Clinical Presentation in Children With Coeliac Disease in Central Europe

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ABSTRACT

Objectives: During the past decades, there has been a shift in the clinical presentation of coeliac disease (CD) to nonclassical, oligosymptomatic, and asymptomatic forms. We assessed clinical presentation of CD in children and adolescents in Central Europe.

Methods: Paediatric gastroenterologists in 5 countries retrospectively reported data of their patients diagnosed with CD. Clinical presentation was analyzed and the differences among very young (<3 years) and older children and adolescents were studied.

Results: Data from 653 children and adolescents (median age 7 years 2 months; 63.9% girls) from Croatia, Germany, Hungary, Italy, and Slovenia were available for the analysis. One fifth (N = 134) of all children were asymptomatic. In symptomatic children, the most common leading symptom was abdominal pain (33.3%), followed by growth retardation (13.7%) and diarrhoea (13.3%). The majority of symptomatic children (47.6%; N = 247) were polysymptomatic. Abdominal pain was the most common symptom in polysymptomatic (66.4%) as well as in monosymptomatic children (29.7%). Comparing clinical presentation of CD in very young children (younger than 3 years) with older children (3 years or older), we found that symptoms and signs of malabsorption were significantly more common in younger ($P < 0.001$), whereas abdominal pain and asymptomatic presentation were more common in older children and adolescents (both $P < 0.001$).

Conclusion: In children with CD, abdominal pain has become the most common symptom. However, in younger children, symptoms of malabsorption are still seen frequently. This raises a question about the underlying mechanism of observed change in clinical presentation in favour of nonclassical presentation and asymptomatic disease at certain age.

Key Words: Central Europe, children, clinical presentation, coeliac disease

What Is Known

- Coeliac disease has a diverse clinical presentation.
- There has been a shift in the clinical presentation from the historically classic symptoms of malabsorption to nonclassical, oligosymptomatic, and asymptomatic forms.

What Is New

- Abdominal pain is the most common leading symptom in children with coeliac disease in Central Europe.
- Abdominal pain is the most common in preschool and school-aged children, but in very young children (younger than 3 years) abdominal distension and diarrhoea have most often been observed.
- There is an important shift in clinical presentation at a certain age in favour of nonclassical presentation and asymptomatic disease.

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Coeliac disease (CD) is a lifelong systemic autoimmune disorder, elicited by gluten and related prolamines in genetically susceptible individuals and is one of the most common chronic diseases, affecting about 1% of the population. It has a very diverse clinical presentation, involving intestinal, extraintestinal, and even asymptomatic presentations (1–10). Due to its genetic background, CD is more common among family members of affected individuals and is associated with a number of other conditions, including type 1 diabetes mellitus, immunoglobulin A deficiency, autoimmune thyroiditis, and certain chromosomal anomalies such as Down, Turner, or Williams syndrome (1,11–18).

Symptoms of CD can be attributed to a combination of inflammation, nutrient deficiency caused by malabsorption, and autoimmune response to the enzyme tissue transglutaminase. In the past, CD has been known as the illness of the childhood, with characteristic clinical presentation of diarrhoea with malabsorption syndrome (19). Nowadays, we know that CD is a systemic disease that can occur at any age and is not limited to the digestive tract. Extraintestinal manifestations of the disease can affect almost every organ, including the nervous system, liver, skin, reproductive system, cardiovascular system, and musculoskeletal system, and are usually associated with a more serious clinical and histological picture (20,21). In addition, some of these manifestations can present in early childhood, whereas the others do not appear until adulthood or advanced age (20).

Several studies have shown a gradual shift in clinical presentation of CD from the historically classic symptoms of malabsorption to now more common nonclassical, oligosymptomatic, or even asymptomatic forms (2,10,19,22–31).

Therefore, the aim of our study was to assess the clinical presentation of CD in children and adolescents in Central Europe.

METHODS

The study was carried out as a part of the Focus IN CD project (Central Europe [CE] 111), co-financed by the Interreg CE Programme. Twelve partners from 5 CE countries (Croatia, Germany, Hungary, Italy, and Slovenia) participated in the project.

Participants and Study Design

For the collection of patient data, a special Web-based questionnaire that included questions regarding the clinical presentation of coeliac disease was designed and translated into the languages of all project partners. It is available at the following link: *https://www.interreg-central.eu/Content.Node/surveys.html*. The questionnaire was designed based on the clinical practice and European Society for Paediatric Gastroenterology Hepatology and Nutrition guidelines for diagnosing CD 2012 (32).

Paediatric gastroenterologists from different parts of Central Europe-Slovenia, Germany, Hungary, Italy, and Croatia, who work with children and adolescents with CD, were encouraged to participate via local and international networks of project partners. They were asked to complete the questionnaire using medical documentation of the children and adolescents younger than 19 years of age, diagnosed with CD in the 2016. Complete anonymization of the reported data was ensured. In Croatia, Hungary, and Slovenia the majority of patients with CD diagnosed by paediatric gastroenterologists during the study year were included, because almost all centres in the country participated in the study.

Medical records of children and adolescents with CD were analysed. We focused on the clinical presentation of CD at the time of diagnosis. We calculated median z score for weight for age and height for age at diagnosis based on the World Health Organization (WHO) standards.

We studied the differences between very young younger than 3 years), preschool (3–6 years), and school-aged (6 years or older) children. Also, the correlation of the diagnostic delays with the clinical presentation and diagnostic approach was assessed. Regional differences regarding the studied parameters were analysed.‘

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 for Windows. Descriptive statistics, independent samples T test, and chi-square test were used for the analysis.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (0120-383).

RESULTS

Data from 653 children and adolescents (median age 7 years 2 months; 95% confidence interval [CI] 6 years 10 months, 7 years 9 months; 63.9% girls) from Croatia (N = 66), Germany (N = 69), Hungary (N = 381), Italy (N = 83), and Slovenia (N = 54) were available for the analysis. One hundred thirty-four children (20.5%) were asymptomatic at the confirmation of the diagnosis (median age 7 years 5 months; 95% CI [6 years 9 months, 7 years 9 months]; 60.4%), other children were diagnosed with CD due to their signs and symptoms (median age 7 years 2 month; 95% CI [6 years 6 months, 8 years 4 months]; 64.7% girls). There was no significant difference in age at diagnosis between symptomatic and asymptomatic children ($P = 0.146$).

Almost a quarter of children with CD (24.0%) had a family member with known CD (Table 1). Occurrence of CD in first-degree relatives was significantly higher in the group of asymptomatic children (50.0% vs 12.5%; $P < 0.001$). Mothers were the most commonly affected family member (41.7%).

Slightly more than a quarter (177; 27.1%) of all children and adolescents belonged to a higher-risk group for the development of CD because of positive family history, other autoimmune comorbidities or other known conditions (see Table, Supplemental Digital Content 1, *http://links.lww.com/MPG/C100*, which demonstrates the distribution of asymptomatic and symptomatic patients with CD in different CD risk groups). There were no significant differences in sex between patients with CD who belonged (N = 177; 60.4% girls) and did not belong (N = 476; 65.1% girls) to any of the high-risk groups ($P = 0.155$).

Regarding the clinical presentation, we specifically focused on the leading symptom that urged the visit at the paediatric gastroenterologist. All other symptoms were also carefully recorded. One fifth (N = 134) of all children were asymptomatic at the diagnosis. The proportion of asymptomatic children was the highest in Italy and the lowest in Croatia; however, no significant differences were found between countries. Asymptomatic children were diagnosed mostly in the risk groups screening (65.7%) or population screening (22.4%).

The most common leading symptom in symptomatic children (N = 519), was abdominal pain (33.3%), being also the most common in every included country. The second most common leading symptom was growth retardation (13.7%), followed by diarrhoea (13.3%) and iron deficiency (10.2%) (Fig. 1). Among all recorded symptoms, abdominal pain was again the most common symptom (41.2%), followed by abdominal distension (25.7%) and diarrhoea (24.3%). Analysing clinical presentation with the respect to all recorded symptoms, we found abdominal pain to be the most common symptom in all the countries, except Italy, where diarrhoea was the most common (Table 2).

The majority of symptomatic children (47.6%; N = 247) were polysymptomatic, having 3 or more symptoms, followed

TABLE 1. Prevalence of coeliac disease among family members of newly diagnosed children and adolescents

Coeliac disease in the family (N; % within group)	All patients (N = 653)	Symptomatic (N = 519)	Asymptomatic (N = 134)	Sig.
First-degree relative	132 (20.2%)	65 (12.5%)	67 (50.0%)	<0.001
Mother	55 (41.7%)	34 (52.3%)	21 (31.3%)	0.012
Father	20 (15.1%)	8 (12.3%)	12 (17.9%)	0.257
Sister	48 (36.4%)	26 (40.0%)	22 (32.8%)	0.250
Brother	30 (22.7%)	10 (15.4%)	20 (29.8%)	0.037
Second-degree relative*	30 (4.6%)	24 (4.6%)	6 (4.5%)	0.579
Other distant relatives	6 (0.9%)	5 (0.9%)	1 (0.7%)	0.643
None	461 (70.6%)	400 (77.1%)	61 (45.5%)	<0.001
Unknown	35 (5.4%)	32 (6.2%)	3 (2.2%)	0.048

Some patients have >1 affected relative.
*Grandmother, grandfather, aunt, uncle, cousin, niece, nephew.

by monosymptomatic children (28.5%; N = 148). Among the monosymptomatic children, the most common symptom was abdominal pain (29.7%), followed by growth retardation and iron deficiency (16.9% and 14.2%, respectively). In polysymptomatic children abdominal pain was also the most common among symptoms (66.4%), followed by abdominal distension and diarrhoea (56.7% and 54.2%, respectively) (see Table, Supplemental Digital Content 2, *http://links.lww.com/MPG/C101*, which demonstrates the clinical presentation of CD in relation to the number of symptoms).

We also compared clinical presentation between very young children (younger than 3 years), preschool (3–6 years), and school-age children (≥6 years). Abdominal pain was the most common leading symptom in both, preschool (21.3%) and school-aged (31.7%) children. In very young children, diarrhoea was the most common leading symptom (23%), followed by growth retardation (16.2%) and abdominal distension (14.9%). In preschool children, the second most common leading symptoms were iron deficiency and growth retardation (both 11.8%) and in school-aged children growth retardation (9.5%) was second most common, followed by diarrhoea (8.3%) (Figure, Supplemental Digital Content 3, *http://links.lww.com/MPG/C102*, which shows some of the most common leading symptoms in very young, preschool, and school-aged children). In very young children, 6.8% were asymptomatic, in preschool children 18.9%, and in school-aged children 23.7% had no symptoms ($P < 0.05$). Statistically significant difference between very young, preschool, and school-aged children was observed for abdominal pain ($P < 0.001$), diarrhoea, and abdominal

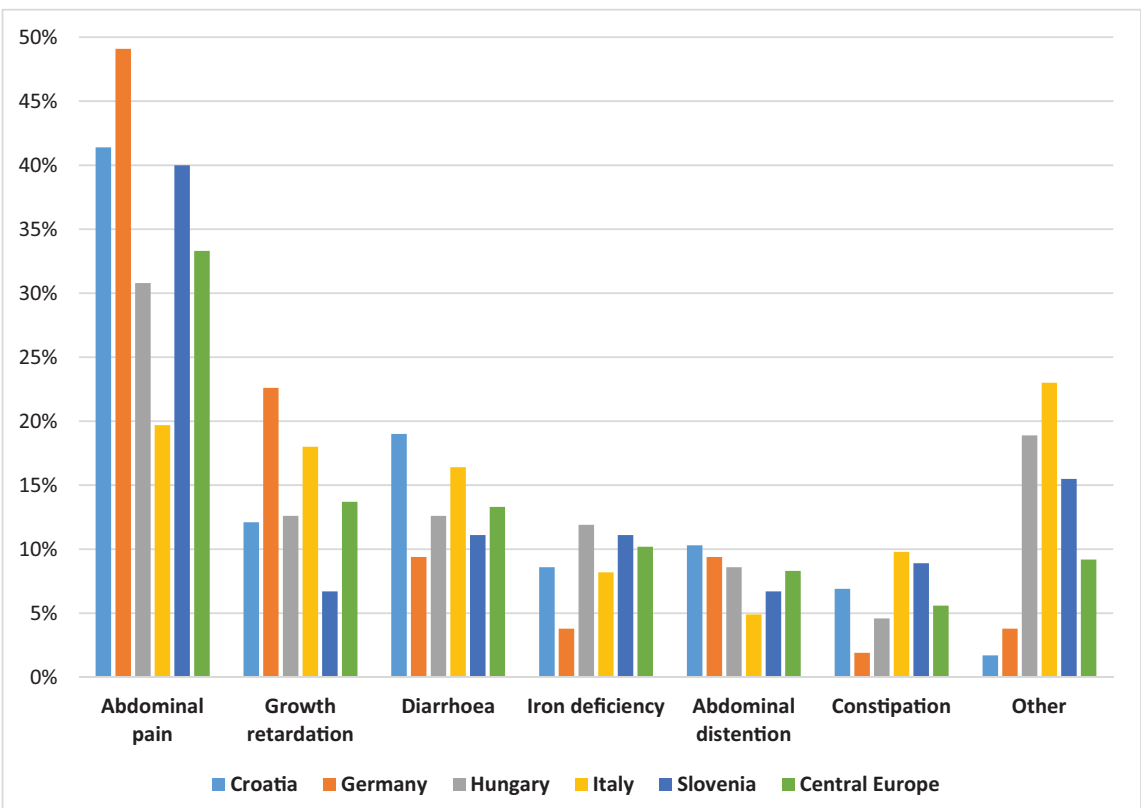

FIGURE 1. The most common leading symptom in symptomatic children and adolescents, presented by country.

TABLE 2. Clinical presentation of newly diagnosed children and adolescents. All recorded symptoms are presented

	Croatia (N = 66)	Germany (N = 69)	Hungary (N = 381)	Italy (N = 83)	Slovenia (N = 54)	CE (N = 653)	*Sig.*
Age at diagnosis	10 y 5 mo	7 y 3 mo	6 y 11 mo	6 y 6 mo	7 y 9 mo	7 y 2 mo	*0.060*
Median (range)	7 mo–18 y 1 mo	13 mo–18 y	15 mo–18 y 2 mo	14 mo–18 y 3 mo	14 mo–18 y 6 mo	7 mo–18 y 6 mo	
Asymptomatic	12.1%	23.2%	20.7%	26.5%	16.7%	20.5%	*0.241*
Abdominal pain	47.0%	58.0%	41.2%	22.9%	40.7%	41.2%	*<0.001*
Growth retardation	16.7%	18.8%	17.8%	19.3%	11.1%	17.5%	*0.761*
Diarrhoea	25.8%	27.5%	23.9%	24.1%	2.2%	24.3%	*0.959*
Iron deficiency	15.2%	4.3%	24.9%	10.8%	14.8%	19.1%	*<0.001*
Abdominal distension	19.7%	21.7%	31.5%	10.8%	20.4%	25.7%	*0.001*
Constipation	9.1%	5.8%	9.4%	19.3%	18.5%	11.0%	*0.017*
Flatulence	12.1%	7.2%	18.4%	3.6%	11.1%	14.1%	*0.002*
Weight loss	13.6%	4.3%	5.5%	10.8%	16.7%	7.8%	*0.007*
Appetite loss	9.1%	11.6%	7.6%	12.0%	18.5%	9.6%	*0.109*
Vomiting	10.6%	7.2%	3.4%	3.6%	9.3%	5.1%	*0.051*
DHD	4.5%	0	1.8%	1.2%	0	1.7%	*0.236*
Unexplained fatigue	9.1%	15.9%	6.8%	14.5%	13.0%	9.5%	*0.047*
Unexplained irritability	1.5%	13.0%	1.6%	3.6%	3.7%	3.2%	*<0.001*
Lactose intolerance	1.5%	1.4%	10.0%	0	9.3%	6.9%	*0.001*

Majority of patients had more than one symptom.
CE = Central Europe; DHD = Dermatitis Herpetiformis Duhring.

distension (both $P < 0.05$). Regarding all symptoms, in very young children, symptoms and signs of malabsorption were significantly more common ($P < 0.001$) than in older. On the contrary, abdominal pain was more common in older children and adolescents ($P < 0.001$). Also, asymptomatic disease was more common among older children ($P < 0.05$) (Table 3). Regarding the growth of children with CD, we found that they had a lower body weight (median z score for weight for age based on the WHO growth standard: −0.41; min −7.57; max 3.53), whereas their height was equal to the median of the WHO standard (median z-score for height: −0.07; min −5.65; max 7.29). We found that children with diagnostic delays longer than 3 years had lower body weight and shorter stature compared to those with delays shorter than 1 year (z score for weight: −0.93 and −0.39, respectively, $P < 0.05$; z score for height: −0.50 and −0.04, respectively; NS). No differences were found between girls and boys. In 9.8% of children and adolescents z score for weight for age was <-2.00 and in 5.4% z score for height for age was below −2.00. In Germany (median z score for height: −0.43), children with CD were smaller compared to children from Hungary and Croatia (median z score for height: −0.02 and 0.35, respectively; $P < 0.05$). There were no statistically significant differences in z scores for height and weight between other countries (see Table, Supplemental Digital Content 4, *http://links.lww.com/MPG/C103*, which shows median z score for weight and height according to the WHO reference). Asymptomatic children were slightly heavier and taller compared to the symptomatic children (median z score for weight: −0.12 and −0.45, respectively, $P < 0.05$; median z score for height: 0.05 and −0.09, respectively; $P < 0.05$) at the confirmation of the diagnosis. In children, in whom growth retardation was claimed to be one of the presenting symptoms, median z score for weight was −1.52 and for height −1.01.

TABLE 3. Difference in clinical presentation among very young (younger than 3 years) and older children

	<3 y Old (N = 74), %	3–6 y Old (N = 169), %	≥6 y Old (N = 410), %	Sig.
Asymptomatic	6.8	18.9	23.7	0.003
Abdominal pain	24.6	45.3	60.7	<0.001
Growth retardation	34.8	24.8	17.9	0.006
Diarrhoea	52.2	35.0	24.0	<0.001
Iron deficiency	23.2	38.0	18.2	<0.001
Abdominal distension	56.5	36.5	25.2	<0.001
Constipation	18.8	13.1	13.1	0.440
Flatulence	18.8	20.4	16.3	0.552
Weight loss	24.6	7.3	7.7	<0.001
Appetite loss	29.0	10.9	8.9	<0.001
Vomiting	13.0	5.1	5.4	0.050
DHD	0	1.5	2.9	0.267
Unexplained fatigue	17.4	8.0	12.5	0.134
Unexplained irritability	10.1	3.6	2.9	0.021
Lactose intolerance	4.3	8.8	9.6	0.375

Majority of patients had more than one symptom.

DISCUSSION

The age at diagnosis of CD has increased in the past decades (10,22,23). Similar to the other studies (10,22,23), median age at the diagnosis in children in our study was 7 years. The majority were girls, which has also been observed in previous studies (23,26,33). It is well known that CD is common among first-degree relatives of patients with CD, occurring in up to 10% or even more family members (11,13,16,17,34–41). In our study familial occurrence of CD was found in almost a quarter of children. In 20% of patients, CD was found among the first-degree family members. In the group of asymptomatic children, more family members with CD were found, probably since those children were intentionally tested due to a higher risk and were diagnosed before symptoms developed. Among first-degree family members, female members (69%) were affected more often, which is in line with other studies showing female predominance for CD (16,35,42,43). Although not statistically significant, Almeida et al (41) found higher prevalence of CD among siblings compared to parents. However, in our study only slightly more siblings than parents were affected (59.1% vs 56.8%). It is interesting that symptomatic patients have more female family

members with CD and asymptomatic more male relatives with CD. The reasons for this are unknown, it may be the influence of genes (X-chromosome) or hormones, or maybe family lifestyle is different when mothers have CD compared to fathers. It could be possible that mothers with CD cook for themselves gluten free, but other family members eat gluten regularly. And, when father is affected, all family members eat less gluten, so the children remain asymptomatic or oligosymptomatic for longer period.

In patients with CD, an increased prevalence of other autoimmune diseases has been observed, mainly due to common genetic background (14,44–46). In our study the most common autoimmune comorbidity of patients with CD was autoimmune thyroid disease, similar to the study of Bibbò et al (14), followed by type-1 diabetes mellitus, which is one of the most common paediatric autoimmune diseases (18).

It has been shown by many studies that clinical presentation of CD has changed during the past decades. Classical symptoms of malabsorption have become less prevalent and nonclassical, oligosymptomatic, or even asymptomatic forms of disease have become more and more common (2,10,19,22–31).

The most common symptom observed in our study was abdominal pain, followed by growth retardation, diarrhoea, and iron deficiency. Among included countries, significant difference was observed regarding the most common symptom, with Italy being the only country where diarrhoea was more common than abdominal pain. Abdominal pain was the most common in preschool and school-aged children; however, in very young children diarrhoea was observed more often than in older. Similar was found in the study of Van Kalleveen et al (26) with abdominal pain being the most common symptom. The classic CD triad of symptoms (chronic diarrhoea, failure to thrive, and distended abdomen) was found mostly in younger children and with increasing age, atypical symptoms became more common. As in our study, iron deficiency anaemia was frequently seen (22.9%) (26). Similar, Jansen et al (47) found abdominal pain to be the most common symptom (57%) and diarrhoea was found in 21%, which is comparable to our results. We found that in very young children (<3 years) symptoms and signs of malabsorption were significantly more common ($P < 0.001$) than in older children, posing a question what is the underlying mechanism of observed shift in clinical presentation at a certain age in favour of nonclassical presentation and asymptomatic disease.

In our study, growth retardation was shown to be common in all age groups. However, it is important to note that majority of patients did not present with major impairment of growth, which means that good nutritional status does not exclude CD. By the calculated *z* score we found shorter stature in children in whom CD has been undiagnosed for many years. Also, children with CD had lower body weight compared to healthy children. Both results are in line with the study of Comba et al (48) where delay in CD diagnosis negatively affected both the height and weight of children. Similar was found by the study of Green et al (19) where recurrent abdominal pain and growth issues (short stature and failure to thrive) were among the most common presentations, each accounting for about 25%. Diarrhoea was seen in less than 10% of cases (19), which is less than observed in our study. Similar to our results, most children who presented with diarrhoea were in the very young age group and as in our study, growth issues occurred in all age groups (19).

Asymptomatic CD has become increasingly prevalent which was shown also by the study of Rutz et al (49), where by the screening of healthy adolescents almost 1% of asymptomatic patients with CD with no family history of CD were found (49). In our study one fifth of included children reported no symptoms and were mostly diagnosed by risk group and population screening, showing the importance of such measures. However, mass screening remains controversial and is currently not recommended (12,50).

To our knowledge, the present study is the first study assessing clinical presentation of children with CD in the Central Europe and also one of the very few in which documented data were obtained from medical records rather than being based on retrospective recall of patients with CD. One of the limitations is the small number of participating diagnostic centres in some countries, which did not allow us to get the complete insight into the patient management in the region. Also, the number of included patients differs between participating countries, with more patients in Hungary than in other countries. A further limitation is the retrospective nature of assessment of existing health care records. This is especially true in unspecific symptoms such as abdominal pain. However, in the majority of regions (Croatia, Hungary, and Slovenia) we could include data of almost all patients diagnosed with CD during the study period, which is a strength of this study.

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REFERENCES

1. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr* 2020;70:141–56.
2. Rampertab DS, Pooran N, Brar P, et al. Trends in the presentation of celiac disease. *Am J Med* 2006;4:355.e9–355.e14.
3. Parzanese I, Qehajaj D, Patrinicola F, et al. Celiac disease: from pathophysiology to treatment. *World J Gastrointest Pathophysiol* 2017;8:27–38.
4. Iwańczak B, Matusiewicz K, Iwańczak F. Clinical picture of classical, atypical and silent celiac disease in children and adolescents. *Adv Clin Exp Med* 2013;22:667–73.
5. Fasano A. Clinical presentation of celiac disease in the pediatric population. *Gastroenterology* 2005;128:S68–73.
6. Catassi C, Gatti S, Fasano A. The new epidemiology of celiac disease. *J Pediat Gastroent Nutr* 2014;5:S7–9.
7. Altobelli E, Paduano R, Di Orilo F. Burden of celiac disease in Europe: a review of its childhood and adulthood prevalence and incidence as of September 2014. *Ann Ig* 2014;26:485–98.
8. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018;391:70–81.
9. Laass MW, Schmitz R, Uhlig HH, et al. The prevalence of celiac disease in children and adolescents in Germany. *Dtsch Arztebl Int* 2015;112:553–60.
10. Ravikumara M, Tuthill DP, Jenkins HR. The changing clinical presentation of coeliac disease. *Arch Dis Child* 2006;91:969–71.
11. Dubé C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. *Gastroenterology* 2005;128:S57–67.
12. Ludvigsson JF, Card TR, Kaukinen K, et al. Screening for celiac disease in the general population and in high-risk groups. *United European Gastroenterol J* 2015;3:106–20.
13. Mustalahti K, Sulkanen S, Holopainen P, et al. Coeliac disease among healthy members of multiple case coeliac disease families. *Scand J Gastroenterol* 2002;37:161–5.
14. Bibbò S, Pes GM, Usai-Satta P, et al. Chronic autoimmune disorders are increased in coeliac disease: a case-control study. *Medicine (Baltimore)* 2017;96:e8562.
15. Hagopian W, Lee HS, Liu E, et al. Co-occurrence of type 1 diabetes and celiac disease autoimmunity. *Pediatrics* 2017;140:e20171305.

16. Singh P, Arora S, Lal S, et al. Risk of celiac disease in the first- and second-degree relatives of patients with celiac disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2015;110:1539–48.
17. Dolinsek J, Urlep D, Karell K, et al. The prevalence of celiac disease among family members of celiac disease patients. *Wien Klin Wochenschr* 2004;116:8–12.
18. Kurppa K, Laitinen A, Agardh D. Coeliac disease in children with type 1 diabetes. *Lancet Child Adolesc Health* 2018;2:133–43.
19. Green PH, Krishnareddy S, Lebwohl B. Clinical manifestations of celiac disease. *Dig Dis* 2015;33:137–40.
20. Laurikka P, Nurminen S, Kivelä L, et al. Extraintestinal manifestations of celiac disease: early detection for better long-term outcomes. *Nutrients* 2018;1:1015.
21. Nurminen S, Kivelä L, Huhtala H, et al. Extraintestinal manifestations were common in children with coeliac disease and were more prevalent in patients with more severe clinical and histological presentation. *Acta Paediatr* 2019;108:681–7.
22. Tapsas D, Hollén E, Stenhammar L, et al. The clinical presentation of coeliac disease in 1030 Swedish children: changing features over the past four decades. *Dig Liver Dis* 2016;48:16–22.
23. Kivelä L, Kaukinen K, Lähdeaho ML, et al. Presentation of celiac disease in Finnish children is no longer changing: a 50-year perspective. *J Pediatr* 2015;167:1109–15.
24. Roma E, Panayiotou J, Karantana H, et al. Changing pattern in the clinical presentation of pediatric celiac disease: a 30-year study. *Digestion* 2009;80:185–91.
25. Visakorpi JK, Mäki M. Changing clinical features of coeliac disease. *Acta Paediatr Suppl* 1994;83:10–3.
26. Van Kalleveen MW, De Meij T, Plötz FB. Clinical spectrum of paediatric coeliac disease: a 10-year single-centre experience. *Eur J Pediatr* 2018;177:593–602.
27. Gokce S, Arslantas E. Changing face and clinical features of celiac disease in children. *Pediatr Int* 2015;57:107–12.
28. Tajuddin T, Razif S, Dhar R, et al. Clinical presentation of adult coeliac disease. *Ir Med J* 2011;104:20–2.
29. Campbell CB, Roberts RK, Cowen AE. The changing clinical presentation of coeliac disease in adults. *Med J Aust* 1977;1:89–93.
30. Green PHR, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: results of a national survey. *Am J Gastroenterol* 2001;96:126–31.
31. Agardh D, Lee H, Kurppa K, et al. Clinical features of celiac disease: a prospective birth cohort. *Pediatrics* 2015;135:627–34.
32. Husby S, Koletzko S, Korponay-Szabo IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediat Gastroent Nutr* 2012; 54:136–60.
33. Tanpowpong P, Broder-Fingert S, Katz AJ, et al. Age-related patterns in clinical presentations and gluten-related issues among children and adolescents with celiac disease. *Clin Transl Gastroenterol* 2012;3:e9.
34. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut* 2013;62:43–52.
35. Mishra A, Prakash S, Kaur G, et al. Prevalence of celiac disease among first-degree relatives of Indian celiac disease patients. *Dig Liver Dis* 2016;48:255–9.
36. Uenishi RH, Gandolfi L, Almeida LM, et al. Screening for celiac disease in 1st degree relatives: a 10-year follow-up study. *BMC Gastroenterol* 2014;14:36.
37. Nellikkal SS, Hafed Y, Larson JJ, et al. High prevalence of celiac disease among screened first-degree relatives. *Mayo Clin Proc* 2019;94:1807–13.
38. Doğan Y, Yildirmaz S, Ozercan IH. Prevalence of celiac disease among first-degree relatives of patients with celiac disease. *J Pediatr Gastroentrol Nutr* 2012;55:205–8.
39. Biagi F, Campanella J, Bianchi PI, et al. The incidence of coeliac disease in adult first degree relatives. *Dig Liver Dis* 2008;40:97–100.
40. Rubio-Tapia A, Van Dyke CT, Lahr BD, et al. Predictors of family risk for celiac disease: a population-based study. *Clin Gastroenterol Hepatol* 2008;6:983–7.
41. Lopes de Almeida P, Gandolfi L, Modelli IC, et al. Prevalence of celiac disease among first degree relatives of Brazilian celiac patients. *Arq Gatsroentrol* 2008;45:69–72.
42. Megiorni F, Mora B, Bonamico M, et al. HLA-DQ and susceptibility to celiac disease: evidence for gender differences and parent-of-origin effects. *Am J Gastroenterol* 2008;103:997–1003.
43. Wessels MMS, De Rooij N, Roovers L, et al. Towards an individual screening strategy for first-degree relatives of celiac patients. *Eur J Pediatr* 2018;177:1585–92.
44. Lauret E, Rodrgo L. Celiac disease and autoimmune-associated conditions. *Biomed Res Int* 2013;2013:127589.
45. Lundin KE, Wijmenga C. Coeliac disease and autoimmune disease-genetic overlap and screening. *Nat Rev Gastroenterol Hepatol* 2015;12:507–15.
46. Kahaly GJ, Frommer L, Schuppan D. Celiac disease and endocrine autoimmunity—the genetic link. *Autoimmun Rev* 2018;17:1169–75.
47. Jansen M, Van Zelm M, Groeneweg M, et al. The identification of celiac disease in asymptomatic children: the generation R study. *J Gastroenterol* 2018;53:377–86.
48. Comba A, Çaltepe G, Yüce O, et al. Effects of age of diagnosis and dietary compliance on growth parameters of patients with celiac disease. *Arch Argent Pediatr* 2018;116:248–55.
49. Rutz R, Ritzler E, Fierz W, et al. Prevalence of asymptomatic celiac disease in adolescents of Eastern Switzerland. *Swiss Med Wkly* 2002;132:43–7.
50. Kivelä L, Kurppa K. Screening for coeliac disease in children. *Acta Paediatr* 2018;107:1879–87.