP therefore has an important role in considering CD in the differential diagnosis in a variety of clinical presentations. Antitransglutaminase IgA and total serum IgA are the preferred screening tests but may miss occasional patients with CD. Endoscopic duodenal biopsy while eating gluten is needed for definitive diagnosis. A gluten free diet is complex, and may fail without the involvement of a skilled dietician.

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Coeliac disease (CD) is now recognised as an underdiagnosed life long disease affecting over 250 000 Australians (prevalence 1:70–250 caucasians and west Asians) with a range of presentations in addition to infantile malabsorption and diarrhoea.[1] In Australia, Coeliac Society membership (with the requirement of a doctor's letter indicating the medical need for a gluten free diet) is rising by approximately 14% each year. Reports now rate CD as the commonest cause of chronic diarrhoea in economically disadvantaged countries such as Iran.[2] Expansion of the gluten free food industry has also been dramatic, fuelled by medically diagnosed patients with CD, and individuals with self imposed gluten free diets without a definite diagnosis.

Although caused by a staple food, untreated/undiagnosed CD is associated with doubling of age adjusted mortality; mostly attributable to the increased risk of cancer and infections.[3]

Coeliac disease defined

Coeliac disease is defined as villous atrophy with hyperplasia of crypts and abnormal surface epithelium found on an initial small intestine biopsy while following a gluten containing diet. The combination of an abnormal biopsy and presence of antigliadin and/or transglutaminase (tTG) and/or endomysial (EMA) IgA antibody that disappears in parallel to clinical improvement with a gluten free diet is considered adequate for diagnosis.[4]

Gluten

Gluten is the water insoluble seed storage protein in wheat, rye, barley and oats.[5] Gliadin is the alcohol soluble component of gluten, and is the most toxic

component of gluten in CD. Gluten is responsible for the favourable cooking and baking properties of these grains. Gluten content in food is measured by an ELISA for gliadin. Food without detectable gluten is suitable for individuals with CD. The toxic component of oats is ill defined, and ELISAs for gluten in wheat, rye and barley do not detect equivalent proteins in oats.

Making the diagnosis

Clinical features that prompt screening for CD are shown in *Table 1*.[6] Coeliac disease is not a clinical diagnosis. It is typically a lifelong condition beginning in infancy, and the general practitioner has an important role in considering CD in a range of clinical presentations. Gastrointestinal symptoms and their relationship to wheat consumption, body habitus, and race, are not especially predictive of CD. Anaemia and/or nutrient deficiency, especially iron, fat soluble vitamins (eg. vitamin D and B12), and folic acid in women of reproductive age are important indications for screening and should not be assumed to be due only to gynaecological causes.

Table 1. Clinical features and comorbidities associated with CD

Family history of CD (first degree relatives have a 5–10% risk)
Diarrhoea
Recurrent mouth ulcers
Developmental delay in children
Fatigue
Unexplained abdominal pain
Irritable bowel symptoms that improve with 'gluten' exclusion
Skin rash – typically itchy and blistering
Gluten intolerance as a child
Nutrient deficiency (especially iron, folic acid, vitamin D and B12)
Anaemia
Osteoporosis
Insulin treated diabetes with poor glycaemic control
Thyroid disease (autoimmune hypo- or hyper-thyroidism)
Liver enzyme disturbance (especially autoimmune hepatitis, NASH*, PBC†, PSC‡)
Unexplained neurological complaints (especially neuropathies, ataxia, memory impairment, migraines, epilepsy, or muscular stiffness)
Infertility and recurrent miscarriage
Colitis (especially microscopic/lymphocytic colitis)
IgA deficiency
Other autoimmune diseases (Sjogren syndrome, Addison disease)
Dermatitis herpetiformis
Down or Turner syndromes

*nonalcoholic steatohepatitis, †primary biliary cirrhosis, ‡primary sclerosing cholangitis

Screening

The reliability of coeliac serology has been questioned before about 4 years of age. Screening asymptomatic individuals with a comorbidity or family history associated with CD is controversial unless associated diseases or symptoms are clearly improved by a gluten free diet (eg. osteoporosis, and probably insulin treated diabetes). As there is a lack of evidence base in this area, it is reasonable to screen for CD based on the assumption that a trial gluten free diet will subjectively or objectively 'improve' health. It is important these issues be discussed before screening is undertaken.

Coeliac serology

Tissue tTG IgA is quantified in the sera of more than 90% of individuals with untreated CD, and is extremely rare in unaffected individuals.[7] Sensitivity and specificity of tTG IgA varies according to the assay manufacturer.[8] Anti-endomysial IgA detects tTG-IgA by immunofluorescence and can be used in parallel to tTG IgA as a confirmatory test, but adds little extra information. Positive EMA or tTG IgA indicates the need for confirmatory duodenal biopsy. Antigliadin IgA and IgG are unreliable as screening tests and can be positive in healthy individuals. However, IgA deficiency is present in 2% of CD sufferers, and the risk of CD is increased 10–20 times with IgA deficiency. Hence, total serum IgA should be included in the coeliac screen, and antigliadin IgG may be the only positive coeliac associated antibody (*Table 2a*).

Gene test to exclude CD

As 99.6% of people with CD possess genes encoding HLA-DQ2 or HLA-DQ8 compared to about one-third of the general Australian population, testing for HLA-DQ2 and HLA-DQ8 is emerging as a powerful test of exclusion for the presence of or susceptibility to CD (*Table 2b*).[8] Genetic testing can be useful in:

- people already following a gluten free diet (causing false-negative serology or histology results)
- individuals with elevated antigliadin antibody, but normal tTG IgA and EMA, and
- to predict nonsusceptibility to CD, for example in children.

The presence of HLA-DQ2 or HLA-DQ8 is not helpful as a positive predictor of disease, as only about 1:30 people with these genes will have CD. HLA-DQA and HLA-DQB genotyping is performed on a citrated blood sample or buccal scrape, has a Medicare item number,

and can be bulk billed. It is minimally invasive and typically costs around 5–10 times less than gastroscopy and duodenal histology.

Biopsy is definitive

Definitive diagnosis requires gastroscopy and biopsy of the distal duodenum or jejunum while gluten is being consumed, equivalent to four slices of bread per day in adults (*Table 2c*). The presence of tTG IgA and 'typical' histologic changes of shortened broad duodenal villi infiltrated by chronic inflammatory cells, especially plasma cells and lymphocytes, and increased intra-epithelial lymphocytes lead to a diagnosis of CD. However, diagnosis is not always straightforward (*Table 3*), and the involvement of a specialist gastroenterologist, clinical immunologist and pathologist is helpful.

Treatment – gluten free diet

Patients should not commence a gluten free diet until a definite diagnosis has been reached. Once diagnosed, screening for thyroid disease, osteoporosis, and other nutrient deficiencies is appropriate (*Table 4*). Prolonged nutrient deficiency raises the question of noncompliance or an additional pathology, eg. gynaecological. To ensure adequate intake, long term supplementation with calcium and vitamin D is recommended. The recommendation that parents, siblings, and children of the patient be screened for CD is important, but counselling regarding the implications (eg. increased life insurance premiums, exclusion from entering the military) and treatment of CD is important before screening.

Education and support

Education regarding a gluten free diet (exclusion of foods derived from wheat, barley, rye, and oats) is complex, and is best performed by a dietician with experience in CD. Membership of the Coeliac Society is an important link for patients to up-to-date information on services and local support groups. Poor compliance can be anticipated in various situations (*Table 5*). Generally, it is 2 years before patients adjust to the 'gluten free' lifestyle. Coeliac serology should normalise by 9 months after commencing a strict gluten free diet. A repeat duodenal biopsy after 1 year on a gluten free diet, or when coeliac serology normalises, is useful to gauge compliance. It is critical to have sufficient rapport with patients so they are prepared to admit dietary indiscretions and address issues that may be impeding dietary compliance in a practical fashion.

Table 2. Investigation of CD

a) Screening serology (patient must be consuming gluten >~2 months)
Total serum IgA (IgA deficiency causes false-negative coeliac serology)
Antitransglutaminase IgA (sensitivity and specificity >90%)
Anti-endomysial IgA
Antigliadin IgA
Antigliadin IgG

b) Genetic testing to exclude CD
HLA-DQ (HLA-DQA and HLA-DQB)
Absence of genes encoding HLA-DQ2 (HLA-DQA1*05 and HLA-DQB1*02) and HLA-DQ8 (HLA-DQA1*03 and HLA-DQB1*0302) excludes all but <0.5% of CD

c) Histology of distal duodenum or jejunum
Required for positive diagnosis
Severity of mucosal damage is proportional to gluten consumption

Table 3. Atypical CD*

EMA/tTG IgA normal + duodenal histology villous atrophy

- Consider alternative diagnosis, HLA-DQ gene test

EMA/tTG IgA positive + duodenal histology normal

- HLA-DQ gene test, consider repeat biopsy after gluten challenge (4 slices bread per day >6 weeks)

Duodenal histology no better after 1 year gluten exclusion

- EMA/tTG IgA positive: re-education by dietician
- EMA/tTG IgA negative: consider alternative diagnosis, HLA-DQ gene test

* Involvement of specialist in CD (eg. gastroenterologist, paediatrician, pathologist, and/or clinical immunologist) is suggested

Table 4. On positive diagnosis of CD

Link to support groups and health professionals

- letter to state Coeliac Society confirming medical need for gluten free diet
- referral to dietician experienced in CD

Investigation for comorbidity

- bone mineral density (DEXA)
- full blood count
- iron, vitamin B12, folic acid
- thyroid function tests
- calcium, phosphate, vitamin D, PTH
- liver function tests

Supplements

- short term correction of iron and nutrients
- long term supplementation with calcium and vitamin D

Table 5. Causes of noncompliance to a gluten free diet

- Inadequate education due to
  - no dietician referral
  - neuro-psychiatric conditions
- Inability to read food labels due to
  - impaired vision
  - non-English speaking, illiteracy
- Lack of motivation
- Lack of assertiveness
- Lack of cooking skills
- Food not prepared by patient
- Frequent travel
- Frequent dining out
- Complex multiple exclusion diets
- Cost (~>$2000 annually)
- Disinterest of, or multiple carers
- Residential care

Coeliac disease – a research priority

In the past 2 years, the National Institute of Health (NIH) and patient support groups in Australia and the United Kingdom have acknowledged CD as an under researched and 'greatly underdiagnosed' disease. The NIH and Coeliac UK have released research priorities, many of which focus on immunopathogenesis, specifically host T-cell activation by dietary exposure to gluten proteins in wheat, barley, rye and oats, as it is widely held that better understanding of this interaction is critical and most likely to yield better diagnostics (obviating the need for endoscopic biopsy), alternatives to exclusion diet as the only treatment, and prevention. Closer to home, the Australia New Zealand Coeliac Research Fund was launched in 2003 to nurture local researchers and foster professional education in CD.

Summary of important points

- Coeliac disease is not a clinical diagnosis. It may present in a range of ways other than infantile malabsorption or diarrhoea. Anaemia and/or nutritional deficiency are important indications for screening.
- Tissue transglutaminase is the most appropriate screening test and can be quantified in the sera of over 90% of individuals with untreated CD.
- Definitive diagnosis is by duodenal biopsy in patients consuming gluten (equivalent to four slices of bread per day in adults) for 2 months.
- Treatment is by a lifelong gluten free diet, and referral to a dietician experienced in CD is recommended.
- Long term supplementation with calcium and vitamin D is recommended.
- The Coeliac Society is a valuable resource for patients. Membership requires a doctor's letter confirming the medical need for a gluten free diet.

Resources

Australian Coeliac Society
www.coeliac.org.au/

State coeliac societies
www.qld.coeliac.org.au/
www.nswcoeliac.org.au/
www.vic.coeliac.org.au/
www.tas.coeliac.org.au/
www.sa.coeliac.org.au/
www.wa.coeliac.org.au/

Gastroenterological Society of Australia
www.gesa.org.au/consumer/publications/coeliacdisease/Coeliac_A4Card.pdf

Australia New Zealand Coeliac Research Fund
www.coeliacresearch.com/support_ideas.asp

National Institute of Health
http://consensus.nih.gov/cons/118/118cdc_intro.htm

Conflict of interest: Dr Anderson is a consultant to BTG International, licensee of patents pertaining to the therapeutic and diagnostic use of T-cell determinants in gluten for which he is a named inventor.

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