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Spanish National Registry of Paediatric Coeliac Disease: Changes in the Clinical Presentation in the 21st Century

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Abstract

Objectives: Over the last several decades, there has been a tendency towards a predominance of less symptomatic forms of coeliac disease (CD) and an increase in the patient age at diagnosis. This study aimed to assess the clinical presentation and diagnostic process of paediatric CD in Spain.

Methods: A nationwide prospective, observational, multicentre registry of new paediatric CD cases was conducted from January 2011 to June 2017. The data regarding demographic variables, type of birth, breastfeeding history, family history of CD, symptoms, height and weight, associated conditions, serological markers, human leukocyte antigen (HLA) phenotype, and histopathological findings were collected.

Results: In total, 4,838 cases (61.0% female) from 73 centres were registered. The median age at diagnosis was 4.0 years. Gastrointestinal symptoms were detected in 71.4% of the patients, and diarrhoea was the most frequent symptom (45.9%). The most common clinical presentation was the classical form (65.1%), whereas 9.8% of the patients were asymptomatic. There was a trend towards an increase in the age at diagnosis, proportion of asymptomatic CD cases, and usage of anti-deamidated gliadin peptide antibodies and HLA typing for CD diagnosis. However, there was a decreasing trend in the proportion of patients undergoing biopsies. Some of these significant trend changes may reflect the effects of the 2012 ESPGHAN diagnosis guidelines.

Conclusions: Paediatric CD in Spain is evolving in the same direction as in the rest of Europe, although classical CD remains the most common presentation form, and the age at diagnosis remains relatively low.

Keywords: coeliac disease; epidemiology; diagnosis; children, Europe

What is known

- A shift in the predominant clinical presentation of paediatric coeliac disease (CD) from the classical to less symptomatic forms has been reported. Additionally, there is an upward trend in the age at diagnosis.
- Recent studies have reported that abdominal pain has become the most common symptom detected at the time of diagnosis of CD in children.

What is new

- The evolution of the clinical presentation of CD in Spain has shown reduced predominance of the classical forms and increase in the age at diagnosis.
- In Europe, there are regional differences in the clinical presentations of CD. In Spain, the classical form remains the most common clinical presentation of paediatric CD, and diarrhoea is the most frequent symptom.

Introduction

Coeliac disease (CD) is an immune-mediated systemic disorder triggered by gluten and related prolamins in genetically susceptible individuals and characterised by a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 haplotypes, and enteropathy[1]. The pooled worldwide prevalence of CD is estimated at 1.4% (95% confidence interval [CI] 1.1–1.7%) when diagnosis is based on serological tests[2].

With the improvement in the diagnostic tests for CD over the last several decades, a tendency towards an increase in its incidence and prevalence has become apparent. Moreover, there is an increase in the less symptomatic forms and in the patient age at diagnosis[3, 4].

Between June 2006 and May 2007, the Spanish Gastroenterology, Hepatology and Paediatric Nutrition Society (SEGHNP) compiled the Spanish Coeliac Patient Registry for patients under 15 years of age called REPAC1 to determine the incidence and clinical presentation of CD in Spain. In this study, younger age at diagnosis and a predominance of the classical forms of CD were observed in Spain as compared to other European countries[5]. With the objective of continuing to advance our knowledge regarding the clinical presentation and diagnostic process of paediatric CD in Spain over time, SEGHNP put into motion a new nationwide registry called REPAC2.

Methods

A nationwide prospective, observational, multicentre registry of new CD cases was compiled between January 2011 and June 2017. All paediatric gastroenterology units were invited to participate by the SEGHNP CD Working Group.

Patients under 15 years of age who were diagnosed with CD after the start date of the study at the participating centres were included in this registry. Only patients who met the criteria established by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) in effect at the time of diagnosis were selected (the 1990 ESPGHAN criteria[6] for patients diagnosed in 2011 and the criteria published in 2012[1] for the others).

An electronic data collection questionnaire, accessible on the SEGHNP website, was created. It recorded information regarding the demographic variables, type of birth, breastfeeding history, family history of CD, symptoms of CD, height and weight, associated conditions, and diagnostic tests performed. Gastrointestinal forms of CD were defined as those with at least one gastrointestinal symptom according to the latest update of the ESGPHAN criteria[7], while the remaining symptomatic forms were considered as extra-intestinal. Following the Oslo definitions[8], the clinical presentations were classified as asymptomatic, classical, or non-classical forms. The classical forms included cases with at least one of the following signs or symptoms: chronic diarrhoea, weight loss or failure to thrive, abdominal distension, or malabsorption syndrome.

Z-scores for height, weight, and body mass index (BMI) according to age and sex were calculated based on the World Health Organization's (WHO) growth charts. Overweight was defined as a BMI z-score between 1 and 2, obese as z-score >2, and underweight as z-score <−2. The Waterlow Index (WI) for weight (actual weight divided by the 50th percentile of the weight corresponding to actual height) was also calculated using the same national growth charts[9] used for the REPAC1 registry[5]. A WI score <90% was considered underweight and that ≥115% was considered overweight/obese.

Anti-tissue transglutaminase (ATG), anti-deaminated gliadin peptide (DGP) and anti-endomysium (EMA) antibody testing, as well as HLA typing were performed at each participating centre, according to the methods available at their laboratories. For serological tests, the cut-off points established by the respective laboratories for each individual testing method were used. The centres were required to report their biopsies according to the Marsh-Oberhuber classification[10]. Biopsy samples classified as Marsh 2-3 were considered indicative of CD[1]. The number of samples taken and the taking of duodenal bulb biopsies were not evaluated.

Informed consent was obtained from the parents or legal guardians of the participants. This study was approved by the Research Ethics Committee of the Hospital Universitario Puerta de Hierro, Majadahonda, Madrid (263.2011).

Statistical analysis

The Kolmogorov-Smirnov test was used to assess whether the continuous variables followed normal distribution. Continuous variables are expressed as medians (interquartile ranges [IQRs]) and categorical data as counts (percentages). Chi-square test was used to detect differences in the categorical variables.

Backward stepwise logistic regression analysis was used to explore the association of some variables with the form of clinical presentation. The results are expressed as odds ratios (ORs) and 95% CIs.

Trend analyses over the years 2011 to 2016 were performed; these analyses did not include the year 2017 because data were only partially collected from January to June in that year. Spearman's ρ was used to determine the correlation between the ordinal variables. Chi-square test for trend (Cochran–Armitage test) was used to assess the yearly trends of the clinical presentation form and usage of diagnostic tests. For more detailed monthly trend analyses of the age at diagnosis and the proportion of cases diagnosed by biopsy, segmented regression analyses were performed using *Joinpoint Regression Program* software, version *4.9* (National Cancer Institute, Bethesda, USA).

P-values <0.05 were considered statistically significant. Except for the trend analysis using Joinpoint, all statistical analyses were performed using R Statistical Software 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 73 out of 117 (62.4%) Spanish centres having a Paediatric Gastroenterology unit, representing 15 of the 17 regions in Spain, participated in the registry. A total of 4,838 cases, of which 61.0% were female, were registered. Both parents of the child were from Spain in 4,443 (91.8%) cases. The median age at diagnosis was 4.0 years (IQR: 2.0–8.3; range: 7 months–15 years) in a right-skewed distribution (Figure, Supplemental Digital Content [SDC] 1, http://links.lww.com/MPG/C713). As the study progressed over time, a tendency towards an increase in the median age at diagnosis was observed. Although the trend was weak, it was highly significant, from 3.3 years (IQR: 1.8–7.2) in 2011 to 4.7 years (IQR: 2.0–8.7) in 2016 (Spearman's $\rho = 0.067$, $p < 0.001$).

Regarding family history of CD, 517 (10.8%), 452 (9.5%), and 41 (0.9%) patients had first-degree relatives, second-degree relatives, and both first- and second-degree relatives with CD, respectively. Delivery was by caesarean section in 936 cases (19.3%). Breastfeeding was initiated in 3,402/4,512 (75.4%) patients, of which 1,564 (46.0%) continued breastfeeding for at least 6 months.

Clinical presentation

The most frequent clinical presentation was the gastrointestinal form (3,456 patients; 71.4%). Furthermore 1,382 (28.6%) patients exclusively reported extra-intestinal symptoms, while 473 (9.8%) were asymptomatic. Clinical presentation varied according to the age at diagnosis (Figure 1A). In patients aged <3 years, the gastrointestinal form was observed in 1,837/2,007 (91.5%) cases but was less prevalent in patients aged >6 years (836/1,785, 46.8%). The asymptomatic form was scarcely reported in patients aged <3 years as compared to that in patients aged ≥6 years (46/2,007 [2.3%] versus 330/1,785 [18.5%]). Herpetiform dermatitis was reported in 32 cases (0.7%).

When categorising the clinical presentation as classical or non-classical, the classical form was more frequent than the non-classical form (3,148 patients [65.1%] versus 1,217 patients [25.2%]). The classical form was much more common in patients aged <3 years than those aged ≥6 years (1,828/2,007 [91.1%] versus 651/1,785 [36.5%]).

The symptoms present most frequently at the time of diagnosis are presented in Table 1. Diarrhoea was the most common symptom (45.9%), primarily in patients aged <3 years

(62%). However, in the other age groups, abdominal pain was the most frequent symptom. The most common extra-intestinal symptom was weight loss or failure to thrive (39.7%), followed by hyporexia (31.7%). The evolution of the detection of the main symptoms along the study period is presented in Table, SDC 3, http://links.lww.com/MPG/C715.

The presence of associated conditions was recorded in 207 cases: type 1 diabetes, 93 cases (1.9%); autoimmune thyroiditis, 55 cases (1.1%); immunoglobulin A (IgA) deficiency, 42 cases (0.9%); Down syndrome, 19 cases (0.4%); Turner syndrome, 2 cases; and Williams syndrome, 1 case. Among these patients, the most frequent clinical presentation of CD was the asymptomatic form (93/207, 44.9%).

The clinical presentation of CD varies according to family history. The asymptomatic form was noted in 254/3,770 (6.7%) patients without a family history of CD, 162/517 (31.3%) patients with first-degree relatives having CD, and 42/452 (9.3%) patients with second-degree relatives having CD ($p < 0.001$).

According to the WHO's BMI reference charts, overweight and obesity increased with an increase in the patient age (Table 1). Using the WI with national growth charts, 23.3% of the patients were classified as underweight, 69.9% as normal weight and 6.8% as overweight/obese.

In the logistic regression analysis with the gastrointestinal form as the dependent variable, female sex, family history of CD among first-degree relatives, and belonging to the 3–6-years or the ≥6 years age group were associated with a lower probability of gastrointestinal form (Table 2). On performing the same analysis with classical CD as the dependent variable (Table, SDC 2, http://links.lww.com/MPG/C714), along with family history and older age, female sex was also associated with a lower probability of classical CD (OR: 0.84; 95% CI: 0.73–0.98).

Chi-square test for trend analysis from 2011 to 2016 showed a significant decrease in the proportion of cases presenting gastrointestinal and classical forms and an increase in those presenting extra-intestinal and non-classical forms ($p < 0.01$), as described in Figure 1B and Table, SDC 3, http://links.lww.com/MPG/C715. With respect to age, the Joinpoint trend analyses (Figure 2A) revealed a tendency towards an increase in the age at diagnosis until May 2013. This was followed by a period between May 2013 and March 2014 with no significant changes, further followed by the period of greatest increase up to August 2015, with a monthly percentage change of 2.2% (95% CI: 1.3–3).

Diagnostic Tests

An IgA or IgG ATG analysis was performed for 4,828 patients (99.8%), of which 4,753 (98.4%) tested positive. Among the positive cases, 3,770 (79.3%) showed values that were 10 times more than the cut-off point. DGP analysis was performed in 2,146 patients, and 1,997 (93.1%) of them tested positive. Selective IgA deficiency was observed in 42 patients (0.9%); results from these 42 patients have been included in a recently published study[11].

Duodenal biopsies were performed in 2,994 patients (61.9%), of which 139 (4.6%) cases were classified as Marsh 2, 873 (29.2%) as Marsh 3a, 1,276 (42.6%) as Marsh 3b, and 706 (23.6%) as Marsh 3c.

HLA typing was performed for 4,253 patients (87.9%), of which 4053 (95.3%) carried HLA-DQ2, 145 (3.4%) carried only HLA-DQ8, and 50 (1.2%) carried other different phenotypes.

According to the chi-square test for trend analyses (Table, SDC 3, http://links.lww.com/MPG/C715), usage of HLA typing and DGP and EMA testing significantly increased from 2011 to 2016 (p <0.001). HLA typing mainly increased between 2011 and 2013 (from 631 [70.2%] to 787 [92.2%]). There was a noticeable increase in the proportion of DGP testing from 79 (8.8%) cases in 2011 to 485 (56.8%) in 2013, without any relevant changes after this period. Changes in the diagnostic criteria proposed by ESPGHAN[1] were associated with a decrease in the proportion of patients undergoing biopsies, from 899 (100%) in 2011 to 429/854 (50.2%) in 2013. The trend analysis (Figure 2B) showed a 2.8% monthly decrease from January 2012 to October 2013, without relevant changes after that period.

Discussion

After completing the first national registry, REPAC1, in 2006–2007[4], SEGHNP designed the second registry called REPAC2. This was started with the intention of keeping it active for at least 3 years and increasing the number of participating hospitals. Finally, the registry remained active for 6.5 years, and the participation was three times that of REPAC1, resulting in the largest endeavour of this type at a national level being published in Europe till date[12–14].

When compared to REPAC1, the REPAC2 data showed an increase in the age at diagnosis (median age: 4.0 years versus 2.3 years) and the prevalence of the asymptomatic form of CD (9.8% versus 7.0%), as well as a decrease in the prevalence of the classical form (65.1% versus 70.9%). Likewise, differences in the nutritional status of the patients were observed, with an increase in the proportion of overweight patients (6.8% versus 3.4%) and a decrease of underweight patients (23.3% versus 41.4%). Additionally, a tendency towards an increase in the age at diagnosis can be observed in the ongoing period of REPAC2.

The progressive increase in the age at diagnosis and in the proportion of the milder forms of CD has been observed for decades worldwide. This has primarily been attributed to the increase in awareness of CD among healthcare professionals, as well as the availability of serological testing methods and improved CD screening for certain risk groups[3]. However, it has been suggested that these changes have plateaued in recent years[15], but data from other countries indicate that the situation has not yet stabilised[14]. Spain has not been exempt from this evolution according to the available data[4].

Currently, there are noticeable differences between Spain and its surrounding countries. For instance, the age at diagnosis reported by REPAC2 was lower than that described in other studies conducted at the same time in Europe[13–18] and other continents[19, 20], which ranged from 5.8 to 9.5 years of age. Differences have also been observed in the clinical presentation of CD, with the classical form being more common in Spain[13, 17, 19]. Notably, chronic diarrhoea was the most reported symptom in Spain instead of chronic abdominal pain. Furthermore, the proportion of the asymptomatic form was relatively low (9.8%), slightly higher than that recently reported in the Netherlands (6.7%)[14]. In the Netherlands, the

percentage of gastrointestinal and extra-intestinal forms was also quite similar to ours. In both studies, the data collection was prospective, which might favour a more complete symptom registry and explain the limited number of cases classified as asymptomatic. Some of these differences could be related to the study's inclusion criteria of <15 years compared to <16–18 years in other studies; however, such differences were also reported between this study and those with the same age limit[10]. Social and geographical factors may also play a role, as the previously cited studies were conducted in countries in northern and central parts of Europe, whereas our results more closely resemble those of studies from southern European countries[16, 21, 22]. These differences in the patterns of CD presentation could decrease over time, as suggested by a small study conducted in Valencia, Spain in 2018–2019[23].

Overweight and obesity are becoming progressively common in CD[24]. This was also observed in the REPAC1 and REPAC2 data but did not correspond to the evolution trend in the general population in Spain[25, 26]. Our results are very similar to those of the study by Valetta *et al.*[27], which used the same BMI classification as that in REPAC2 and found that 3% of children with CD were obese, 8% were overweight, and 5% were underweight. It is difficult to make comparisons with other studies because of the disparities in the definition criteria used[24].

In the multivariate analysis, several factors were associated with a lower probability of gastrointestinal and classical forms. Age is a well-established factor that has been discussed previously. Family history of CD among first-degree relatives as a factor could be associated with high probability of being diagnosed through screening and being under close observation for the appearance of even minor symptoms. Differences in sex have not been studied adequately in the paediatric population, although some studies agree that men are more predisposed to classical symptoms than are women[28].

On analysing the diagnostic tests used for CD in the REPAC1 period, there was an increase in the proportion of EMA testing (81.4% versus 69.4%) and HLA typing (87.9% versus 53.1%) and a reduction in the biopsies performed (61.9% versus 98%). Similar trends were observed along the REPAC2 study (Table, SDC 3, http://links.lww.com/MPG/C715) and reflected the impact of the ESPGHAN 2012 guidelines on CD diagnosis[1]. With the recent updates of the guidelines in 2020[7], it is possible that some of these trends could regress. The trend analysis allowed us to explore the delay implementing the new guidelines in clinical practice; the proportion of patients undergoing biopsies progressively declined to an inflection point in October 2013.

The main strengths of our study include its large sample size, prospective nature, and the large number of participating centres. Although 44 out of 117 Spanish centres did not participate, the remaining 73 centres represent almost all the autonomous regions in Spain and the different levels of healthcare. Including only those patients diagnosed according to the criteria established by the ESPGHAN facilitated the internal validity of the results and their comparison with other studies that used the same criteria. On the other hand, there might have been some true CD patients among those excluded for not fulfilling the diagnostic criteria, which may have resulted in some information loss. This may include children with no information about HLA, parents' refusal for endoscopy, or false-negative biopsy results

due to inadequate samples. Another limitation is that, in 2011, the criteria required confirmation by biopsy. As, back then, many paediatric gastroenterologists had become familiar with and applied the criteria published later in 2012, it is possible that some cases were not registered in 2011 that would have been considered valid in subsequent years, thus underestimating the number of symptomatic cases. Additionally, the impact of CD screening must be considered, as older children have higher probabilities of being screened; this could induce a selection bias towards more asymptomatic cases in older children and towards older age at diagnosis.

In conclusion, the clinical presentation of paediatric CD in Spain is evolving in the same direction than in the rest of Europe, with diagnosis at a later age and with a decreased predominance of the gastrointestinal and classical forms, and an increase in extra-intestinal or asymptomatic forms. Nevertheless, there continue to be relevant differences between Spain and other European countries. Further studies are required to understand the cause of these differences adequately.

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Figures

Figure 1. Distribution of the different clinical presentation forms according to (A) age at diagnosis and (B) year of diagnosis

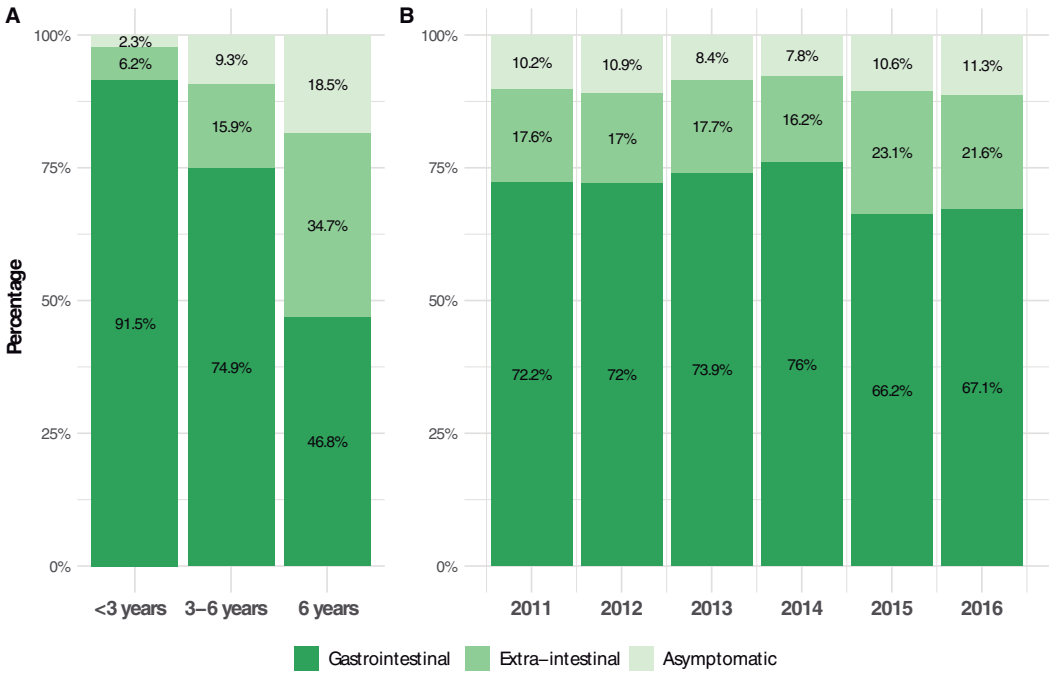

Figure 2. Trend analyses from 2011 to 2016 of (A) the mean age at diagnosis and (B) the proportion of cases diagnosed using biopsy[†].

MPC: Monthly Percent Change. Month 1 refers to January 2011.

* Change significantly different from zero ($p < 0.05$).

[†] Year 2011 was excluded, as only biopsied cases were included that year.

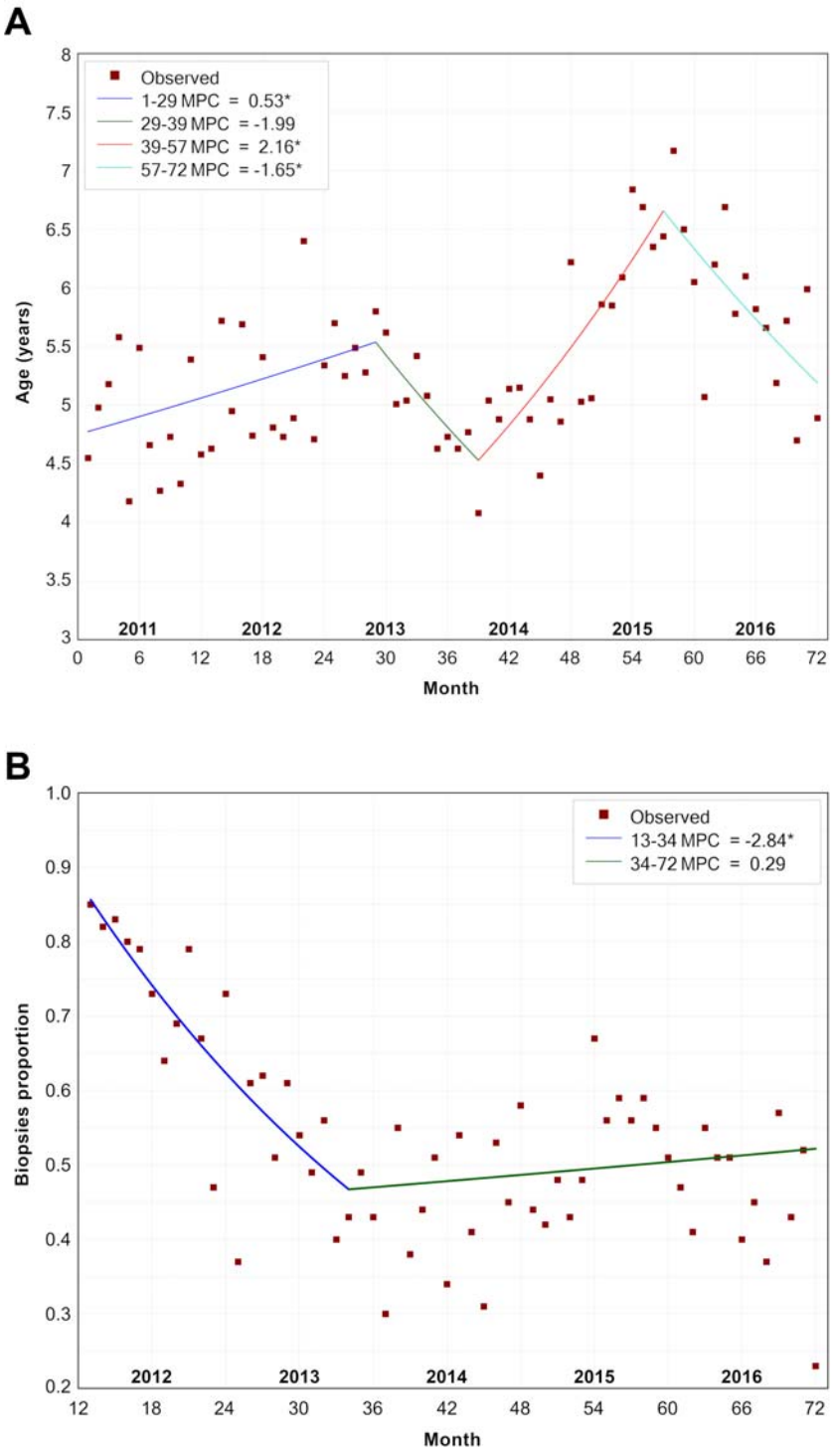

Table 1. Most common symptoms and nutritional status at diagnosis by age groups.

	Overall	**<3 years**	**3-6 years**	**≥6 years**	***p* value***
Gastrointestinal symptoms					
n†	4365	1961	949	1455	
Diarrhoea	2005 (45.9)	1215 (62.0)	398 (41.9)	392 (26.9)	<0.001
Abdominal distension	1742 (39.9)	1208 (61.6)	357 (37.6)	177 (12.2)	<0.001
Abdominal pain	1514 (34.7)	280 (14.3)	417 (43.9)	817 (56.2)	<0.001
Vomiting	682 (15.6)	473 (24.1)	100 (10.5)	109 (7.5)	<0.001
Constipation	665 (15.2)	296 (15.1)	161 (17.0)	208 (14.3)	0.548
Extra-intestinal symptoms					
Weight loss/failure to thrive	1731 (39.7)	1163 (59.3)	284 (29.9)	284 (19.5)	<0.001
Hyporexia	1383 (31.7)	801 (40.8)	302 (31.8)	280 (19.2)	<0.001
Change of mood	925 (21.2)	614 (31.3)	171 (18.0)	140 (9.6)	<0.001
Latent iron deficiency	627 (14.4)	288 (14.7)	150 (15.8)	189 (13.0)	0.170
Iron deficiency anaemia	330 (7.6)	130 (6.6)	110 (11.6)	90 (6.2)	0.820
Short stature	327 (7.5)	86 (4.4)	70 (7.4)	171 (11.8)	<0.001
Hypertransaminasaemia	161 (3.7)	111 (5.7)	25 (2.6)	25 (1.7)	<0.001
Recurrent aphthous stomatitis	105 (2.4)	16 (0.8)	29 (3.1)	60 (4.1)	<0.001
Dental enamel defects	30 (0.7)	6 (0.3)	4 (0.4)	20 (1.4)	0.001
Nutritional status					
n	4838	2007	1046	1785	
Normal weight	3875 (80.1)	1653 (82.4)	856 (81.8)	1366 (76.5)	<0.001
Underweight	223 (4.6)	131 (6.5)	26 (2.5)	66 (3.7)	<0.001
Overweight	584 (12.1)	191 (9.5)	136 (13.0)	257 (14.4)	<0.001
Obesity	156 (3.2)	32 (1.6)	28 (2.7)	96 (5.4)	<0.001

Data expressed as n (%). Percentages calculated over column total.

†Only symptomatic cases were considered to calculate the percentage for each symptom.

*Chi-square test for trend (Cochran–Armitage test).

Table 2. Binary logistic regression analysis of variables associated with gastrointestinal symptoms

Variable	B	OR	95% CI	*p* value
Constant	2.58	13.2	11.0, 15.8	<0.001
Age group				
<3 years	—	—	—	
3-6 years	-1.32	0.27	0.21, 0.33	<0.001
≥6 years	-2.55	0.08	0.06, 0.09	<0.001
Breastfeeding				
<6 months	—	—	—	
≥6 months	-0.13	0.88	0.76, 1.03	0.11
Family history				
None	—	—	—	
1st degree	-0.80	0.45	0.36, 0.56	<0.001
2nd degree	0.23	1.25	0.97, 1.63	0.088

OR = Odds Ratio, CI = Confidence Interval
Dependent variable: at least one gastrointestinal symptom.
Variables entered on step 1: age group (<3 years, 3-6 years, ≥6 years), sex, family history for coeliac disease, mode of delivery, breastfeeding ≥ 6 months.