Celiac Disease Revealed in 3% of Swedish 12-year-olds Born During an Epidemic


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ABSTRACT

Objective: Sweden experienced a marked epidemic of celiac disease between 1984 and 1996 in children younger than 2 years of age, partly explained by changes in infant feeding. The objective of this study was to determine the prevalence of celiac disease in 12-year-olds born during the epidemic (1993), including both symptomatic and screening detected cases.

Patients and Methods: All sixth-grade children in participating schools were invited (n = 10,041). Symptomatic and, therefore, previously diagnosed celiac disease cases were ascertained through the National Swedish Childhood Celiac Disease Register and/or medical records. All serum samples were analyzed for antihuman tissue transglutaminase (tTG)-IgA (Celickey), and serum-IgA, and some for tTG-IgG and endomysial antibodies. A small intestinal biopsy was recommended for all children with suspected undiagnosed celiac disease.

Results: Participation was accepted by 7567 families (75%). Previously diagnosed celiac disease was found in 67 children; 8.9/1000 (95% confidence interval [CI] 6.7–11). In another 192 children, a small intestinal biopsy was recommended and was performed in 180. Celiac disease was verified in 145 children, 20/1000 (95% CI 17–23). The total prevalence was 29/1000 (95% CI 25–33).

Conclusions: The celiac disease prevalence of 29/1000 (3%)—with two thirds of cases undiagnosed before screening—is 3-fold higher than the usually suggested prevalence of 1%. When these 12-year-olds were infants, the prevailing feeding practice was to introduce gluten abruptly, often without ongoing breast-feeding, which might have contributed to this unexpectedly high prevalence. JPGN 49:170–176, 2009. Key Words: Celiac disease—Children—Infant nutrition—Prevalence—Screening. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Celiac disease, or gluten sensitive enteropathy, was still in the 1970s considered a rare disease that mainly affected European children. It is evident today that its occurrence is global, although most cases are undiagnosed (1). Screening studies in children report a prevalence varying between 3 and 14/1000 (2–8), with the exception of 56/1000 among Saharawi children in Algeria (9). However, population characteristics and screening methods vary (10,11).

Celiac disease is induced in some genetically predisposed individuals by dietary intake of wheat gluten and related prolamines in rye and barley, which maintains an inflammatory reaction if continued to be consumed (12). The majority of individuals with celiac disease carry the HLA-DQ2 or DQ8 haplotype, as do about 30% of the general population (13). Classically, the disease presents in childhood with diarrhea and failure to thrive, but may develop throughout life with varying clinical expressions (1,14). Serological markers indicative of
celiac disease are available, but diagnostic ascertainment by morphological evaluation of the small intestinal mucosa is still required (15,16). The disease is treated with a gluten-free diet.

Sweden experienced an epidemic of celiac disease between 1984 and 1996 with a magnitude without comparison anywhere in the world (17). The incidence rate of symptomatic celiac disease in children younger than 2 years of age increased 4-fold within a few years and declined in an equally abrupt manner about 1 decade later. The epidemic was partly explained by changes in infant feeding (18). In Sweden, parents of almost all infants (>99%) attend well-baby clinics for which they have a high level of confidence, and changes in dietary recommendations are thereby effectively implemented. Before the epidemic, a national recommendation was made to postpone introduction of gluten from 4 to 6 months of age, an interval during which breast-feeding was often discontinued. At the same time, but unrelated to this, the gluten content of commercially available milk cereal drinks and porridges was increased. When the epidemic ended it was preceded by a recommendation to introduce gluten gradually, preferably while still breast-feeding, as well as a reduction in the gluten content in commercially available infant foods (17). Thus, as a result, Sweden has birth cohorts that differ with respect to infant feeding. Notably, the latter infant feeding pattern has been suggested to reduce the risk for celiac disease (18,19), although the issue is still controversial (20).

Children in birth cohorts of the epidemic period experienced a high risk for symptomatic celiac disease during their first 2 years of life, according to the National Swedish Childhood Celiac Disease Register (17). A screening of 2.5-year-old children in southern Sweden from the high-incidence birth cohorts of 1992 to 1993 revealed an additional one third of cases that were previously undiagnosed (21); thus, in spite of a high-incidence rate, not all cases were clinically identified. The register allows following the risk for symptomatic celiac disease by birth cohort up through childhood; however, a follow-up screening is also needed to reveal previously undiagnosed cases. Therefore, the objective of this study was to determine the prevalence of celiac disease in 12-year-old children born during the Swedish epidemic (1993), including both previously diagnosed cases and screening detected cases.

PATIENTS AND METHODS

Study Design

A cross-sectional screening study entitled Exploring the Iceberg of Celiacs in Sweden (ETICS) was performed during a 1-year period starting from September 2005. This multicenter study comprised 5 sites ranging from northern to southern Sweden; Umeå, Norritäle, Norrköping, Växjö, and Lund. Each site included a major city with municipalities in the surrounding suburbs and countryside. The birth cohort of 1993 was chosen to represent the cohorts of the epidemic period (1984–1996). Children in sixth-grade school classes (n = 549) were invited to participate in the study. In the invitation, parents were asked whether their child had celiac disease. The study was approved by the Regional Ethical Review Board at Umeå University. Informed consent was obtained from all participating families.

Subjects

Out of 10,041 invited children, 7567 (approximately 75%) consented to participate, with no significant differences between the study sites. Most children were born in 1993 (95%), whether the others were born in 1991, 1992, or 1994. The female/male ratio was 0.94 (3666/3901). Blood samples were collected from 7207 (72%) children without previously diagnosed celiac disease.

Laboratory Analyses

Antihuman tissue transglutaminase (tTG) of isotypes IgA and IgG were determined by ELISA in accordance with the manufacturer’s instructions (Celikey, Phadia GmbH, Freiburg, Germany) and expressed as arbitrary units per milliliter (U/mL). Serum analyses were performed in duplicate within the measuring range 0.1 to 100 U/mL. Endomysial antibodies (EMAs) of isotypes IgA and IgG were analyzed with indirect immunofluorescence technique using tissue sections from mar-moset monkey esophagus mounted on glass slides according to the manufacturer’s instructions (The Binding Site, Birmingham, UK). Sera yielding fluorescent binding to the endomysial structure were diluted to determine the lowest titer detectable. Total serum-IgA (s-IgA) levels were analyzed using a routine nephelometric method according to the manufacturer’s instructions (BN Pro Spec System, Dade Behring, Marburg GmbH, Germany). IgA deficiency was defined as serum levels below 0.06 g/L.

Screening Strategy

All serum samples were analyzed for tTG-IgA. The manufacturer’s recommended cutoff for positive tTG-IgA was 5 U/mL; however, to increase the sensitivity of the test, all values above 4 U/mL were considered elevated. If the tTG-IgA level was intermediate (2-4 U/mL), then EMA-IgA was analyzed with 1:5 dilution as the cutoff for positivity. All samples were also analyzed for s-IgA, and serum with values below 0.5 g/L were further analyzed for tTG-IgG. The cutoff for positive tTG-IgG were set at 6 U/mL, and serum samples with intermediate values (3–6 U/mL) were further analyzed for EMA-IgG with 1:5 dilution as the cutoff for positivity. Children with s-IgA >0.5 g/L and tTG-IgA <2 U/mL were classified as nonceliac disease cases. All other children were recommended a small intestinal biopsy according to the criteria given in Table 1.

Case Ascertainment by Small Intestinal Biopsy

Criteria for celiac disease diagnosis were a small intestinal mucosa with villous atrophy (VA) or borderline mucosa, that is,
>30 intraepithelial lymphocytes (IEL) per 100 enterocytes, in combination with symptoms and/or other signs compatible with celiac disease. Symptoms and signs considered were divergence in standard laboratory tests, deviation in weight and/or height, or autoimmune disorders. Reported celiac disease cases were ascertained through the National Swedish Childhood Celiac Disease Register and/or the child’s medical record. Children with elevated serological markers were referred to a pediatric clinic for small intestinal biopsy, taken either by endoscope or capsule. Biopsies were taken from the distal duodenum and for multiple biopsies also from the proximal duodenum. Mucosal specimens were classified into the following groups: subtotal/total VA (Marsh 3b and 3c), partial villous atrophy (PV A) (Marsh 3a), increased IEL count (Marsh 1), or normal mucosa (Marsh 0) (15). Marsh 2 was not distinguished.

### Statistical Analyses

Microsoft Access was used for data handling and SPSS 15.0 (SPSS Inc, Chicago, IL) for statistical analyses. Prevalence was calculated as the proportion of celiac disease cases in the study population as a whole and for subgroups, that is, previously diagnosed and screening detected, and also by sex and study site. Prevalence was reported as cases per 1000 individuals with a 95% confidence interval (CI). Relative risk (RR) with 95% CI was calculated to illustrate the variation with respect to sex and study site.

## RESULTS

### Serological Markers

In this study, 7207 serum samples from children without diagnosed celiac disease were analyzed for serological markers indicative of celiac disease, yielding 167 children with elevated tTG-IgA (Fig. 1). Intermediate tTG-IgA levels were found in 104 cases, of whom 20 were EMA-IgA positive. S-IgA were analyzed in 7161 (99%) children resulting in 170 with values <0.5 g/L, of whom 27 had IgA deficiency (S-IgA <0.06 g/L in 0.4% of all children). Among these 170 children, 5 had elevated tTG-IgG and 5 had intermediate values. In the latter 5 children, EMA-IgG were analyzed and found negative. Out of the 10 children with raised tTG-IgG, 5 had IgA deficiency. In total, 192 children fulfilled criteria for small intestinal biopsy (Fig. 1).

### Evaluation of Small Intestinal Mucosa

Out of 192 children, 180 (94%) had a small intestinal biopsy performed and the mucosa evaluated, resulting in identification of 145 celiac disease cases, 70 boys and 75 girls (Fig. 1). Elevated tTG-IgA led to identification of 133 cases. Another 10 cases had intermediate tTG-IgA in conjunction with positive EMA-IgA, and 2 cases had increased tTG-IgG. The biopsies showed the following: 89 (49%) subtotal/total VA, 39 (22%) PVA, 18 (10%) increased number of IEL, and 34 (19%) normal mucosa. Out of the 18 children with increased IEL, all but 1 also had symptoms and/or signs compatible with celiac disease (Table 2).

### Elevated Serological Markers Without Celiac Disease Diagnosis

In total, 46 children had elevated serological markers without being diagnosed as celiac disease cases. Out of 34 children with a normal mucosa, 23 had elevated tTG-IgA, 8 intermediate tTG-IgA in conjunction with positive EMA-IgA, and 3 had elevated TtG-IgG (Fig. 1). Twelve children did not have a small intestinal biopsy performed and were thus not included as cases in the prevalence estimates.

### Prevalence of Celiac Disease

Previously diagnosed celiac disease was confirmed in 21 boys and 46 girls, corresponding to a prevalence of 8.9 per 1000 (95% CI 6.7–11). The screening revealed 145 new cases, corresponding to a prevalence of 20/1000 (95% CI 17–23). When combined, these figures resulted in a total prevalence of 29/1000 (95% CI 25–33) (Fig. 2). The prevalence was 24/1000 (95% CI 19–29) among boys and 34/1000 (95% CI 28–40) among girls, resulting in a female/male ratio of 1.4. The prevalence across the different study sites varied between 20

### Table 1. Criteria for recommending a small intestinal biopsy with the suspicion of celiac disease

<table>
<thead>
<tr>
<th>Criteria</th>
<th>tTG-IgA (U/mL)</th>
<th>EMA-IgA</th>
<th>S-IgA (g/L)</th>
<th>tTG-IgG (U/mL)</th>
<th>EMA-IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;4</td>
<td></td>
<td></td>
<td>≥1:5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2–4</td>
<td></td>
<td>&lt;0.5</td>
<td>&gt;6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&lt;0.5</td>
<td>&gt;6</td>
<td>3–6</td>
<td>≥1:5</td>
<td></td>
</tr>
</tbody>
</table>

**EMA** = endomysial antibodies; **tTG** = tissue transglutaminase.

1 Serum anti-human tTG antibodies (arbitrary units).

2 Serum endomysial antibodies (serial dilutions).

3 Serum-IgA.
FIG. 1. Results from a Swedish celiac disease screening of 12-year-olds born during an epidemic. Blood samples were analyzed for antihuman tTG, and some also for EMAs. Serum-IgA <0.5 g/L was defined as low. Small intestinal biopsies were subcategorized into subtotal/total VA, PVA, increased IEL count, or normal mucosa (N). Celiac disease diagnosis required VA, PVA, or IEL combined with symptoms and/or signs compatible with the disease (1 child with IEL did not fulfill these criteria). EMA = endomysial antibodies; IEL = intraepithelial lymphocytes; PVA = partial villous atrophy; tTG = tissue transglutaminase; VA = villous atrophy.

TABLE 2. Characteristics of children with a small intestinal mucosa with >30 intraepithelial lymphocytes per 100 enterocytes

<table>
<thead>
<tr>
<th>Child</th>
<th>Sex</th>
<th>tTG-IgA (U/mL)</th>
<th>Additional laboratory results</th>
<th>Symptoms and/or signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>98</td>
<td></td>
<td>Tiredness</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>4.7</td>
<td>EMA-IgA 1:10</td>
<td>Stomachache</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>23</td>
<td></td>
<td>Tiredness</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>2.6</td>
<td>EMA-IgA 1:5</td>
<td>Tiredness, nausea, underweight</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>12</td>
<td>EMA-IgA 1:20, hypothyroidism</td>
<td>Constipation, underweight</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>6.6</td>
<td>EMA-IgA 1:5</td>
<td>Secondary lactose intolerance</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>44</td>
<td></td>
<td>Tiredness, flatulence</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>14</td>
<td>EMA-IgA 1:5</td>
<td>Tiredness, flatulence</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>36</td>
<td></td>
<td>Stomachache, heredity for autoimmune disorders</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>&gt;100</td>
<td></td>
<td>Flatulence</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>31</td>
<td></td>
<td>Stomachache</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>97</td>
<td></td>
<td>Tiredness, flatulence, heredity for celiac disease</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>51</td>
<td></td>
<td>Constipation, tiredness, short for age, heredity for celiac disease</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>4.6</td>
<td>EMA-IgA 1:5</td>
<td>Stomachache, loose stools</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>50</td>
<td></td>
<td>Alternate constipation and loose stools, underweight</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>32</td>
<td>Iron deficiency anemia</td>
<td>Tiredness, nausea</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>7.0</td>
<td>EMA-IgA 1:5, hypothyroidism</td>
<td>Nausea</td>
</tr>
<tr>
<td>18*</td>
<td>F</td>
<td>32</td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

EMAs = endomysial antibodies; F = female; M = male; tTG = tissue transglutaminase.
\* Serum anti-human tTG antibodies (arbitrary units).
\* Serum endomysial antibodies (serial dilutions).
\* Not considered a celiac disease case because symptoms and/or signs were absent.
DISCUSSION

Our study revealed a celiac disease prevalence of 29/1000 (3%)—with two thirds of cases undiagnosed before the screening—among Swedish 12-year-old children born in 1993. This prevalence is significantly higher than found previously in the Swedish population and higher than reported in any population in Europe or in the United States.

The prevalence estimate was probably representative for Swedish 12-year-old children in general and also for the other birth cohorts from the decade of the epidemic period. Participation was high at all study sites, the female/male ratio corresponded to the national ratio (22), and the prevalence of previously diagnosed disease was in accordance with the National Swedish Childhood Celiac Disease Register (17). Despite a high participation rate, selection bias may have contributed to an overestimation of prevalence because individuals experiencing health problems may be more prone to participate. However, assuming not a single further case among nonparticipants would still result in a prevalence as high as 21/1000 on the basis of all invited children. Our screening strategy prioritized high sensitivity to identify as many cases as possible, but we nevertheless avoided overestimation of prevalence by requiring a small intestinal biopsy for the celiac disease diagnosis. Thus, 12 children with suspected celiac disease based on elevated serological markers, but without confirmatory

and 41/1000, with a significantly increased risk in southern compared with northern Sweden (Table 3).

**TABLE 3. Prevalence of celiac disease at the different study sites**

<table>
<thead>
<tr>
<th>Study sites</th>
<th>Participants</th>
<th>Cases</th>
<th>Blood samples</th>
<th>Cases</th>
<th>Prevalence per 1000</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umeå</td>
<td>1395</td>
<td>11</td>
<td>1355</td>
<td>16</td>
<td>20</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Norrtälje</td>
<td>869</td>
<td>5</td>
<td>845</td>
<td>18</td>
<td>27</td>
<td>1.4</td>
<td>0.79–2.4</td>
</tr>
<tr>
<td>Norrköping</td>
<td>954</td>
<td>8</td>
<td>912</td>
<td>17</td>
<td>27</td>
<td>1.4</td>
<td>0.80–2.3</td>
</tr>
<tr>
<td>Växjö</td>
<td>1108</td>
<td>14</td>
<td>1017</td>
<td>29</td>
<td>41</td>
<td>2.1</td>
<td>1.3–3.4</td>
</tr>
<tr>
<td>Lund</td>
<td>3241</td>
<td>29</td>
<td>3078</td>
<td>65</td>
<td>30</td>
<td>1.5</td>
<td>1.0–2.3</td>
</tr>
</tbody>
</table>

CI = confidence interval; RR = relative risk.
1 Study sites listed from north to south of Sweden.
2 Reported celiac disease cases ascertained through the National Swedish Childhood Celiac Disease Register, and/or the child’s medical record.
3 Celiac disease cases detected through screening.
biopsy, were not included as cases in the prevalence estimate. Notably, the celiac disease diagnosis was confirmed in most children who were subjected to a biopsy (81%).

The prevalence of celiac disease in the Swedish population has evidently increased over time. A previous population-based adult screening reported a prevalence of 5.3/1000 (95% CI 2.5–9.7) (23), as compared with our present finding among 12-year-olds of 29/1000 (95% CI 25–33). An increase in prevalence has also been seen in the neighboring country of Finland (24). In contrast, a higher prevalence could be expected in adults than in children, because celiac disease is a chronic disease with autoimmune features, and without any substantial increase in mortality (25). Our screening study confirmed a previously reported regional variation in celiac disease risk, with a higher prevalence in the southern as compared with the northern part of Sweden (Table 3) (26). We previously reported a doubled risk for symptomatic celiac disease in boys compared with girls (RR 1.9) (27). In the present study, also including screening detected cases, the difference was less pronounced (RR 1.4). This difference in male/female ratio suggests that a larger proportion of girls with celiac disease are identified in clinical practice. To further explore the increase in prevalence over time, as well as the regional and gender variations, may contribute to an increased understanding of the etiology and clinical expression of celiac disease.

The 12-year-old children who participated in the present study were born in 1993, and thus were infants during a period when it was common in Sweden to introduce gluten-containing foods abruptly after discontinued breast-feeding (18). We have previously shown that breast-feeding continuing beyond gluten introduction more than halves the risk for celiac disease (odds ratio [OR] 0.36; 95% CI 0.26–0.51) and introduction of large amounts of gluten, compared with small to medium amounts, was associated with a 50% increased risk (OR 1.5; 95% CI 1.1–2.1). Thus, such an infant feeding pattern has been suggested to increase the risk for celiac disease (18,19), and most likely contributed to the Swedish epidemic. This birth cohort had a cumulative incidence of 4.4/1000 at 2 years of age (17). Nevertheless, screening of 2.5-year-old children in southern Sweden revealed additional cases, resulting in an estimated prevalence of 10/1000 at this early age (Fig. 2) or even as high as 20/1000 (21). When following this cohort through childhood using the national register, it became evident that symptomatic cases successively continued to emerge (28), probably also accompanied by an increase in unidentified cases over time. Our present study revealed that at 12 years of age, although a high risk for symptomatic celiac disease (8.9/1000) (Fig. 2) most cases remained undiagnosed (20/1000) (Fig. 2). Hence, our findings suggest that exposures during infancy affect celiac disease risk throughout childhood, and possibly also throughout the life span (29). This increased risk may result from early exposures affecting the immune system in a way that makes the individual more susceptible to lose oral tolerance to gluten. In addition to early infant feeding practices, other exposures should be explored as possible contributors to celiac disease risk, especially in children developing the disease after 2 years of age.

In the mid-1990s, action was taken to promote the infant feeding pattern prevailing during the preepidemic period, with gradual introduction of gluten-containing foods while breast-feeding was still ongoing (18). The incidence rate of symptomatic celiac disease in children younger than 2 years of age then abruptly declined to the preepidemic level (17). A screening of children from such a low-incidence birth cohort at about 2.5 years of age revealed only half as many cases when compared with the previously screened high-incidence cohort (30). Although the difference in incidence was not statistically significant, these findings support the contention that infant feeding affected celiac disease risk, at least during the first years of life. The postepidemical reduced celiac disease risk during the first 2 years of life could hypothetically have been indicative of a postponed disease onset. However, when birth cohorts of the epidemic and postepidemic periods were compared, the gender cumulative incidence was still striking at 6 years of age (5.4/1000 for the cohort of 1993 vs 2.9/1000 for the cohort of 1997), indicating a remaining difference in celiac disease risk (28). This follow-up was limited to symptomatic cases, because it was based on the national register. The present study revealed that two thirds of the cases in an epidemic cohort were undiagnosed, and such cases are also likely to be present in the postepidemical cohorts, especially as the recognized symptoms of celiac disease have become more diffuse over time (31). Thus, it is crucial that children born after the epidemic also undergo a screening like the one reported here, which we plan for in 2009 to 2010 when children born in 1997 reach 12 years of age.

The “Swedish population experiment,” with considerable changes over time in infant feeding, has resulted in cohorts that differ with respect to exposure early in life, which allows for studies that can increase our understanding of both celiac disease etiology and clinical expression. Our present study revealed that celiac disease has emerged as a public health problem in Sweden, with 29/1000 (3%) already affected at 12 years of age, and with two thirds of the cases undiagnosed before screening. The birth cohort studied here (1993), as well as cohorts of an entire decade, had been exposed to an unfavorable infant feeding pattern, which may have contributed to the high prevalence of celiac disease. Later, after also screening the cohort of 1997, we will compare celiac disease prevalence at 12 years of age, including both previously diagnosed cases and screening
detected cases, in 2 birth cohorts that differ with respect to exposures early in life. Thus, we will be able to evaluate to what extent the differences in exposure have influenced the clinical expression of celiac disease, and thereby the proportion of cases diagnosed, and to what extent cases have been truly prevented.

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