

# COELIAC DISEASE IN CHILDREN: A DIAGNOSTIC CHALLENGE

The diagnosis of coeliac disease in young children can often be elusive. However, given the severity of symptoms and the effectiveness of dietary management, the importance of early diagnosis is paramount. Here, Siba Paul and Christine Spray explore the lessons from two case studies.

**Dr Siba Prosad Paul**

Specialty Trainee  
Year 6 in  
Paediatric  
Gastro-  
enterology,  
Bristol Royal  
Hospital for  
Children

**Dr Christine Spray**

Consultant  
Paediatric  
Gastro-  
enterologist,  
Bristol Royal  
Hospital for  
Children

Coeliac disease (CD) has been defined by NICE as 'a state of heightened immunological response to ingested gluten in genetically susceptible people'.<sup>1</sup> It is an autoimmune enteropathy typically affecting the proximal small intestine and is characteristically seen in people who have a genetic susceptibility to 'gluten' protein found in wheat, rye, barley and oats.<sup>2,3</sup> CD occurs in about 1% of children, classically presenting with gastrointestinal symptoms such as diarrhoea, abdominal pain, bloating and indigestion.<sup>1,3</sup> However, atypical features can cause significant diagnostic challenge and delay.<sup>3,4</sup> CD is different from wheat intolerance, and differential diagnosis is crucial to preventing long term complications such as osteoporosis, infertility and small lymphoma.

## CHALLENGING CASES FROM CLINICAL PRACTICE

### Case 1: unexplained anaemia

Hassan, a 2-year-8-month boy, reported as healthy with regular bowel habit, was detected to be pale by his GP and was referred for blood investigations. This showed unexpectedly low haemoglobin (Hb) 2.8gm/dl (normal 11.5–15.5gm/dl). Although leukaemia or serious haematological disorder was initially suspected, blood analysis showed features consistent with chronic iron deficiency anaemia (IDA).

He was admitted to the paediatric ward for monitoring, iron supplements were started and further investigations were undertaken to determine the cause of his unexplained IDA. Screening blood tests suggested CD (positive IgA tissue transglutaminase [tTGA] and IgA endomyseal antibodies [EMA] titres), which was confirmed by endoscopy and intestinal biopsy. Dietetic history revealed adequate iron intake and drinking around 450mls of cow's milk (age appropriate). Hassan's parents were informed about the diagnosis of CD and he was immediately started on a strict gluten-free diet (GFD). His iron levels returned to normal in 4 months solely on oral iron supplements and GFD.

### Case 2: Impaired growth

Sophie, a 13-year-old girl was noted to have impaired growth and delayed onset of puberty by the school nurse. She also complained of feeling very tired and failing to keep pace with peers during physical activities. After repeated visits to the GP, the girl was referred for a non-urgent appointment with local paediatricians. While awaiting clinic assessment, she acutely presented to the emergency department with abdominal pain and irregular bowel habits. Pallor was noted and faecal loading was confirmed on abdominal palpation. Her weight and height were on 0.4th centile; this had fallen from 75th centile over the preceding three years. An abdominal X-ray ruled out acute intestinal obstruction but showed constipation. Haemoglobin was 4.8 gm/dl with severe hypochromia and microcytosis consistent with IDA. She was admitted to the paediatric ward, iron supplementation was started and further investigations were sent in view of IDA. A dietetic history revealed that she was drinking 1 to 1.5 litres of cow's milk per day. Tests showed normal thyroid function and tTGA of >100 unit/L (normal range 0 – 5 U/L). The diagnosis of CD was subsequently confirmed by an endoscopic duodenal biopsy. She was started on a GFD by the specialist dietitian and IDA resolved with oral iron supplementation; puberty progressed well and growth accelerated on GFD.

## Discussion

Both children were referred from primary care without a suspicion of CD, and serious pathologies such as leukaemia and acute intestinal obstruction were initially considered. Only on further investigation was a diagnosis of CD confirmed. It is important that health professional

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working with children remain aware of the varied presentations of CD.

### Epidemiology

The clinical features of childhood CD were first described in 1888 by Samuel Gee.<sup>3</sup> Willem Dicke, a Dutch paediatrician, first described the aetiology of CD who in the 1940s and developed the concept of GFD as the treatment for CD.<sup>3,5</sup> The prevalence of CD is approximately 1% (both in children and adults), although some studies found the incidence of CD ranging from 0.18% to 5.66%. CD is considered to exhibit a 'tip-of-the-iceberg' phenomenon, with only about 10% of cases being diagnosed.<sup>6</sup> The overall incidence of CD among children appears to be increasing, perhaps due to increased awareness among parents and health professionals, but also possibly due to the availability of reliable screening tests.<sup>1,7</sup>

It is important that health professionals have a lower threshold of considering CD in general, but particularly in high-risk groups: children with autoimmune conditions, such as type 1 diabetes, autoimmune thyroid disease and alopecia areata, and in first degree relatives of children with CD.<sup>1</sup> CD has also been found in association with IgA deficiency, Down's syndrome, Turner's syndrome and Williams' syndrome.<sup>3</sup> Children belonging to genotypes HLA DQ2 (seen in 20% of Caucasians, North Africans, South and West Asians) and HLA DQ8 (10% of all Caucasians and Asians) are at high risk for CD.<sup>7,8</sup>

### Clinical features

Classically, CD is seen in young children (6 months to 2 years) presenting with gastrointestinal symptoms,

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such as abdominal discomfort, bloating, flatulence and vomiting; sometimes with signs of malabsorption, such as diarrhoea, steatorrhoea, weight loss, failure to thrive and developmental regression due to muscle weakness secondary to fat soluble vitamin-E deficiency.<sup>1,3,4,7</sup>

Children with CD can be relatively asymptomatic, but CD should be considered in children with IDA, hepatitis, short stature or delayed onset/progress of puberty. Some children with normal growth may also present with constipation due to compensatory water absorption by distal intestine.<sup>1,3,4</sup> Studies have suggested that CD may be the cause of short stature in 2–8% of children with no gastrointestinal symptoms.<sup>4</sup>

### Diagnosing CD

Significant progress in serological testing has made testing and diagnosis of CD easier.<sup>7</sup> However, the first step towards diagnosis is a suspicion about CD from the history, followed by serological testing. Table 1 highlights the recommendations made by NICE and the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) on criteria for serological testing.<sup>1,7</sup> The initial blood tests can be arranged in the primary care; a referral may be made to secondary care if the child is unwell (as highlighted in our case studies) or in young child where phlebotomy may be technically difficult. All children with a diagnosis of possible CD should be referred to a paediatrician or paediatric gastroenterologist. It is essential that even with positive coeliac serology, the patient remains on a normal diet until seen by a paediatrician, as further testing by endoscopy and small bowel biopsy may be required.<sup>1,3,12</sup>

**TABLE 1: WHEN TO DO SEROLOGICAL TESTING FOR CD<sup>1,7,9</sup>**

■ Chronic constipation or vomiting
■ Chronic or intermittent diarrhoea
■ Dental enamel hypoplasia (thinning enamel) of permanent teeth (symmetric distribution)
■ Failure to thrive or faltering growth (in children)
■ Idiopathic short stature
■ Prolonged fatigue ('tired all the time')
■ Recurrent abdominal pain, cramping or distension
■ Sudden or unexpected weight loss
■ Unexplained IDA, IDA non-responsive to treatment or other unspecified anaemias.
■ Dermatitis herpetiformis.

Studies have shown that tTGA is the best screening test for diagnosing CD, and EMA should be reserved if the result of tTGA test is equivocal.<sup>1,10,11</sup> Children with IgA deficiency will have falsely low tTGA levels (screening therefore will miss CD); so IgA levels should be requested by the GP at the same time while ordering screening blood investigations for CD.<sup>3</sup> Other blood tests, such as full blood count, liver function, urea and electrolytes, and fat soluble vitamins (A,D,E,K), may be indicated in patients with significant nutritional compromise.<sup>1,3</sup>

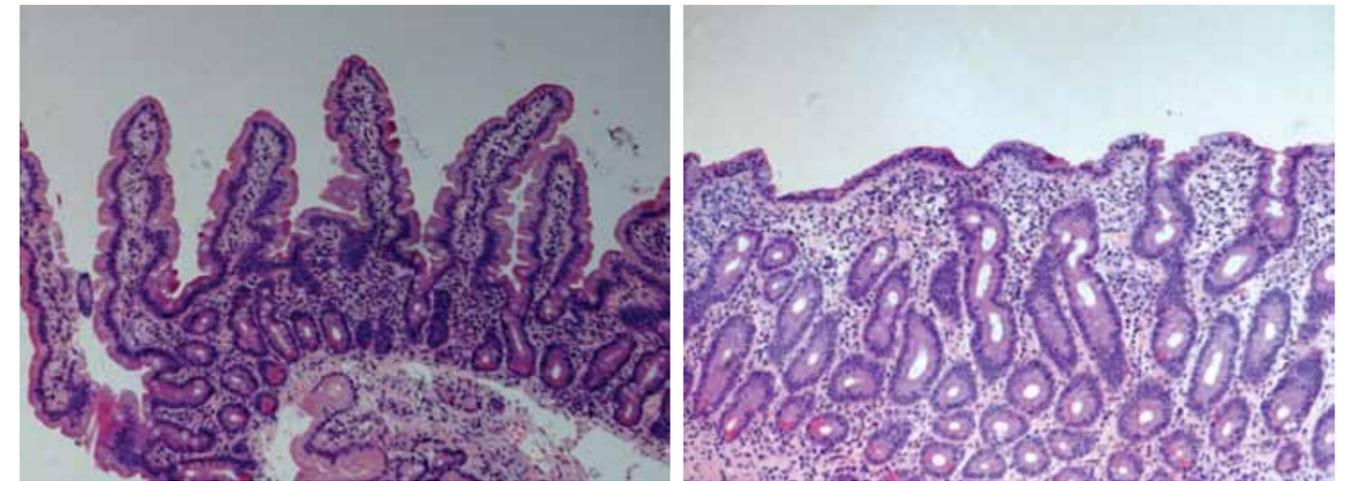


Fig1. Small intestinal mucosa: normal (l) and in CD (r)

*Upper gastrointestinal endoscopy and biopsy remains the gold standard for diagnosing CD in children.<sup>1</sup>*

Upper gastrointestinal endoscopy and biopsy remains the gold standard for diagnosing CD in children.<sup>1</sup> It is important that health professionals should inform parents and older children not to selectively withdraw gluten from their diet prior to the biopsy test, otherwise the results will be falsely negative.<sup>1,3,12</sup> Ideally the GFD should only be started once the histological results become available and confirm the diagnosis. Recent changes in guidelines from the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) have suggested that small bowel biopsy may be unnecessary in symptomatic patients but only in the presence of high titres, i.e. tTGA > 150 U/L with a positive result for HLA DQ2/DQ8. These children still need to be referred to paediatricians and paediatric dietitians.<sup>9</sup> Macroscopic findings at endoscopy may show reduced or absent duodenal folds and flattening of mucosa, while histopathology would show structural loss of villi in small intestine (see Figure 1).<sup>1,3</sup>

Genetic testing (HLA DQ2/DQ8) should be reserved for special situations and not requested as an initial investigation.<sup>1</sup> The high negative predictive value of HLA testing may be useful to paediatric gastroenterologists in specific clinical situations, such as positive tTGA and negative/equivocal biopsy results, or where parents may refuse an endoscopy biopsy testing.<sup>1</sup>

If the picture remains unclear, it is important to consider other diagnoses. These may include cow's

milk protein intolerance, food allergy, postenteritis syndrome, Crohn's disease, irritable bowel syndrome, bacterial overgrowth, giardiasis, tropical sprue, Whipple disease, autoimmune enteropathy, and common variable immunodeficiency.<sup>8,12</sup>

### Management of CD

CD is a lifelong condition and the diagnosis should be explained to the family in simple language, and through an interpreter if necessary.<sup>3,12</sup> It is preferable that the news is given jointly by the paediatrician and specialist paediatric dietitian, so that the implications about the diagnosis of CD is well explained and true emphasis is given about the need for a lifelong GFD. Dietitians play a very important role in educating families on both identification and avoidance of foods and other substances (e.g. play dough) containing gluten.<sup>3</sup> Due consideration about dietary needs of different cultural groups is necessary, and discussion about GFD should be tailored to suit their cultural needs while advising substitute food items; otherwise adherence is unlikely to be successful.<sup>12</sup> GPs have a key supportive role in prescribing appropriate gluten free products to maximise adherence to a GFD.<sup>1</sup>

GPs also have an important part to play in facilitating serological testing for first degree relatives, which should be arranged in the primary care setting after adequate counseling. This may identify CD in some asymptomatic relatives;<sup>13</sup> a study involving 484 first-degree relatives (of 195 patients) confirmed a higher prevalence (4.8%) of CD in this specific group.<sup>2</sup>

Children with CD are followed up at least once every year in secondary care; however, GPs also play an important role in monitoring growth, onset and progress of puberty and resolution of symptoms, as well as checking for 'red flags', such as loss of weight and bedwetting, in order to help ensure that other autoimmune associations such as diabetes, hypothyroidism, etc are not silently developing.<sup>14</sup> Families

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should be encouraged to join the charity Coeliac UK (<http://www.coeliac.org.uk>), which has an expert helpline and publishes an annual directory of GFD food and drink, listing around 9,000 products.

It is important to note that tTGA and intestinal mucosa will return to normal if GFD is strictly followed. Serological re-testing is required after 6 months of starting GFD to demonstrate that the levels have returned to normal. Further serological testing, although not routinely advised, may be useful for children who continue to report symptoms relating to CD and when non-adherence to strict GFD is suspected. GPs need to highlight issues with non-adherence or development of any associations to the child's paediatrician so that appropriate management can be initiated early. Children with asymptomatic CD (detected on screening) may find adherence to GFD difficult in comparison to children who have been symptomatic at diagnosis and are likely to feel much better within weeks of commencing GFD.

### Complications

The consequences of missing a diagnosis of CD – or non-adherence to strict GFD – can vary and may include persistence of gastrointestinal symptoms, impaired nutrition, impaired growth, delayed pubertal development and reduced bone mineralisation (due to impaired calcium absorption), leading to osteoporosis with the concomitant risk of pathological fractures.<sup>1</sup> Studies suggest that this risk is reduced by long-term adherence and compliance with a GFD.<sup>1,3,7,12</sup> Other complications may include bowel cancer (risk normalized to normal population with GFD), spontaneous abortion, low birth weight in offspring and possibly development of other autoimmune disease.<sup>1</sup>

### Conclusion

CD is common in children and diagnosis is often not considered on early presentation. It is important that health professionals working with children have an understanding of both typical and atypical features of CD and make early referral to paediatric services. An appropriate diagnostic approach should include testing with tTGA, followed by a duodenal biopsy on a gluten containing diet. Lifelong GFD is crucial and early involvement of a specialist paediatric dietitian is essential for successful treatment.

GPs play a vital role in supporting, educating and ensuring adherence to GFD, as well as monitoring long term adherence to GFD and development of any complications/associations.

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## KEY POINTS

- 1 CD is an autoimmune enteropathy typically affecting the proximal small intestine. It is clinically different from wheat intolerance
- 2 The prevalence of CD is approximately 1% for all ages
- 3 Only about 10% of cases of CD are diagnosed; therefore increased awareness and vigilance is needed by clinicians
- 4 High risk groups include children with type 1 diabetes, autoimmune thyroid disease, alopecia areata as well as first degree relatives of children with CD
- 5 Typical clues include gastrointestinal symptoms, weight loss, short stature and failure to thrive
- 6 Where CD is suspected, a serological test should usually be arranged by the GP. If positive, the child should be referred to a paediatrician
- 7 A gluten-free diet (GFD), tailored to cultural needs, should be started only once diagnosis is confirmed
- 8 It is important to ensure that first degree relatives of children with newly diagnosed CD are tested for the condition
- 9 CD is a lifelong condition. Undiagnosed CD may cause a range of complications, including gastrointestinal conditions, impaired/delayed development and reduced bone mineralisation.