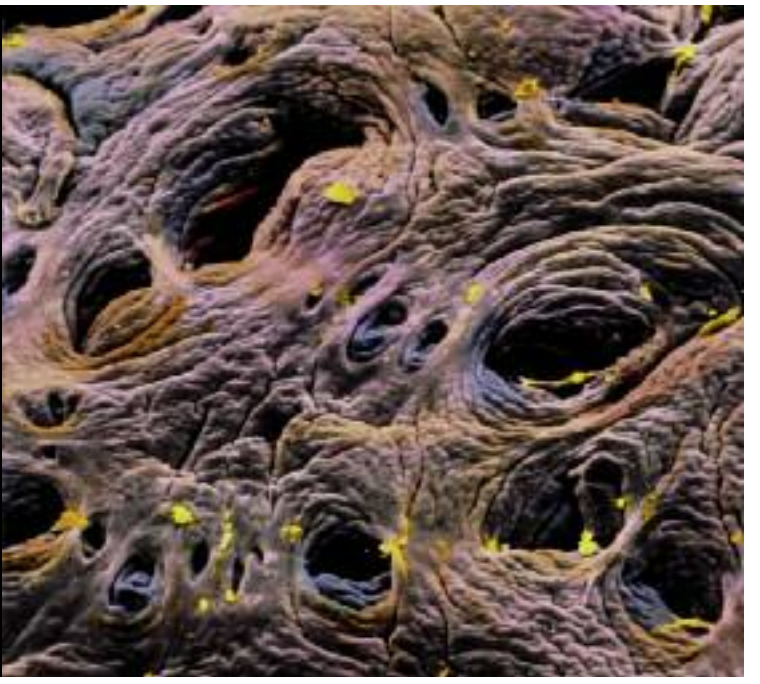
Coeliac disease: new tests, new genes and rising prevalence



BOB ANDERSON PhD, FRACP

New guidelines suggest that patients with digestive symptoms, unexplained weight loss or anaemia should be serologically tested for coeliac disease, or genetic gluten intolerance as it might preferably be called.

MedicineToday 2011; 12(6): 69-71

REMEMBER

- Recent data suggest that coeliac disease is becoming more common, not just because of increased clinical awareness, but also because the incidence is climbing. In the USA, the incidence of young males who are seropositive for both anti-tissue transglutaminase antibodies (tTG IgA) and endomysial antibodies rose almost five-times over 50 years to 0.9% in 2000.[1] A similar rise has been observed in Finland, with a doubling in the prevalence of coeliac disease since 1980 to about 2% of the adult population in 2000.[2] A rising prevalence of coeliac disease has been associated with a generally milder presentation; however, recent reports indicate an increased mortality associated with unrecognised coeliac disease whether it be manifest by subtotal villous atrophy or subtle intraepithelial lymphocytosis on small bowel histology.[3]
- There is a steady shift among some opinion leaders to adopt the concept of 'genetic gluten intolerance' rather that the current diagnostic term 'coeliac disease'.[4] Such a change acknowledges the limitations of diagnosis based ultimately on small bowel histology with demonstration of villous atrophy. Various technical shortcomings of small bowel histology in the diagnosis of coeliac disease result in a false-negative rate of at least 10%. A recent Finnish study indicates that the severity of small bowel damage steadily progresses from mild to severe in patients who are seropositive for tTG IgA, possess the susceptibility genes for coeliac disease (*HLA DQ2* or *DQ8*) and continue to consume a normal diet.[4] Digestive symptoms often respond to a gluten-free diet in patients who are sero-positive for tTG IgA and possess the *HLA DQ2* or *DQ8* genes but do not fulfil the present histological criteria for coeliac

Dr Anderson is a Laboratory Head in the Division of Immunology at the Walter and Eliza Hall Institute, and a gastroenterologist at the Alfred Hospital and The Royal Melbourne Hospital. Melbourne, Vic. He is also Chief Scientist/Chief Medical Officer for ImmusanT Inc., Cambridge, MA, USA.

Series Editor: Professor Anne Duggan, FRACP, MHP, PhD, Associate Director, Clinical Governance, Hunter New England Area Health; Senior Staff Specialist in Gastroenterology, John Hunter Hospital; and Conjoint Professor, University of Newcastle, NSW.

The views published in this Series are those of the author and not necessarily indicative of those held by all members of the Digestive Health Foundation or GESA.

TABLE. CLINICAL FEATURES THAT WARRANT TESTING FOR COELIAC DISEASE ACCORDING TO NATIONAL INSTITUTE OF HEALTH AND CLINICAL EXCELLENCE (NICE)[5]*

A. Offer serological testing to children and adults with any of the following signs, symptoms and conditions

Signs and symptoms

- Chronic or intermittent diarrhoea
- Failure to thrive or faltering growth (in children)
- Persistent or unexplained gastrointestinal symptoms including nausea and vomiting
- Prolonged fatigue ('tired all the time')
- Recurrent abdominal pain, cramping or distension
- Sudden or unexpected weight loss
- Unexplained iron-deficiency anaemia or other unspecified anaemia

Conditions

- Autoimmune thyroid disease
- Dermatitis herpetiformis
- Irritable bowel syndrome
- Type 1 diabetes
- First-degree relatives (parents, siblings or children) with coeliac disease

B. Consider offering serological testing to children and adults with any of the following

- Addison's disease
- Amenorrhoea
- Aphthous stomatitis (mouth ulcers)
- Autoimmune liver conditions
- Autoimmune myocarditis
- Chronic thrombocytopenia purpura
- Dental enamel defects
- Depression or bipolar disorder
- Down syndrome
- Epilepsy
- Low-trauma fracture
- Lymphoma
- Metabolic bone disease (such as rickets or osteomalacia)
- Microscopic colitis
- Persistent or unexplained constipation
- Persistently raised liver enzymes with unknown cause
- Polyneuropathy
- Recurrent miscarriage
- Reduced bone mineral density
- Sarcoidosis
- Sjögren's syndrome
- Turner syndrome
- Unexplained alopecia
- Unexplained subfertility

* National Institute for Health and Clinical Excellence (2009). Adapted from *Clinical Guideline 86. Coeliac disease: recognition and assessment of coeliac disease*. London: NICE. Available from www.nice.org.uk/guidance/CG86. Reproduced with permission.

disease (i.e. the presence of villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis in the small intestinal mucosa).[4] However, there remains no place for the diagnosis of coeliac disease based on symptoms responsive to a gluten-free diet alone or in the presence of anti-gliadin IgG or IgA.

ASSESSMENT

- Evidence-based guidelines released by the UK National Institute of Health and Clinical Excellence (NICE) now support case finding for coeliac disease in a substantial number of patients presenting to GPs.[5]
- The NICE report finds that serological testing for coeliac disease is appropriate in patients with digestive symptoms (including diarrhoea and constipation), unexplained weight loss or anaemia with or without digestive symptoms, and in children with failure to thrive or faltering growth. In fact, screening for and consideration of coeliac disease is considered appropriate for many patients presenting to their GPs with digestive symptoms (Table). A recent randomised trial indicates that there is an improved quality of life and nutritional parameters in asympto - matic, screen-detected patients with coeliac disease when they are treated with a gluten-free diet.[6]
- According to the economic analysis performed by NICE, testing for coeliac disease in these patient groups is more cost-effective than many of the screening procedures widely imple-mented in general practice, such as mammography, and reduces the use of sometimes extensive and inappropriate investigations.[7]
- Despite extensive evidence supporting widespread case finding for coeliac disease, Medicare item number claims indicate rates of testing varies substan-tially between states and territories. Per capita testing in eastern states is higher than in South Australia and Western Australia, and overall testing is disproportionately focused on adult females.[8] These trends in testing are at odds with the epidemiology of coeliac disease; most cases of coeliac disease could be diagnosed if 7-year-old children were screened, and males are also commonly affected.[2,9]
- Increasingly, it is apparent that serological screening for tTG IgA misses 10 to 20% of cases of coeliac disease. However, addition of new-generation serological tests for deamidated gliadin peptide (DGP) antibodies to tTG IgA increases the sensitivity of this screening test; DGP serology is far superior to the traditional whole protein-based gliadin enzyme-linked immunosorbent assays.[10] Use of the combination of tTG IgA and DGP IgG appears to overcome the need to test total IgA levels to detect patients with coeliac disease who are IgA deficient and also detects some further patients who are seronegative for tTG IgA.[11]
- Genome-wide association studies indicate that the genes implicated in

coeliac disease shape cellular and innate immunity rather than the gut epithelium.[12] More than two-thirds of the 40 genes implicated in coeliac disease are also associated with various autoimmune diseases, in particular type 1 diabetes. These recent findings offer an explanation for the over-representation of autoimmune thyroid, adrenal and liver diseases along with Sjögren's syndrome and type 1 diabetes in patients with coeliac disease. However, alleles encoding *HLA DQ2* and *DQ8* remain by far the most important genes determining risk for coeliac disease, and the absence of these genes effectively excludes the presence of coeliac disease.[13]

MANAGEMENT

- Several therapeutic developments offer the prospect of agents to complement the use of a gluten-free diet.[14]
- In Australia, clinical development of an agent to re-establish immune tolerance to gluten is underway; a successful phase 1 clinical trial of the agent Nexvax2 has recently been reported.[15]
- Meanwhile, the efficacy of a gluten-free diet is increasingly questioned as follow-up biopsy one to two years after exclusion of gluten from the diet becomes more widely practised. Overseas studies indicate histological healing of the gut occurs in fewer than half of adult patients after five years on a gluten-free diet.[16] Long-term failure to heal the small intestine is associated with increased osteoporosis and possibly cancer.[17]
- More data on this important issue are awaited, but increased and more systematic clinical follow up by GPs is warranted to ensure adequate compliance with a gluten-free diet and avoidance of complications.

CONCLUSION

Considering the possibility of coeliac disease in the workup of patients with digestive complaints is now standard in general practice. However, coeliac disease continues to be overlooked in men and children, and especially as an explanation for atypical presentations.

The rising incidence and robust clinical evidence now support early and wide usage of serology to address the possibility of unrecognised coeliac disease in many patients presenting to GPs. MT

REFERENCES

1. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology 2009; 137: 88-93.
2. Lohi S, Mustalahti K, Kaukinen K, et al. Increasing prevalence of coeliac disease over time. Aliment Pharmacol Ther 2007; 26: 1217-1225.
3. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. JAMA 2009; 302: 1171-1178.
4. Kurppa K, Collin P, Viljamaa M, et al. Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study. Gastroenterology 2009; 136: 816-823.
5. National Institute for Health and Clinical Excellence. Clinical guideline 86. Coeliac disease: recognition and assessment of coeliac disease. London (UK); 2009. Available at: http://www.nice.org.uk/CG86 (accessed May 2011).
6. Kurppa K, Collin P, Lindfors K, et al. Should screen-detected and asymptomatic celiac disease patients be treated? A prospective, randomized trial. Digestive Disease Week 2011, Chicago. Abstract 620.
7. Stout NK, Rosenberg MA, Trentham-Dietz A, et al. Retrospective cost-effectiveness analysis of screening mammography. J Natl Cancer Inst 2006; 98: 774-782.
8. Medicare Australia. Medicare Group Reports. Available at: https://www.medicareaustralia.gov.au/statistics/mbs_group.shtml (accessed May 2011).
9. Bingley PJ, Williams AJ, Norcross AJ, et al; Avon Longitudinal Study of Parents and Children Study Team. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. BMJ 2004; 328: 322-323.
10. Collin P, Mäki M, Kaukinen K. Revival of gliadin antibodies in the diagnostic work-up of celiac disease. J Clin Gastroenterol 2010; 44: 159-160.
11. Sugai E, Hwang HJ, Vázquez H, et al. New serology assays can detect gluten sensitivity among enteropathy patients seronegative for anti-tissue transglutaminase. Clin Chem 2010; 56: 661-665.
12. Dubois PC, Trynka G, Franke L, et al. Multiple common variants for celiac disease influencing immune gene expression. Nat Genet 2010; 42: 295-302.
13. Hadithi M, von Blomberg BM, Crusius JB, et al. Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. Ann Intern Med 2007; 147: 294-302.
14. US National Institutes of Health. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/results?term=celiac+disease (accessed May 2011).
15. Brown GJ, Daveson J, Marjason JK, et al. A phase 1 study to determine the safety, tolerability and bioactivity of Nexvax2 in HLA DQ2+ volunteers with celiac disease following a long-term, strict gluten-free diet. Digestive Disease Week 2011, Chicago. Abstract Su1235.
16. Bardella MT, Velio P, Cesana BM, et al. Coeliac disease: a histological follow-up study. Histopathology 2007; 50: 465-471.
17. Kaukinen K, Peräaho M, Lindfors K, et al. Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease. Aliment Pharmacol Ther 2007; 25: 1237-1245.

COMPETING INTERESTS: Dr Anderson is a Director and substantial shareholder of Nexpep Pty Ltd, and ImmusanT Inc. (USA). He has been a consultant for INOVA Diagnostics (USA), Prometheus Laboratories (USA) and Given Imaging (USA).