Diagnosing coeliac disease in children

Small bowel biopsies and histology had been the gold standard for diagnosis of coeliac disease, an immune-mediated systemic disorder. European guidelines recommend that in certain symptomatic patients, coeliac disease can be diagnosed without small bowel biopsies. A gluten-free diet is the only method of managing coeliac disease.

The British Society of Paediatric Gastroenterology, Hepatology and Nutrition defines coeliac disease as: 'an immune mediated systemic disorder elicited by ingestion of gluten and related prolamines in genetically susceptible individuals and characterised by the presence of a variable combination of gluten dependent clinical manifestations, coeliac disease specific antibodies, human leucocyte antigen (HLA)-DQ2 or HLA-DQ8 haplotypes and enteropathy' (Murch et al, 2013). Gluten is found in wheat, rye and barley. Coeliac disease most commonly presents with gastrointestinal symptoms of persistent diarrhoea, abdominal pain and weight loss (Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition, 1990; Mehta et al, 2008; Husby et al, 2012). However, symptoms may also include unexplained iron deficiency anaemia, idiopathic short stature, faltering growth, constipation, liver disease, arthropathy, mouth ulcers, muscle weakness, delayed menarche or onset of puberty, dermatitis herpitiformis and in older people infertility and osteoporosis (Mehta et al, 2008; National Institute for Health and Care Excellence, 2009; Husby et al, 2012; Murch et al, 2013).

The changing face of coeliac disease

Over the last 20 years, understanding of coeliac disease has changed from an uncommon enteropathy (incidence 1 in 2500 to 3000) to a multi-organ disease with a strong genetic predisposition associated with HLA-DQ2 and HLA-DQ8 (Hawkes et al, 2000; Bingley et al, 2004; Mehta et al, 2008; Husby et al, 2012; Jenkins et al, 2012). The incidence of coeliac disease in children based on a number of paediatric studies including the confidential Avon Longitudinal Study of Parents and Children (ALSPAC) was found to be 1% (Bingley et al, 2004). Despite greater awareness, 90% of cases of coeliac disease remain unidentified and hence coeliac disease exhibits the 'tip of the iceberg' phenomenon (National Institute for Health and Care Excellence, 2009). This is further evident from the birth cohort study of 5470 children who underwent serological screening at 7.5 years of age in the confidential ALSPAC study. Some of them had subsequent confirmed coeliac disease with biopsy and histology, but because the ALSPAC study was anonymous other seropositive children could not be individually identified to undergo small bowel biopsy (Ravikumara et al, 2007).

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Current practice

Diagnosis of coeliac disease in children has been based on symptom recognition followed by serological screening, and subsequent small bowel biopsies and histology, based on the modified Marsh classification of gluten-induced small intestinal damage, as recommended by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines (Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition, 1990; National Institute for Health and Care Excellence, 2009). Histological confirmation has been considered the 'gold standard' for diagnosis of coeliac disease in children. It is imperative that they remain on a normal gluten-containing diet until the small bowel biopsies are taken (National Institute for Health and Care Excellence, 2009). Each child with suspected coeliac disease previously required hospital admission to undergo an oesophago-duodenoscopy, commonly performed under general anaesthetic, to obtain small bowel biopsies. Waiting time to endoscopy could be prolonged. The tools for screening for coeliac disease have improved as a result of the availability of coeliac disease-specific antibody tests, based mainly on IgA-based anti-tissue transglutaminase (Abrams et al, 2006). IgA level should be checked as 1% of children with coeliac disease are known to be IgA deficient (Abrams et al, 2006; National Institute for Health and Care Excellence, 2009; Jenkins et al, 2012).

Guidelines for non-biopsy diagnosis of coeliac disease

In 2012, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines were modified and now recommend that a diagnosis of coeliac disease can be made without small bowel biopsies in symptomatic patients with an anti-tissue transglutaminase titre of >10 times the upper limit of normal (10xULN) and who are also positive for HLA-DQ2 and/or DQ8 (Husby et al, 2012). These children also need to have a blood sample taken for anti-endomysial antibody (EMA) at the same time that they are tested for HLA DQ2/DQ8 (*Figure 1*). Following the release of the

European Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines, the revised joint British Society of Paediatric Gastroenterology, Hepatology and Nutrition and Coeliac UK guidelines for the diagnosis and management of coeliac disease were released, avoiding the need to confirm diagnosis on histology obtained from small bowel biopsies in a specific group of patients. This is an important shift in diagnostic strategy, aimed at simplifying and shortening the diagnostic pathway in selected symptomatic cases (Murch et al, 2013). The association between positive HLA-DQ2/DQ8 and serological testing was found to have a high predictive value for coeliac disease in children with a sensitivity of 98.8% and a specificity of 96.2% (Clouzeau-Girard et al, 2011). It is important to note that HLA DQ2/DQ8 can also be positive in the normal population and a positive result in isolation does not mean the patient has coeliac disease.

Having introduced these guidelines to readers, this article examines some of the available literature on the selective use of high anti-tissue transglutaminase titres in diagnosing coeliac disease in symptomatic children without a biopsy (*Table 1*). The authors also provide a simple algorithm for clinical practice (*Figure 1*) where the guidelines are applicable. It must be remembered that the guidelines are not applicable in cases where the anti-tissue transglutaminase titre is <10xULN, the child is asymptomatic and/or positive anti-tissue transglutaminase titres were detected on screening. The new diagnostic pathway is also not applicable in cases where the anti-tissue transglutaminase titres are >10xULN but the HLA DQ2 or HLA DQ8 status is negative (Husby et al, 2012; Murch et al, 2013). These children will still need an endoscopic small bowel biopsy and histology to confirm the diagnosis of coeliac disease (Husby et al, 2012; Murch et al, 2013).

Asymptomatic children at risk of coeliac disease

Clinicians need to be aware of the group of children who may be asymptomatic but are considered to have an increased lifetime risk of developing coeliac disease. This group includes children identified following family screening for first degree relatives with coeliac disease or for other autoimmune conditions such as type 1 diabetes, autoimmune thyroiditis, autoimmune liver disease, selective IgA deficiency, and children with unexplained raised levels of transaminases without known liver disease. This group also includes children with certain genetic conditions: Down, Williams and Turner syndromes (National Institute for Health and Care Excellence, 2009; Jenkins et al, 2012; Murch et al, 2013). According to the guidelines, this group of asymptomatic children still requires small bowel biopsy for confirmation of a diagnosis of coeliac disease, even in situations where the anti-tissue transglutaminase titres are >10xULN (Husby et al, 2012; Murch et al, 2013).

Figure 1. Algorithm for diagnosis of coeliac disease in symptomatic children. EMA = endomysial antibody; tTG = anti-tissue transglutaminase; ULN = upper limit of normal.

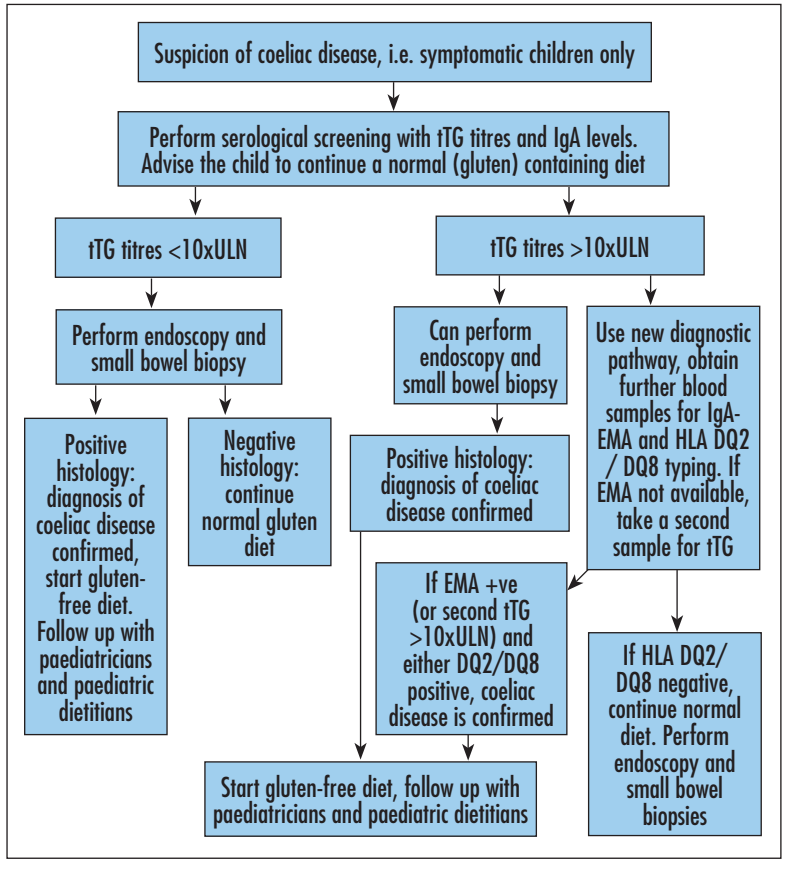

Table 1. Analysis of studies comparing high tTG titres (>10xULN) to histological diagnosis of coeliac disease

Authors	Nature of study	Total number of children	Number of children with tTG >10xULN	Positive biopsy with tTG >10xULN	Sensitivity
Barker et al (2005)	Retrospective chart review of data	103	49	48	98%
Vivas et al (2009)	Prospective recruitment in two tertiary centres	97 (age ≤14 years)	91	90	99%
Al-Musawi (2010)	Case control study	116	72	70	97%
Mubarak et al (2011)	Retrospective analysis	283	128	124	97%
Mubarak et al (2012)	Prospective recruitment	183	87	87	100%
Onyeador at al (2014)	Prospective recruitment	126	58	57	98%

tTG = anti-tissue transglutaminase; ULN = upper limit of normal.

Clinical bottom line

The incidence of coeliac disease in children is increasing and the clinical presentation is changing – severe gastrointestinal symptoms are less prevalent and diagnosis is being made at an older age. A significant proportion of asymptomatic children is also likely to be identified on serological screening and subsequent biopsies. The overall incidence of paediatric coeliac disease appears to be increasing, as highlighted in a retrospective cohort study from southeast Scotland where a 6.4-fold increase has been noted over 20 years (1990–2009) (White et al, 2013). A shift to an older age at diagnosis has been noted in different studies including an epidemiological study from South Wales: the median age at diagnosis increased to 14 years between 2005 and 2011 from a median age of diagnosis at 8 years between 1999 and 2004 (Whyte and Jenkins, 2013).

The European Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines on selective use of anti-tissue transglutaminase titres of >10xULN along with a positive HLA DQ2 and/or DQ8 status in diagnosing coeliac disease in children without a small bowel biopsy is likely to diminish the diagnostic time and be cost effective. However, children diagnosed with coeliac disease either through the new diagnostic pathway or by the biopsy route will need a lifelong gluten-free diet. They will continue to need to be seen by the paediatrician or paediatric gastroenterologist and specialist dietitian to confirm the diagnosis, give support with the diet to ensure adherence and to monitor for possible complications.

Conclusions

Coeliac disease is a lifelong condition and a gluten-free diet is the only available management. Improved sensitivity and specificity of serological screening and increased awareness of the condition has improved the identification and diagnosis of coeliac disease. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines on diagnosing coeliac disease without the need for small bowel biopsy in symptomatic children are expected to decrease the time to diagnosis, be less invasive for the child and family and are likely to be financially beneficial to health services. It remains essential for patients with suspected coeliac disease to be seen by a paediatrician or paediatric gastroenterologist and dietitian for diagnosis and long-term follow up. **BJHM**

KEY POINTS

- Children with suspected coeliac disease whose anti-tissue transglutaminase titres are <10x the upper limit of normal or are asymptomatic still require small bowel biopsies and histology for diagnosis.
- All children with suspected coeliac disease should be referred to a specialist, including symptomatic patients with anti-tissue transglutaminase titre of >10x the upper limit of normal, and should remain on a normal diet until diagnosis is confirmed.
- Children diagnosed with coeliac disease will require a lifelong gluten-free diet.
- Yearly follow up is needed to review adherence to a gluten-free diet, symptom resolution and identification of other autoimmune associations such as diabetes and hypothyroidism.
- Consider diagnosing coeliac disease serologically in symptomatic children whose anti-tissue transglutaminase titres are >10x the upper limit of normal, have positive endomysial antibody tests and who have a positive HLA DQ2 or DQ8 status.

Conflict of interest: none.

Abrams JA, Brar P, Diamond B et al (2006) Utility in clinical practice of immunoglobulin A anti-tissue transglutaminase antibody for the diagnosis of celiac disease. *Clin Gastroenterol Hepatol* **4**: 726–30

Al-Musawi ZM (2010) Is high tissue transglutaminase antibody titers enough to diagnose celiac disease in children? *Karbala J Med* **3**(3): 860–6

Barker CC, Mitton C, Jevon G et al (2005) Can tissue transglutaminase antibody titers replace small-bowel biopsy to diagnose celiac disease in select pediatric populations? *Pediatrics* **115**(5): 1341–6

Bingley PJ, Williams AJ, Norcross AJ et al (2004) Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. *BMJ* **328**(7435): 322–3

Clouzeau-Girard H, Rebouissoux L, Taupin JL et al (2011) HLA-DQ genotyping combined with serological markers for the diagnosis of celiac disease: is intestinal biopsy still mandatory? *J Pediatr Gastroenterol Nutr* **52**(6): 729–33

Hawkes ND, Swift GL, Smith PM, Jenkins HR (2000) Incidence and presentation of coeliac disease in South Glamorgan. *Eur J Gastroenterol Hepatol* **12**(3): 345–9

Husby S, Koletzko S, Korponay-Szabó IR et al (2012) European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* **54**(1): 136–60

Jenkins HR, Murch SH, Beattie RM et al (2012) Diagnosing coeliac disease. *Arch Dis Child* **97**(5): 393–4

Mehta G, Taslaq S, Littleford S et al (2008) The changing face of coeliac disease. *Br J Hosp Med (Lond)* **69**(2): 84–7

Mubarak A, Wolters VM, Gerritsen SA et al (2011) A biopsy is not always necessary to diagnose celiac disease. *J Pediatr Gastroenterol Nutr* **52**(5): 554–7

Mubarak A, Wolters VM, Gmelig-Meyling FH et al (2012) Tissue transglutaminase levels above 100 U/mL and celiac disease: a prospective study. *World J Gastroenterol* **18**(32): 4399–403

Murch S, Jenkins H, Auth M et al (2013) Joint BSPGHAN and Coeliac UK guidelines for the diagnosis and management of coeliac disease in children. *Arch Dis Child* **98**(10): 806–11

National Institute of Health and Care Excellence (2009) Recognition and assessment of coeliac disease. CG86. www.nice.org.uk/cg86 (accessed 6 March 2014)

Onyeador N, Jennings N, Paul SP et al (2014) The relationship between tissue transglutaminase antibody titres and histological classification in coeliac disease. *Arch Dis Child* **99**(Suppl 1): A34 (doi: 10.1136/archdischild-2014-306237.80)

Ravikumara M, Nootigattu VK, Sandhu BK (2007) Ninety percent of celiac disease is being missed. *J Pediatr Gastroenterol Nutr* **45**(4): 497–9

Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition (1990) Revised criteria for diagnosis of coeliac disease. *Arch Dis Child* **65**(8): 909–11

Vivas S, Ruiz de Morales JG, Riestra S et al (2009) Duodenal biopsy may be avoided when high transglutaminase antibody titers are present. *World J Gastroenterol* **15**(38): 4775–80

White LE, Merrick VM, Bannerman E et al (2013) The rising incidence of celiac disease in Scotland. *Pediatrics* **132**(4): e924–31

Whyte LA, Jenkins HR (2013) The epidemiology of coeliac disease in South Wales: a 28-year perspective. *Arch Dis Child* **98**(6): 405–7