ORIGINAL ARTICLE

The changing clinical presentation of coeliac disease

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Background: There has been a growing recognition that coeliac disease is much more common than previously recognised, and this has coincided with the increasingly widespread use of serological testing.
Aim: To determine whether the age at presentation and the clinical presentation of coeliac disease have changed with the advent of serological testing.
Methods: A 21-year review of prospectively recorded data on the mode of presentation of biopsy confirmed coeliac disease in a single regional centre. Presenting features over the past 5 years were compared with those of the previous 16 years. Between 1983 and 1989 (inclusive), no serological testing was undertaken; between 1990 and 1998, antigliadin antibody was used with occasional use of antiendomysial antibody and antireticulin antibody. From 1999 onwards, anti-tissue transglutaminase was used.
Results: 86 patients were diagnosed over the 21-year period: 50 children between 1999 and 2004 compared with 25 children between 1990 and 1998 and 11 children between 1983 and 1989. The median age at presentation has risen over the years. Gastrointestinal manifestations as presenting features have decreased dramatically. In the past 5 years, almost one in four children with coeliac disease was diagnosed by targeted screening.
Conclusion: This study reports considerable changes in the presentation of coeliac disease—namely, a decreased proportion presenting with gastrointestinal manifestations and a rise in the number of patients without symptoms picked up by targeted screening. Almost one in four children with coeliac disease is now diagnosed by targeted screening. Most children with coeliac disease remain undiagnosed. Paediatricians and primary care physicians should keep the possibility of coeliac disease in mind and have a low threshold for testing, so that the potential long-term problems associated with untreated coeliac disease can be prevented.

Coeliac disease is now believed to be the most common genetically predetermined condition in humans, with a childhood prevalence of 1% in many European countries and in the US.[1] Major advances in the understanding of this disease have expanded it from a gastrointestinal disease with diarrhoea and malabsorption to a multisystem immunological disorder.[2] With the advent of increasingly sensitive and specific non-invasive serological tests and the use of such tools in patients, especially those in high-risk groups (eg, with family history, type 1 diabetes, autoimmune thyroid and liver disease, Down's syndrome), the ability to identify the disease is increasing.

Serological prevalence data from several studies have indicated that coeliac disease may be far more common in the US, Europe and North Africa than previously thought, with prevalence rates varying between 1:85[3 4] and 1:230,[5] and may also be frequently underdiagnosed in childhood. Therefore, under-reporting of coeliac disease is possible in the UK. This may have important health consequences, as dietary avoidance of gluten results in complete remission of the disease and avoids the two major complications, malignancy and osteoporosis,[6] as well as resulting in a decreased mortality of patients with coeliac disease.[7] We have previously shown a high prevalence of unrecognised coeliac disease in healthcare students, with the incidence of coeliac disease confirmed by biopsy as at least 1 in 166 in this selected young adult population.[8] Most of these affected students were asymptomatic. This incidence is double that of the estimate of 1 in 300[9] described in the current standard UK paediatric textbook is increasing and higher than our previously published data from the 1990s in South Glamorgan, where the incidence was reported as 1:2500 to 1:3000 live births in 1998.[10]

Early reports suggested that there have been considerable changes in the presenting features of coeliac disease in adults[11] and possibly in children,[12] with the dramatic gastrointestinal manifestations as the main presenting feature of coeliac disease in childhood becoming less common. Our hypothesis was that as serological testing has become more prevalent, both the "milder" and asymptomatic cases of coeliac disease will have been increasingly diagnosed. Therefore, we expected a change in the presentation of coeliac disease in childhood over this time. If milder cases are being diagnosed more often and the incidence is not truly increasing in the population, then the age of diagnosis should also rise. The aim of our study was to investigate whether the clinical presentation of coeliac disease in childhood has changed over 20 years.

PATIENTS AND METHODS

The ages and presenting features of children (0–16 years) with coeliac disease seen at the University Hospital of Wales, Cardiff, UK, between February 1983 and August 2004, were recorded prospectively. These case records were also retrospectively cross-checked with our local coeliac disease database maintained in the department, and with histopathology, regional immunology database and dietetic records, to ensure full ascertainment of cases. Children were referred to the unit for endoscopy unit from South and East Wales. Over the study period, the population of children and young adults aged $\leqslant$ 16 years was relatively stable at 200 000 in the relevant geographical area (data from Welsh Assembly Government). All patients were confirmed by biopsy as having coeliac disease according to the criteria set by the European Society of Paediatric Gastroenterology Hepatology and Nutrition.[13] Until 1989, biopsies were performed using the Crosby capsule, and from 1989 all

Table 1 Presenting symptoms of the 50 patients diagnosed with coeliac disease between 1999 and 2004

Symptom	Patients (n)
Diarrhoea	18
Weight faltering	3
Non specific recurrent abdominal pain	8
Constipation	4
Recurrent mouth ulcers	1
Short stature	2
Persistent iron deficiency	1
Targeted screening	13

biopsy specimens were obtained endoscopically by a paediatric gastroenterologist. The age at diagnosis and presenting features of children diagnosed with coeliac disease between 1999 and 2004 were compared with those diagnosed before this period.[14] Between 1983 and 1989 (inclusive), no serological testing was undertaken; between 1990 and 1998 serological testing was carried out using immunoglobin(Ig)A antigliadin antibody (AGA; Pharmacia, Sweden) with occasional use of antiendomysial and antireticulin antibody. From 1999 onwards, IgA anti-tissue transglutaminase was used as the primary serological test (human recombinant TTG kit; Orgentec Diagnostika GmbH, Germany).

RESULTS

Between 1999 and 2004 (inclusive), 50 children were diagnosed with coeliac disease, compared with 25 children between 1990 and 1998, and 11 children between 1983 and 1989. In the past 5 years, the median age at diagnosis was 8 (range 1–16) years compared with 7.5 (range 4.5–10.5) years between 1990 and 1998 and 4 (range 2–6) years between 1983 and 1989, when serological testing was not available. Younger children seemed to present with more gastrointestinal symptoms throughout the study period. In the past 5 years, the median age in the subgroup presenting with gastrointestinal symptoms was 4.5 years compared with the median age of 12 years in those presenting without gastrointestinal symptoms. The median age in the group with symptoms was 5 years compared with 12.1 years in the group without symptoms.

The presenting features altered over this time, with 88% having gastrointestinal manifestations between 1983 and 1989 compared with only 42% during the past 5 years. Table 1 shows the presenting symptoms of children with coeliac disease between 1999 and 2004.

Table 2 shows the presenting features of children with coeliac disease during the three time periods: 1983–9 (no serological testing), 1990–8 (serological testing with AGA and antiendomysial antibody if AGA-positive) and 1999–2004 (serological testing with anti-tissue transglutaminase).

With a stable population of children of 200 000 in the catchment area, the incidence of diagnosis of coeliac disease in children in the past 5 years has doubled to approximately 1 in 4000.

DISCUSSION

The incidence, the age at presentation and the presenting features of coeliac disease in children have changed considerably over the past 20 years. We and others have previously shown a rise in the incidence of coeliac disease in children after the introduction of serological testing.[10 14 15] Also from our present study, clearly, the presentation of coeliac disease has changed over the same period. Our single-centre study shows that the proportion of children presenting with gastrointestinal manifestations (diarrhoea, weight loss and abdominal distension) has decreased, with an increase in non-gastrointestinal manifestations and a rise in the number of asymptomatic patients, identified by targeted screening. Between 1999 and 2004, only 42% of children had gastrointestinal manifestations, with 9 of 50 (18%) children being monosymptomatic, compared with 75–88% of children diagnosed between 1983 and 1998. Clearly, several children present with relatively non-specific symptoms, such as recurrent abdominal pain, constipation and recurrent oral ulceration, in contrast with previous time periods, highlighting the fact that coeliac disease is heterogeneous and more subtle in its presentation than previously recognised.

It is becoming increasingly common for children in high-risk groups for coeliac disease to undergo regular serological screening, although there is ongoing debate on when to start and how often to screen.[4] From 1990, in our centre, we have undertaken targeted screening of those children who have a family history of coeliac disease in a first-degree relative, type 1 diabetes, Down's syndrome, or autoimmune thyroid and liver disease.

Data from studies on adults are similar, with Lo *et al*[11] reporting that of 227 patients only 43% presented with diarrhoea after 1993 compared with 73% before 1993. In a study on the Dutch children, the presentation of coeliac disease in children seems to have changed considerably after 1993 and the introduction of serological testing, with fewer children presenting with diarrhoea and failure to thrive, and more children presenting with lassitude and other non-gastrointestinal symptoms.[16] Our study is the first UK report confirming this change in presentation of coeliac disease in children, with more children presenting with subtle or non-gastrointestinal manifestations and at a later age. Indeed, one in four children with coeliac disease was diagnosed by targeted screening of high-risk groups during the past 5 years. This group was relatively symptom free, which may have implications in terms of adherence to a lifelong gluten-free diet.

The frequency of diagnosis of patients with coeliac disease during the past 5 years was 0.25 per 1000 people, and the prevalence of known coeliac disease in our population is considerably less than that would be expected from the recent prevalence data,[3 5] indicating that most patients with coeliac disease remain undiagnosed.

CONCLUSION

Over the past 20 years, the incidence of coeliac disease has risen, and symptoms at diagnosis have become fewer and less severe. Increasing numbers of children now present with

Table 2 Clinical presentation of children with coeliac disease in different time periods

Time period	Serological tests used	Median age (years)	Total number	Age <2 years	Patients with GI symptoms (%)	Patients without GI symptoms (%)	Targeted screening (asymptomatic)
1983–1989	None	4	11	1	88	12	0%
1990–1998	AGA and AEA	7.5	25	5	75	14	11%
1999–2004	ATTG	8	50	7	42	32	26%

AEA, antiendomysial antibody; AGA, antigliadin antibody; ATTG, anti-tissue transglutaminase; GI, gastrointestinal.

What is already known on this topic

- Coeliac disease is common, with a prevalence of 0.5–1% in the populations tested.
- The risk of having coeliac disease is much higher in certain groups: first-degree relatives with coeliac disease, type 1 diabetes, autoimmune thyroid and liver disease, Down's syndrome, Turner's syndrome and Williams syndrome.
- Sensitive and specific serological testing is widely available.

What this study adds

- With the advent of serological testing, the age at diagnosis of coeliac disease has increased and the presentation has changed.
- Dramatic gastrointestinal manifestation as the presenting feature is now less common.
- Almost 25% of children with coeliac disease are diagnosed by targeted screening.
- However, most children with coeliac disease still remain undiagnosed.

non-gastrointestinal symptoms, with almost one in four children being diagnosed by targeted screening; a large proportion of these are without symptoms. Our data also suggest that most children with coeliac disease remain undiagnosed.

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