

Presentation Patterns and Nutritional Impact of Coeliac Disease in New Zealand Children

Mustafa A Adamji, Martin Whitehead, Andrew S Day

Mustafa A Adamji, Andrew S Day, Department of Paediatrics, Christchurch Hospital, Christchurch, New Zealand

Martin Whitehead, Department of Pathology, Christchurch Hospital, Christchurch, New Zealand

Andrew S Day, Department of Paediatrics, University of Otago Christchurch, Christchurch, New Zealand.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Professor Andrew S Day, Department of Paediatrics, University of Otago Christchurch, Riccarton Avenue, Christchurch 8140, New Zealand.

Email: andrew.day@otago.ac.nz

Telephone: +64-3-3640747

Fax: +64-3-3640919

Received: May 7, 2017

Revised: August 28, 2017

Accepted: September 1, 2017

Published online: October 21, 2017

ABSTRACT

INTRODUCTION: Recent studies have shown increasing numbers of children diagnosed with coeliac disease (CD), with many having few or no symptoms.

AIM: To evaluate the presentation patterns of a cohort of children diagnosed with coeliac disease at Christchurch Hospital, New Zealand.

METHODS: Children aged 15 years or less diagnosed with CD (based upon standard histological criteria) over a five year period were identified retrospectively. Presenting symptoms, anthropometry, serology and micronutrients were reviewed.

RESULTS: Over the study period, 110 children were diagnosed at mean age of 7.37 years. The most common presenting symptom was abdominal pain. Sixteen children were diagnosed following screening in high risk groups, with 14 being asymptomatic. Eighteen children were iron deficient and twelve vitamin D deficient.

CONCLUSIONS: CD was diagnosed in children of all ages, with various presentation patterns. Micronutrient deficiencies were commonly seen at diagnosis. Ongoing assessment of patterns of CD in NZ children is required.

Key words: Coeliac disease; Children; Screening; Antibodies; Small bowel biopsy

© 2017 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Adamji MA, Whitehead M, Day AS. Presentation Patterns and Nutritional Impact of Coeliac Disease in New Zealand Children. *Journal of Gastroenterology and Hepatology Research* 2017; **6(5)**: 3430-2434 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2066>

INTRODUCTION

Coeliac disease (CD) is an autoimmune disease of the small bowel, triggered by dietary exposure to gluten in genetically susceptible individuals^[1]. Ingestion of gluten provokes immune-mediated damage to the small intestinal mucosa. The optimal management of CD currently involves institution of a life-long gluten free diet (GFD)^[2].

The features of CD can develop at any age whilst on a gluten containing diet^[3]. CD can have variable presentations from gastrointestinal symptoms to non-specific symptoms such as headaches or lethargy^[4-6]. In addition, many individuals are increasingly identified consequent to active screening in groups at higher risk of CD (such as those with positive family history or type 1 diabetes) and a number of these individuals may be asymptomatic at diagnosis^[7].

CD appears to be increasing in prevalence in many countries around the world, including New Zealand^[7]. A population-based study conducted in the Christchurch region of New Zealand in the last years of the 20th century using electoral roll records, showed a prevalence of 1.2%^[8]. A further study in the same region documented more individuals being diagnosed with CD each year^[9]. Subsequently

further data has shown increasing numbers of children diagnosed with CD during the first decade of this century, with more diagnosed after active screening in high risk groups^[10]. The primary aim of this retrospective study was to evaluate the rates of diagnosis and presentation patterns of CD in children in Christchurch region over a five year period from 2011 to 2015, with additional focus upon micronutrient status at diagnosis.

MATERIALS AND METHODS

Population

Children aged 15 years or less (defined as diagnosis before their sixteenth birthday) diagnosed with CD at Christchurch Hospital, Christchurch, New Zealand between 1st January 2011 and December 31st 2015 were identified retrospectively. The study population did not include children diagnosed by adult gastroenterologists in the private sector within the city.

The Christchurch Hospital Pathology Department database was interrogated to identify children investigated for and/or diagnosed with CD. Each patient's hospital record (hard copy and electronic) was then retrieved and reviewed. Further information was obtained from the relevant general practitioner (GP) in the community with regards to outcomes subsequent to diagnosis.

Diagnosis of CD was based upon standard histological criteria. Lesions on biopsies consistent with Marsh-Oberhuber criteria (including increased intraepithelial lymphocytes, partial to complete villous atrophy) were considered to be diagnostic^[19]. The duodenal biopsies were analysed within the same pathology laboratory, although by different pathologists.

Clinical Features

Relevant background features, such as age, gender, presenting signs and symptoms, risk group status and blood test results were extracted from clinical records where available. Anthropometric measures recorded at diagnosis and subsequently were collected using either GP or hospital records.

Endoscopy reports and pathology results were reviewed. Serological test results [anti-endomysial antibodies (EMA), tissue transglutaminase (tTG)] before and after diagnosis were reviewed where available. tTG assays were conducted using Varelisa IgA immunoassay (Phadia, Uppsala, Sweden) with normal range of 0-20 Units (U). EMA assays were conducted using indirect immunofluorescence (Inova Diagnostics, San Diego CA). Micronutrient levels (haemoglobin, ferritin, vitamin D, folate levels, vitamin B12) before and after diagnosis were also noted where available. Patients with serum ferritin and vitamin D levels below the normal reference range (15-50 µg/L and 50-150 nmol/L respectively) were classified as iron and vitamin D deficient. Iron or vitamin D supplementation at before or after diagnosis was noted.

Statistical Analysis

Weight and height Z scores were calculated using an online calculator employing data from the National Health and Nutrition Evaluation Survey (<http://www.emmes.com/study/ped/resources/htwtcal.htm>). Data analysis were performed using GraphPad Instat 3.0 (GraphPad Software, Inc., La Jolla, CA). One-way analysis of variance (ANOVA) used for analysis, with the normality *p* value set to be equal to or less than 0.05.

RESULTS

Study Population

A total of 110 children were diagnosed with CD over the time period

(Table 1). The mean age of the study population was 7.37 years (range 1- 15 years) and 77 (70%) were female. The largest number of children (*n* = 47, 43%) was aged between 0 and 5 years of age at diagnosis (Figure 1).

At least one risk factor for CD was seen in 45 (41%) of the 110 children. These high risk groups were positive family history (*n* = 26), Trisomy 21 (*n* = 3), type 1 diabetes mellitus (T1DM) (*n* = 9) and other autoimmune or genetic conditions (*n* = 7). Diagnosis was made after screening in 16 (15%) children; 14 of whom were reported to be asymptomatic. The other two children were incidentally noted to have minor clinical symptoms upon review of their medical records.

Table 1 Gender and ethnicity distribution of 110 children diagnosed with coeliac disease over 5 years in Christchurch, NZ.

| Study Cohort | |
|----------------|-----|
| N | 110 |
| female | 77 |
| Ethnicity | |
| European | 103 |
| Maori | 2 |
| Middle-eastern | 2 |
| Asian | 1 |
| Indian | 1 |
| Tongan | 1 |

Table 2 Presenting features of 110 children diagnosed with coeliac disease in Christchurch, NZ [n (%)].

| | Presenting Feature | Children |
|------------------|--------------------------------|----------|
| Gastrointestinal | Abdominal Pain | 56 (50) |
| | Diarrhoea | 24 (22) |
| | Constipation | 14 (13) |
| | Vomiting/nausea | 9 (8) |
| | Reflux | 4 (4) |
| Nutritional | Poor appetite/Faltering growth | 19 (17) |
| | Iron deficiency | 4 (4) |
| | Weight loss | 3 (3) |
| Extra-Intestinal | lethargy | 11 (10) |
| | Headaches | 2 (2) |
| | Poor concentration | 2 (2) |
| | Anxiety | 2 (2) |
| | Developmental delay | 2 (2) |
| | Skin (alopecia, rash) | 2 (2) |
| Asymptomatic | Identified following screening | 14 (13) |

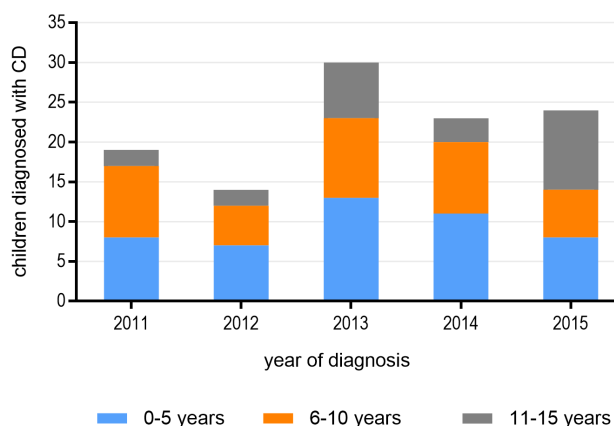


Figure 1

Presenting features

Details of presenting features were available for all 110 children. Abdominal pain ($n = 56$, 51%) and diarrhoea ($n = 24$, 22%) were the most commonly reported symptoms (Table 2). Fifty three of the children (48%) presented with multiple symptoms at time of diagnosis. Faltering growth or poor appetite ($n = 19$, 17%) predominated in the children aged less than 5 years of age, while abdominal pain and diarrhoea predominated in the older children.

Growth parameters

Weight measurements were available for all 110 children at diagnosis, with post-diagnosis measurements in 105 of the 110 children at various time points. Height measurements were available for 102 of the 110 children prior to and following diagnosis. The median duration of follow up post diagnosis was eight months.

The mean weight Z score at diagnosis was -0.04 (range from -3.08 to 2.78) and mean after diagnosis was 0.07 (-3.58 to 2.64). The mean height Z score at diagnosis was 0.86 (-2.12 to 1.94), while post diagnosis mean was 0.88 (-2.36 to 2.48). When assessed across the three age groups the youngest children were more likely to have lower mean weight Z scores at diagnosis, while the older children had lower mean height Z scores at diagnosis. ($p < 0.01$) (Table 3) At diagnosis, two children (2%) had a height Z score 2 standard deviation (SD) less than the mean (low height for age) and five children (5%) had a weight Z score 2 SD less than the mean (low weight for age). In addition, one child (1%) had a height Z score 2 SD greater than the mean and four children (4%) had a weight Z score 2 SD greater than the mean.

Follow up post diagnosis

Details of follow-up assessments were available for the 108 of the 110 children. Ninety-nine children were initially reviewed in the paediatric general or gastroenterology clinic prior to being discharged to primary care. Nine children (8%) were followed up directly by their primary care physician post diagnosis at varied times. Overall follow up period varied widely in primary care.

Results of serological tests prior to and after diagnosis

The results of IgA or IgG tTG testing were available in 108 children, whilst EMA results were available in 97 children. While 29 children (27%) had tTG measured as greater than 150 U, 31 (29%) had levels between 100 and 150 U, and 48 (44%) had levels less than 100U. Four children shown to be IgA deficient; all had positive IgG tTG tests. Genetic testing for HLA DQ2/DQ8 was not routinely undertaken during this period; 12 children had undergone this investigation, all of whom had positive results.

After diagnosis of CD, follow up serological surveillance tests results were available in 93 of the children, at an interval of 6 to 12 months post diagnosis. Seventy seven (83%) of the children had normalisation of their serological tests within a year of diagnosis. Nine of the sixteen children (56%) with elevated serology beyond a year of diagnosis, had not maintained a strict GFD. One of the children had elevated serology despite being on a strict gluten free diet, needing repeat endoscopic assessment.

Results of other investigations

Iron status results were available in 90 of the 110 children at diagnosis (Table 3). Iron deficiency was seen in 18 (20%) children, whilst, only two children had anaemia and one had microcytosis with normal haemoglobin. Twelve (67%) of the 18 children with low ferritin levels were treated with oral iron supplements; follow up measurements

Table 3 Nutritional parameters in 110 children diagnosed with coeliac disease (Weight and height parameters available for 110 and 102 children respectively. Iron and Vitamin D status available in 90 and 46 children respectively).

| Age group (year) | Mean weight Z score | Mean height Z score | Iron deficiency | Vitamin D deficiency |
|------------------|---------------------|---------------------|-----------------|----------------------|
| 0-5 | -0.152 | 0.062 | 10 | 4 |
| 6-10 | 0.06 | 0.083 | 2 | 3 |
| 11-15 | 0.002 | -0.249 | 6 | 5 |

were not available.

Vitamin D status was measured in 46 (42%) of the 110 children at diagnosis (Table 3). Twelve (26%) children were vitamin D deficient: ten of these children received oral vitamin D supplements. Follow up measurements where available showed normal vitamin D levels in each case. There was no seasonal variation to the vitamin D measurements. Folate and vitamin B12 results were available in 47 (43%) of the 110 children; two (5%) children had low folate levels.

Endoscopic and Histological Findings

Endoscopy findings were available for 107 of the 110 children. Eighty-nine (82%) of these children had endoscopic abnormalities consistent with CD, including flattened mucosa, mosaic appearance and scalloped duodenal folds. All 110 children had histological features consistent with CD. Three children were also diagnosed with eosinophilic esophagitis at the time of their assessment for possible CD.

DISCUSSION

This retrospective study showed continued high rates of diagnosis of CD in children from the Christchurch region of New Zealand, similar to that observed previously^[10]. The earlier study documented the diagnosis of CD in 263 children less than 16 years of age over 10 years whilst the current study included 110 children over a five-year period. The presenting features varied widely and a large number of children were diagnosed following screening. The current study continues to show that CD is an important condition in New Zealand children, with continued frequent diagnosis made.

A previous electoral-roll based study of adults showed a prevalence rate of CD in New Zealand of 1.2%^[8], similar to rates described in other parts of the world^[7]. A further study, including adult and children, showed a large increase in CD in the Christchurch region over the last decades of the 20th century^[9]. In contrast, earlier reports had suggested much lower rates in children (0-12years) in New Zealand: 0.10/1000 in Wellington^[11], 0.35/1000 in Otago^[12] and 0.40/1000 in Canterbury^[9]. More recently the prevalence of childhood CD was assessed in the New Zealand Asthma and Allergy cohort^[13]. This birth-cohort was established between 1997 and 2001, with 1000 children recruited in two NZ centres (Wellington and Christchurch). Parental reporting (without validation of medical records) indicated a prevalence of 1% in these children.

The pattern of increasing diagnosis with CD in New Zealand may be related in part to enhanced awareness of CD and more frequent screening of individuals at higher risk of developing CD. Advances in serological tests and diagnostic approaches may be additional factors^[14]. Environmental factors, such as infant breast feeding practices, age at introduction of gluten and amount of gluten in diet are likely to be relevant^[15]. International data also supports a recent increase in the prevalence of CD, with rates in Finland rising to 2.4%^[16]. However, the nature of the current study did not allow any clarification of these environmental risk factors.

The current study demonstrates that CD can be diagnosed at any

age through childhood with varied presentation. Abdominal pain remains a common presenting feature. Preschool children more commonly presented with growth concerns and gastro-intestinal symptoms. Few children at any age presented with the classical malabsorptive phenotype. These patterns are similar to recent Australasian reports^[4,5,17].

A number of children in the current study were diagnosed with CD following screening within a high risk group. Groups at highest risk of CD include those with a first degree family member, children with Down syndrome and T1DM^[7]. Children with a first degree family history of CD comprised the largest high risk group in the current study. These patterns are similar to other recent reports^[5,17].

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines for the diagnosis of CD include provision for diagnosis without obtaining duodenal biopsies in symptomatic children with positive gene markers and serological tests assessed on more than one occasion^[18]. The current study did not follow these guidelines, and nor can these guidelines be applied retrospectively given the information available. Diagnosis was, however, based upon histological findings consistent with CD in children with consistent serological results. Genetic testing for HLA DQ2/DQ8 was not undertaken routinely. tTG and EMA were measured concurrently in the current study at just one point in time. In addition, more than two thirds of the children included in this series of patients had a tTG less than ten times the normal range. Prospective assessment of the validity of the ESPGHAN criteria would need to be considered in this setting prior to adopting this approach in the NZ setting.

Impaired mucosal absorption of various micronutrients is well-described in the setting of active CD^[20,21]. Although the lack of complete assessment limited interpretation, a number of children in the current cohort were found to have micronutrient deficiencies. Vitamin D deficiency was seen most commonly in those in whom this was measured. Although some of the children were treated with oral supplements of vitamin D, others were noted to have improvement in vitamin D status solely with commencement of a GFD. Vitamin D status did not appear to be related to the season of testing: data on socio-economic status and ethnicity were not available. In relevance to vitamin D status, bone mineral density is known to be diminished in untreated CD, but improves rapidly with GFD in children. Bone mineral density was not assessed in the current cohort.

The limitations of this study relate to its retrospective nature, leading to incomplete data in some key areas. Follow-up arrangements varied and anthropometric data was recorded in various settings (community and hospital), potentially limiting the validity of this data. Furthermore, this study was not population based, as any children diagnosed outside this tertiary hospital setting were not included. However, the included population was diagnosed within a single setting over a 5 year period, following on from the previous assessment in the same setting^[10]. Together, these two datasets include almost 400 children diagnosed with CD over 15 years in the Christchurch region.

In conclusion, these data reflect a large number of children diagnosed with CD at this single tertiary centre. Practitioners must be aware of the varied presentations of CD and consider screening for this diagnosis. A prospective, population-based assessment is now required to establish the incidence and prevalence of CD in children in NZ.

REFERENCES

1. Tack GJ, Verbeek WH, Schreurs MW, Mulder CJ. The spectrum of

- celiac disease: epidemiology, clinical aspects and treatment. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 204-213. [PMID: 20212505]; [DOI: 10.1038/nrgastro.2010.23]
2. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. *Gastroenterology*. 2009; **137**: 1912-1933. [PMID: 19766641]; [DOI: 10/1053/j.gastro.2009.008]
3. Kennedy NP, Feighery C. Clinical features of coeliac disease today. *Biomed Pharmacother*. 2000; **54**: 373-380. [PMID: 10989976]; [DOI: 10.1016/s0753-3322(01)80004-4]
4. Westerbeek E, Mouat S, Wesley A, Chin S. Coeliac disease diagnosed at Starship Children's Hospital: 1999-2002. *N Z Med J*. 2005; **118**: U1613. [PMID: 16132074]
5. Stone ML, Bohane TD, Whitten KE, Tobias VH, Day AS. Age related clinical features of childhood coeliac disease in Australia. *BMC Pediatr*. 2005; **5**: 11. [PMID: 15907214]; [DOI: 10.1186/1471-2431-5-11]
6. Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. *Arch Pediatr Adolesc Med*. 2008; **162**: 164-168. [PMID: 18250242]; [DOI: 10.1001/archpaediatrics.2007.38]
7. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2005; **40**: 1-19. [PMID: 15625418]; [DOI: 10.1097/00005176-200501000-00001]
8. Cook HB, Burt MJ, Collett JA, Whitehead MR, Frampton CM, Chapman BA. Adult coeliac disease: prevalence and clinical significance. *J Gastroenterol Hepatol*. 2000; **15**: 1032-1036. [PMID: 11059933]; [DOI: 10.1046/j.1440-1746.2000.02290.x]
9. Cook B, Oxner R, Chapman B, Whitehead M, Burt M. A thirty-year (1970-1999) study of coeliac disease in the Canterbury region of New Zealand. *N Z Med J*. 2004; **117**: U772. [PMID: 15014561]
10. Kho A, Whitehead M, Day AS. Coeliac disease in children in Christchurch, New Zealand: Presentations and patterns from 2000-2010. *World J Clin Pediatr* 2015; **4**: 148-154 [PMCID: PMC4637806]; [DOI: 10.5409/wjcp.v4.i4.148]
11. Ussher R, Yeong ML, Stace N. Coeliac disease: incidence and prevalence in Wellington 1985-92. *N Z Med J*. 1994; **107**: 195-197. [PMID: 8196863]
12. Carrington JM, Hewitt CJ, Dowsett LR, Barbezat GO. The prevalence of coeliac disease in Otago. *N Z Med J*. 1987; **100**: 460-462. [PMID: 3451125]
13. Tanpowpong P, Ingham TR, Lampshire PK, Kirchberg FF, Epton MJ, Crane J, Camargo CA Jr; New Zealand Asthma and Allergy Cohort Study Group. Coeliac disease and gluten avoidance in New Zealand children. *Arch Dis Child*. 2012; **97**: 12-16. [PMID: 22075107]; [DOI: 10.1136/archdischild-2011-300248]
14. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: impact of serological testing. *Pediatrics*. 2009; **124**: 1572-1578. [PMID: 19948628]; [DOI: 10.1542/peds.2008-2373]
15. Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. *Am J Clin Nutr*. 2002; **75**: 914-921. [PMID: 11976167]
16. Lohi S1, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, Lohi O, Bravi E, Gasparin M, Reunanen A, Mäki M. . . Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther*. 2007; **26**: 1217-1225. [PMID: 17944736]; [DOI: 10.1111/j.1365-2036.2007.3502x]
17. Aurangzeb B, Leach ST, Lemberg DA, Day AS. Nutritional status of children with coeliac disease. *Acta Paediatr*. 2010; **99**: 1020-1025. [PMID: 20178518]; [DOI: 10.1111/j.1651-2227.2010.01732.x]
18. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips

- A, Shamir R, Troncone R, Giersiepen K, Branski D, Catassi C, Leigeman M, Mäki M, Ribes-Koninckx C, Ventura A, Zimmer KP; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr.* 2012; **54**: 136-160. [PMID: 22197856]; [DOI: 10.1097/MPG.0b013e31821a23d0]
19. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol.* 1999; **11**: 1185-1194. [PMID: 10524652]; [DOI: 10.1097/00042737-199910000-00019]
20. Erdem T, Ferat C, Nurdan YA, et al. Vitamin and mineral deficiency in children newly diagnosed with coeliac disease. *Turk J Med Sci.* 2015; **45**: 833-6. [PMID: 26422854]
21. Deora V, Aylward N, Sokoro A, El-Matary W. Serum vitamins and minerals at diagnosis and follow up in children with coeliac disease. *J Pediatr Gastroenterol Nutr.* 2017 Aug; **65**(2): 185-189. [PMID: 28738401]; [DOI: 10.1097/MPG.0000000000001475]