Clinical Presentation in Children With Coeliac Disease in Central Europe

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 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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Clinical Presentation in Children

Celiac disease (CD) is a lifelong systemic autoimmune disorder, elicited by gluten and related prolamine 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 present (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) 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 assured. 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 months; 95% CI [6 years 6 months, 7 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% vs 26.5%; P = 0.002).

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...
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

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

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

FIGURE 1. The most common leading symptom in symptomatic children and adolescents, presented by country.
Majority of patients had more than one symptom. CE = Central Europe; DHD = Dermatitis Herpetiformis Duhring.

**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

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

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Croatia (N = 66)</th>
<th>Germany (N = 69)</th>
<th>Hungary (N = 381)</th>
<th>Italy (N = 83)</th>
<th>Slovenia (N = 54)</th>
<th>CE (N = 653)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>7 mo–18 y 1 mo</td>
<td>13 mo–18 y</td>
<td>14 mo–18 y</td>
<td>14 mo–18 y</td>
<td>14 mo–18 y</td>
<td>7 y 2 mo</td>
<td>0.060</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>12.1%</td>
<td>23.2%</td>
<td>20.7%</td>
<td>26.5%</td>
<td>26.5%</td>
<td>20.5%</td>
<td>0.241</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>47.0%</td>
<td>58.0%</td>
<td>41.2%</td>
<td>22.9%</td>
<td>22.9%</td>
<td>40.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>16.7%</td>
<td>18.8%</td>
<td>17.8%</td>
<td>19.3%</td>
<td>19.3%</td>
<td>11.1%</td>
<td>0.761</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>25.8%</td>
<td>27.5%</td>
<td>23.9%</td>
<td>24.1%</td>
<td>24.1%</td>
<td>2.2%</td>
<td>0.959</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>15.2%</td>
<td>4.3%</td>
<td>24.9%</td>
<td>10.8%</td>
<td>14.8%</td>
<td>19.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>19.7%</td>
<td>21.7%</td>
<td>31.5%</td>
<td>10.8%</td>
<td>20.4%</td>
<td>25.7%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>&lt;3 y Old (N = 74),</th>
<th>3–6 y Old (N = 169),</th>
<th>≥6 y Old (N = 410),</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>6.8</td>
<td>18.9</td>
<td>23.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24.6</td>
<td>45.3</td>
<td>60.7</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>34.8</td>
<td>24.8</td>
<td>17.9</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>52.2</td>
<td>35.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>23.2</td>
<td>38.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>56.5</td>
<td>36.5</td>
<td>25.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>18.8</td>
<td>13.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>18.8</td>
<td>20.4</td>
<td>16.3</td>
</tr>
<tr>
<td>Weight loss</td>
<td>24.6</td>
<td>7.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>29.0</td>
<td>10.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13.0</td>
<td>5.1</td>
<td>5.4</td>
</tr>
<tr>
<td>DHD</td>
<td>0.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Unexplained fatigue</td>
<td>17.4</td>
<td>8.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Unexplained irritability</td>
<td>10.1</td>
<td>3.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>4.3</td>
<td>8.8</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Majority of patients had more than one symptom.
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 Bibbo 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, diarrhea, and iron deficiency. Among included countries, significant difference was observed regarding the most common symptom, with Italy being the only country where diarrhea was more common than abdominal pain. Abdominal pain was the most common in pre-school and school-aged children; however, in very young children diarrhea 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 diarrhea, 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 anemia was frequently seen (22.9%) (26). Similar, Jansen et al (47) found abdominal pain to be the most common symptom (57%) and diarrhea 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 questionnaire to the physicians and patients with CD from Croatia, Germany, Hungary, Italy, and Slovenia, who answered the questionnaire, thus enabling us to the study. We are also grateful to all the project partners, who helped in designing the questionnaire and its translation to the partner languages as well as in distributing the questionnaire to the physicians and patients with CD from participating regions.

Acknowledgments: The authors wish to thank all the participating physicians and coeliac disease patients or their caregivers from Croatia, Germany, Hungary, Italy, and Slovenia, who answered the questionnaires, thus enabling us to the study. We are also grateful to all the project partners, who helped in designing the questionnaire and its translation to the partner languages as well as in distributing the questionnaire to the physicians and patients with CD from participating regions.

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