Usefulness of Symptoms to Screen for Celiac Disease

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KEY WORDS

case-finding, celiac disease, questionnaire, screening, symptom

ABBREVIATIONS

CD—celiac disease
EMA—endomysial antibody
Ig—immunoglobulin
tTG—tissue transglutaminase

Dr Rosén conceptualized and designed the study, constructed questionnaires, collected data, performed the analyses, and wrote the manuscript; Dr Sandström contributed to the design of the study and interpretation of the data and critically revised the manuscript; Drs Carlsson and Högberg contributed to the design of the study and data collection and critically revised the manuscript; Dr Olén contributed to interpretation of the data and critically revised the manuscript; Mr Stenlund contributed to the design of the study, assisted with the statistical analyses and interpretation of the data, and critically revised the manuscript; Dr Ivarsson is the principal investigator and contributed to the design of the study, data collection, and interpretation of data and critically revised the manuscript; and all authors approved the final manuscript.

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WHAT’S KNOWN ON THIS SUBJECT:

Celiac disease (CD) often goes undiagnosed. Current guidelines suggest intensified active case-finding, with liberal testing of children with CD-associated symptoms and/or conditions. However, methods for also finding undiagnosed CD cases in the general population should be explored and evaluated.

WHAT THIS STUDY ADDS:

In a population-based CD screening, information on CD-associated symptoms and conditions, obtained before knowledge of CD status, was not useful in discriminating undiagnosed CD cases from non-CD children. The majority of screening-detected CD cases had no CD-associated symptoms or conditions.

abstract

OBJECTIVE: To describe the frequency of symptoms and associated conditions among screening-detected celiac disease (CD) cases and non-CD children and to evaluate questionnaire-based case-finding targeting the general population.

METHODS: In a population-based CD screening of 12-year-olds, children and their parents completed questionnaires on CD-associated symptoms and conditions before knowledge of CD status. Questionnaire data for those who had their CD detected in the screening (n = 153) were compared with those of children with normal levels of CD markers (n = 7016). Hypothetical case-finding strategies were also evaluated. Questionnaires were returned by 7054 (98%) of the children and by 6294 (88%) of their parents.

RESULTS: Symptoms were as common among screening-detected CD cases as among non-CD children. The frequency of children with screening-detected CD was similar when comparing the groups with and without any CD-related symptoms (2.1% vs 2.1%; P = .930) or CD-associated conditions (3.6% vs 2.1%; P = .07). Case-finding by asking for CD-associated symptoms and/or conditions would have identified 52 cases (38% of all cases) at a cost of analyzing blood samples for 2282 children (37%) in the study population.

CONCLUSIONS: The current recommended guidelines for finding undiagnosed CD cases, so-called active case-finding, fail to identify the majority of previously undiagnosed cases if applied in the general population of Swedish 12-year-olds. Our results warrant further studies on the effectiveness of CD case-finding in the pediatric population, both at the clinical and population-based levels. Pediatrics 2014;133:211–218
Celiac disease (CD) is a chronic systemic autoimmune disorder triggered by ingestion of dietary gluten and is characterized by small intestinal inflammation and villous atrophy.\(^4\) The disease may present at any age and with a large variety of symptoms and signs.\(^2,3\) Serological markers with high sensitivity and specificity for CD are available, but unless the values of the CD markers are very high, a small intestinal biopsy revealing villous atrophy is required for final diagnosis.\(^4\) The only available treatment is lifelong strict adherence to a gluten-free diet.\(^2\)

Population-based screening studies in children have revealed a CD prevalence ranging from 0.3% to 3%, always with the majority of cases being previously undiagnosed.\(^5–10\) The highly variable clinical expression probably contributes to the difficulties in identifying children with untreated CD. International guidelines suggest active CD case-finding by identifying and testing groups with an increased risk of CD.\(^4\) According to recommendations, testing with CD serological markers should be offered to all children seeking health care with any of the wide range of symptoms that should lead to a suspicion of CD (eg, failure to thrive, nausea, vomiting, abdominal pain, anemia, diarrhoea, or constipation). Testing should also be offered to children with conditions known to be associated with an increased risk of CD (eg, type 1 diabetes, thyroid disease, and trisomy 21) or to those with a family history of CD, even if they are asymptomatic.

Several studies have presented active case-finding strategies and concluded that they are effective by showing an increased incidence of CD in the group subjected to the case-finding, both in the clinical setting and at a population-based level.\(^11–15\) However, these earlier studies have limitations because control groups were lacking, and the sensitivity, specificity, and predictive values of the suggested strategies therefore remain to be evaluated.

The aim of this study was twofold: first, to describe CD-associated symptoms and conditions among screening-detected CD cases and non-CD children, reported before knowledge of their CD status; and second, to evaluate questionnaire-based case-finding targeting the general population.

**METHODS**

**Overall Study Design**

This study emanates from a population-based CD screening of 12-year-olds, known as the ETICS (Exploring The Iceberg of Celiacs in Sweden) study, which is described in detail elsewhere.\(^7,16\) Before knowledge of CD marker results, all children completed questionnaires regarding their CD-associated symptoms. Questionnaires were completed at school, in their classrooms, and supervised by a teacher or a school nurse. Parents were asked to report on the child’s CD-associated conditions, including CD family history, in a questionnaire brought home by the children. Blood samples from all children without previously known CD were analyzed for anti-tissue transglutaminase antibodies (tTG) of immunoglobulin A (IgA)-type (Celikey; Phadia, Freiburg, Germany) and for total serum IgA (BN ProSpec System; Dade Behring Marburg GmbH, Marburg, Germany). When intermediate tTG-IgA levels were found, additional analysis of endomyosal antibodies (EMA-IgA) was performed (The Binding Site, Birmingham, UK). Samples with serum IgA <0.5 g/L were also analyzed for tTG-IgG, and if intermediate levels were found they were also analyzed for EMA-IgG. The study was approved by the Regional Ethical Review Board of Umeå university, Umeå.

Serological criteria for recommending a small intestinal biopsy were as follows: tTG-IgA >4 U/mL, tTG-IgG >6 U/mL, or intermediate levels of tTG-IgA (2–4 U/mL) or tTG-IgG (3–6 U/mL), in combination with EMA positivity (≥1.5). Children with CD marker levels below these criteria were considered as non-CD children.

Criteria for a screening-detected CD diagnosis were as follows: villous atrophy (Marsh IIIa–IIIc), crypt hyperplasia (Marsh II), or increased count of intraepithelial lymphocytes (Marsh I) in combination with HLA-DQ2 or DQ8 haplotype, signs or symptoms suggestive of CD, and clinical or serological response to a gluten-free diet. Small intestinal biopsy samples were obtained either by endoscopy or by suction capsule. Clinical characteristics of the CD cases and details of the centralized biopsy evaluation have been described elsewhere.\(^17\)

**Study Population**

All children in the sixth grade (\(n = 10\,041\)) from 5 regions across Sweden were invited to participate in the study. When asking parents for informed consent, we also asked for previously diagnosed CD in their child. A previous diagnosis of CD was confirmed through the National Swedish Childhood Celiac Disease Register\(^18\) and/or medical records. Children with previously diagnosed CD were excluded from the main analyses of the study. Inclusion criteria for the main analyses were as follows: (1) having a blood sample analyzed for CD markers and (2) having returned questionnaire(s) before knowledge of the results of the CD markers and either (3a) fulfilling CD diagnosis criteria (screening-detected CD) or (3b) having CD marker levels below the criteria for recommending a biopsy (non-CD children).

**Questionnaires**

A working group of clinicians guided the development of questionnaires, in which
we opted for retrieving information that is usually obtained in the medical history of children seeking health care for suspected CD. Because CD may present with a large variety of symptoms, the questionnaire completed by the children covered items on tiredness, poor appetite, nausea, stomach ache, upset stomach, abdominal gas, bloating, hard stools, loose stools, and lactose intolerance. Response alternatives were never, seldom, sometimes, often, and always over the past 6 months. Parents were asked to report the presence of CD-associated disorders in the child (anemia, type 1 diabetes, thyroid disease, rheumatic disease, inflammatory bowel disease, vitiligo, alopecia areata, dermatitis herpetiformis, trisomy 21, and Turner syndrome), as well as the presence of CD among the child’s first-degree relatives.

Statistical Analysis

Questionnaire data were compared at the group level, and the distribution of categorical variables was summarized as counts and proportions. Comparisons of proportions were made with the \( \chi^2 \) test (Fisher’s exact test). Self-reported symptoms were originally captured with 5 predetermined response alternatives, but each symptom was dichotomized as present if the response was “always” or “often.” Internal nonresponses were excluded from the analysis. Logistic regression analysis, controlled for gender, was performed to estimate the probability of undiagnosed CD if having a certain CD-associated symptom or condition, and the results are presented as odds ratios with 95% confidence intervals. In addition, we calculated summated scores for symptoms, in which the response alternative “never” was graded as 1, “seldom” as 2, and so forth. Thus, the 10 symptoms gave a minimum score of 10 and a maximum score of 50. Median values of summated scores between groups were compared with the Mann-Whitney \( U \) test. The predictive ability of hypothetical case-finding strategies was tested, and sensitivity, specificity, and predictive values were calculated. In these calculations, internal nonresponse was categorized as no symptom or no CD-associated condition. A 2-sided \( P \) value of <.05 or an odds ratio with a confidence interval not including 1 was considered to be statistically significant.

RESULTS

Of 10,041 who were invited, 7567 children (and their parents) consented to participate, 66 (0.9%) of whom already had previously detected CD. Blood samples from 7208 children without previously detected CD were analyzed for CD serological markers, and of these, 153 (2.1%) later had their CD confirmed (Fig 1). Those with elevated levels of CD markers (\( n = 39 \)) but no confirmed CD diagnosis were excluded from further analyses. Questionnaires returned after knowledge of CD markers was obtained (\( n = 112 \)) were excluded from the analyses. In total, we analyzed 7054 questionnaires completed by children without previously known CD: 149 (97%) from screening-detected CD children and 6905 (98%) from non-CD children. Parental questionnaires for 6294 children without previously known CD were included in the main analyses: 140 (92%) completed by parents of screening-detected CD cases and 6154 (88%) completed by parents of non-CD children. For the majority of children (\( n = 6226; 87\% \)), there were questionnaire data for both them and their parents. In addition, parental questionnaires (\( n = 58; 88\% \)) regarding previously diagnosed CD cases were included in a subanalysis. The proportion of participating girls was 52% among screening-detected CD cases, 49% among non-CD children, and 67% among previously diagnosed cases.

Symptoms

In a logistic regression modeling procedure, adjusted for gender, the presence of a symptom or symptoms did not significantly increase the odds of having undiagnosed CD (Table 1). The median (interquartile range) value of summed scores of symptoms for
screening-detected cases, which was 16 (8), did not differ significantly from the median value for the non-CD children, which was 17 (7) (Mann-Whitney U test, P = .20).

**Associated Conditions**

As shown in Table 2, children with either thyroid disease or trisomy 21 had significantly increased odds of having undiagnosed CD, although with large confidence intervals due to few cases. Children with a family history of CD did not have statistically significant increased odds of having undiagnosed CD.

Questionnaire data available for children with previously diagnosed CD revealed that 24 of 58 (41%) had any CD-associated condition, compared with 14 of 140 (10%) among screening-detected cases and 367 of 6154 (6%) among non-CD children (Pearson’s χ² test, P < .001). A similar pattern was found for family history of CD, where 12 of 58 (21%) of previously detected CD children had a first-degree relative with CD compared with 6 of 140 (4.3%) among screening-detected cases and 138 of 6154 (2%) among non-CD children (Pearson’s χ² test, P < .001).

**How Effective Is Questionnaire-Based Case-Finding in a General Population of 12-Year-Olds?**

As shown in Fig 2A, 2333 (33%) of the children without a previous CD diagnosis reported having ≥1 of the listed symptoms. If the presence of ≥1 of these symptoms were to be used as a case-finding tool for CD, 50 of 149 (34%) of the previously undiagnosed CD cases in our study population would have been identified. Such a strategy had a sensitivity of 34%, a specificity of 67%, a positive predictive value of 2%, and a negative predictive value of 98%. CD prevalence was similar in the groups with and without symptoms (2.1% vs. 2.1%; Fisher’s exact test, P = .93).

With a similar approach, testing only those with CD-associated conditions would have resulted in finding 14 of 140 (10%) of the previously undiagnosed CD cases at a cost of analyzing blood samples for 381 (6.0%) of the study population. Such a case-finding tool had a sensitivity of 10%, a specificity of 94%, a positive predictive value of 3.7%, and a negative predictive value of 98%. There was no significant difference in CD prevalence between the groups with and without any CD-associated condition (3.7% vs. 2.1%; Fisher’s exact test, P = .07).

### TABLE 1 Non-CD Children and Screening-Detected CD Children Reporting Symptoms Before Knowledge of Results of CD Serological Markers

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Non-CD (n = 6905)</th>
<th>CD (n = 149)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1175</td>
<td>17.3</td>
<td>26</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>338</td>
<td>5.1</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>250</td>
<td>3.4</td>
<td>4</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>473</td>
<td>7.1</td>
<td>10</td>
</tr>
<tr>
<td>Upset stomach</td>
<td>353</td>
<td>5.2</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal gas</td>
<td>337</td>
<td>5.0</td>
<td>10</td>
</tr>
<tr>
<td>Bloating</td>
<td>150</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>Hard stools</td>
<td>493</td>
<td>7.4</td>
<td>17</td>
</tr>
<tr>
<td>Loose stools</td>
<td>157</td>
<td>2.4</td>
<td>4</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>336</td>
<td>5.0</td>
<td>9</td>
</tr>
<tr>
<td>Any symptom†</td>
<td>2283</td>
<td>33.1</td>
<td>50</td>
</tr>
</tbody>
</table>

CD, celiac disease; CI, confidence interval; OR, odds ratio.

† Self-reported symptoms present often or always during the past 6 months.

### TABLE 2 Non-CD Children and Screening-Detected CD Children With CD-Associated Conditions, Reported by Their Parents Before Knowledge of Results of the CD Serological Markers

<table>
<thead>
<tr>
<th>CD-Associated Condition</th>
<th>Non-CD (n = 6154)</th>
<th>CD (n = 149)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Vitiigo</td>
<td>83</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>57</td>
<td>0.9</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>17</td>
<td>0.3</td>
<td>2</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>22</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>Alopecia</td>
<td>16</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>4</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>17</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>19</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>5</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CD family history†</td>
<td>138</td>
<td>2.2</td>
<td>6</td>
</tr>
<tr>
<td>Any associated condition‡</td>
<td>367</td>
<td>6.0</td>
<td>14</td>
</tr>
</tbody>
</table>

CD, celiac disease; CI, confidence interval; OR, odds ratio.

† OR of being a screening-detected CD case if condition(s) present compared with if condition(s) not present (with 95% CI) calculated by logistic regression, adjusted for gender.

‡ CD reported as present in the child’s biological mother, father, and/or siblings.
In total, 2282 (36.7%) of the children without a previous CD diagnosis would have fulfilled the criteria for having a blood sample taken if the presence of any of the listed symptoms and/or CD-related conditions had been used in a hypothetical case-finding strategy (Fig 2B). The sensitivity for this combined case-finding tool was 38%, the specificity was 63%, the positive predictive value was 2%, and the negative predictive value was 98% (Fig 2B).

**DISCUSSION**

In this large, population-based CD-screening study we found that CD-associated symptoms and conditions are as common among screening-detected CD cases as among non-CD children when reported before knowledge of their CD status. We also found that there is no difference in CD prevalence among symptomatic and asymptomatic children, and that CD case-finding conducted by asking for CD-associated symptoms and conditions had a poor diagnostic accuracy in a general Swedish population of 12-year-olds.

This study has several strengths. To the best of our knowledge, this is the first study of a hypothetical case-finding strategy with prospective collection of questionnaire data and CD serological marker testing of all children in the study population, allowing for evaluation of the diagnostic performance of a questionnaire-based approach as a first step in finding CD in a general pediatric population. A limitation of the study is that the questionnaires were constructed specifically for this study and cannot be used for comparison with other validated instruments measuring symptoms. Because neither the reliability nor the validity of the questionnaires had been tested before, there may be symptomatic children whose symptoms were not reported, and vice versa. The associated conditions asked for were not validated against medical records, and the accuracy of the information can be questioned. However, because the parents were the reporters and the diseases asked for in the questionnaires were well defined, we believe that their answers are reliable.

Due to ethical and practical reasons, only children with elevated levels of CD markers were referred for small intestinal biopsy, and we acknowledge that among the children considered as non-CD children, a few might actually have CD. However, because the cutoff for the serological markers was set to prioritize sensitivity, and because of the large sample of non-CD children, we do not believe that this possibility had a substantial effect on the results. We performed a sensitivity analysis of the case-finding strategies by including those with elevated CD markers but no confirmed CD (n = 39) in the estimate, but because there were no differences...
in the conclusions, they were excluded for purposes of clarity when presenting the data. Although we conducted a large screening, this study includes a relatively small number of cases \( (n = 149) \), which could have been a power issue. However, considering that \( > 7000 \) children have been screened, we are convinced that the study is large enough for us to be able to make relevant inferences.

We found that even if some of the CD cases were symptomatic, symptoms were reported to the same extent as in non-CD children. These findings are in line with a study by Hoffenberg et al., who showed that before knowledge of CD status the number of symptoms reported among CD cases was similar to that in the control group. Interestingly, they also showed that after knowledge of elevated CD markers, a significantly greater number of symptoms were reported. In a follow-up study in the screening-detected CD children involved in the current study, we also observed a phenomenon of retrospective recognition of symptoms in relation to the CD diagnosis. This finding reflected the experience of becoming aware of symptoms first when perceiving improvement after initiated treatment, but interestingly some of the children also stated that perhaps they were prone to identifying previous symptoms to justify that something good came out of receiving the diagnosis.

Our findings indicate that a questionnaire concerning symptoms cannot be used to discriminate unrecognized CD children from their non-CD peers, which is in line with a recent CD-screening study in adults in the United States. Despite the fact that this is an article with so-called negative findings, our results corroborate the challenge in finding CD cases by means other than using serological CD markers. Although this study was population-based, our findings may indicate that active CD case-finding within clinical practice that is based on symptoms may also be difficult. In fact, our findings are in accord with a recent Swedish study evaluating the use of tTG-IgA in clinical practice, which found that among 26 180 children screened for CD primarily by general practitioners or pediatricians (and presumably because of symptoms or conditions suggestive of CD), only 1.3% were diagnosed with CD. A systematic overview of diagnostic testing for CD among adult patients with abdominal symptoms within primary care also revealed that gastrointestinal symptoms alone were not sufficiently accurate for predicting CD.

Case-finding by asking for CD-associated conditions also revealed poor diagnostic performance in this population, and the prevalence of undiagnosed CD among children with these conditions was lower than the CD prevalence usually described for these groups. However, policies for active case-finding in certain risk groups have already been introduced in Sweden, which was underscored by the fact that the children in this study with a previous CD diagnosis were \(~ 4 \) times as likely to have a CD-associated condition than were the screening-detected cases. Hence, our findings do not refute an association between CD and these conditions but rather reflect that active case-finding in Sweden on the basis of CD-associated conditions seems to be successful, albeit not complete.

Mass screening for CD as a public health intervention is controversial. An alternative to serological testing of a general population might be to administer a simple tool, such as a questionnaire, with the purpose of identifying people with a higher risk of having CD, and as a next step invite these individuals for serological testing. In a Danish population-based study, parents of 8- to 9-year-olds were approached with a questionnaire concerning 5 symptoms indicative of CD, which was used to select children for blood sampling and consecutive testing of CD markers. The known CD prevalence in the study population doubled, but, as the authors pointed out, without knowing the CD prevalence in the children who did not report symptoms (and therefore were not offered analysis with CD markers), the diagnostic performance of such a population-based case-finding strategy cannot be assessed. Our findings complement the Danish study by suggesting that CD prevalence is as high among those without symptoms, and the number of cases found is simply proportional to the number of children tested, irrespective of reported symptoms.

However, whether to search for and diagnose CD in children without obvious CD-associated symptoms or conditions is a complicated issue. Studies involving the same children as in the current study showed that, before knowledge of CD status, the screening-detected CD children reported similar health-related quality of life as their peers. One year after diagnosis, 72% strictly complied with the diet and 54% subjectively perceived improved health, but at the same time they described social sacrifices in relation to the diagnosis and treatment. Nevertheless, mass screening seemed to be acceptable to most of those being diagnosed and their parents. A Dutch study in children with screening-detected CD, diagnosed at 2 to 4 years of age, revealed that 10 years later, 66% of those adhering to a gluten-free diet experienced health improvements, indicating that screening efforts may have a beneficial effect on health in the long run. Still, further evidence is needed to judge if the benefits of diagnosing CD in children without obvious CD-associated symptoms or conditions outweigh the...
children with CD-associated symptoms as it is among asymptomatic children. Our questionnaire-based case-finding strategy for finding undiagnosed CD, on the basis of CD-associated symptoms and conditions, was not efficient when applied to the general population. However, CD may present with a large variety of symptoms, and there might be other questionnaire-based approaches that could be more precise in finding undiagnosed cases.

**REFERENCES**


(Continued from first page)

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Usefulness of Symptoms to Screen for Celiac Disease
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