Prevalence of asymptomatic celiac disease in adolescents of eastern Switzerland

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Coeliac disease (CD) is an autoimmune enteropathy characterised by chronic inflammation of the small intestinal mucosa and by the presence of typical autoantibodies. CD develops in genetically predisposed individuals after mucosal contact with gluten and secondarily to hitherto unknown triggering factors [1, 2]. Infants with CD exhibit symptoms of malnutrition, whereas only 30–40% of adults with the disease have such symptoms [2]. Adult coeliac patients tend to remain asymptomatic or oligosymptomatic. However, the increased risk of autoimmune diseases and intestinal lymphoma or carcinoma in individuals with CD calls for screening even when there are no symptoms [3, 4]. Screening studies have therefore been performed in several countries which show that 0.03–0.046% of Italian adolescents [5, 6], 1.06% of Sardinian schoolchildren [7], 0.05% of Dutch [8] and 2% of Swedish infants [9] have asymptomatic CD. To make these screening studies as sensitive as possible they were carried out using anti-endomysium IgA combined with either anti-gliadin IgA or anti-tissue transglutaminase IgA [10, 11]. The aim of the present study is to assess the prevalence of asymptomatic CD in Swiss adolescents in a rural area with a low migration rate.

Background: The prevalence of symptomatic CD in Switzerland is thought to be 1 in 1,000 inhabitants. As in other countries, oligo- and asymptomatic CD is being diagnosed with increasing frequency in all age groups. Aim: To assess the prevalence of asymptomatic CD in adolescents in eastern Switzerland.

Method: Between September 1999 and July 2000 total serum IgA titres, anti-endomysium IgA (EMA) titres and anti-human tissue transglutaminase IgA (hTTG) titres were measured in the serum of healthy 11- to 18-year-old Swiss lower and upper secondary school students.

Results: Of the 1,450 students (871 f = 60.1%, CI 95%) tested, 11 (10 f) had elevated levels of both EMA and TTG. The diagnosis of CD was confirmed in eight of these students by mucosal jejunal morphology (Marsh III); one exhibited normal histology. Two of the 11 students refused to undergo mucosal biopsy. None of the students, however, had symptoms suggestive of CD, nor were they stunted or underweight, and none of them had family members with known CD. All of the eight students with enteropathy went on a gluten-free diet and felt subjectively better than on a normal diet. Of the remaining students, 38 (2.6%) had family members with known CD. None of those with the relevant family history had elevated EMA or TTG levels.

Conclusion: Asymptomatic CD is common. It occurs in 1 in 132 (0.75%) Swiss adolescents. The absence of subjectively recognisable symptoms suggestive of family history or other risk factors makes it difficult to diagnose this type of CD.

Key words: coeliac disease; asymptomatic prevalence; Switzerland; adolescents

Introduction

Coeliac disease (CD) is an autoimmune enteropathy characterised by chronic inflammation of the small intestinal mucosa and by the presence of typical autoantibodies. CD develops in genetically predisposed individuals after mucosal contact with gluten and secondarily to hitherto unknown triggering factors [1, 2]. Infants with CD exhibit symptoms of malnutrition, whereas only 30–40% of adults with the disease have such symptoms [2]. Adult coeliac patients tend to remain asymptomatic or oligosymptomatic. However, the increased risk of autoimmune diseases and intestinal lymphoma or carcinoma in individuals with CD calls for screening even when there are no symptoms [3, 4]. Screening studies have therefore been performed in several countries which show that 0.03–0.046% of Italian adolescents [5, 6], 1.06% of Sardinian schoolchildren [7], 0.05% of Dutch [8] and 2% of Swedish infants [9] have asymptomatic CD. To make these screening studies as sensitive as possible they were carried out using anti-endomysium IgA combined with either anti-gliadin IgA or anti-tissue transglutaminase IgA [10, 11]. The aim of the present study is to assess the prevalence of asymptomatic CD in Swiss adolescents in a rural area with a low migration rate. The incidence of symptomatic CD in this region was estimated to be 1 in 1,165 live-born children between 1966 and 1975 [12].
Methods

With an estimated CD prevalence of 1–5‰, in adolescents, students aged between 12 and 18 appeared to be both a highly suitable and homogeneous test population. A total of 120,000 people aged 0–19 live in the Canton of St. Gallen, 22,000 of whom attend either one of the canton’s 108 lower secondary schools or one of its 8 upper secondary schools [13]. Thus, 1,400 samples (CI 95%) were needed to calculate the prevalence of asymptomatic CD. After the aims and procedure of the study had been approved by the ethics committee, the schools’ head teachers and the public health authority, students from randomly selected schools were informed of the study by post and sent a questionnaire and a consent form. The questionnaire asked for names, birth date and present height and weight, and sought information on intermittent abdominal pain, constipation, diarrhoea, known chronic diseases and family history of coeliac disease. Capillary blood samples were taken during the school day from consenting volunteer students aged 12–18. Known coeliac disease was an exclusion criterion. First, anti-endomysium IgA (EMA) titres were assessed using indirect immunofluorescence on monkey oesophagus tissue (Nova Lite, Inova Diagnostics, Zurich), anti-tissue transglutaminase IgA (TTG) was measured by an ELISA test using guinea pig antigen (Quanta Lite tTG ELISA Kit, Inova Diagnostics), and total serum IgA titres were measured using turbidimetry (Unimod 3, Roche Diagnostics, lower threshold value 0.2 g/l). The same blood samples were later retested using recombinant human antigen (Celikey™ human recombinant anti-tissue transglutaminase IgA Antibody Assay [hTTG], Pharmacia Diagnostics, Düben- dorf). Second, venous blood samples were taken from those who tested positive for EMA and hTTG to measure anti-gliadin IgG (AGG) and IgA (AGA) (Quanta Lite, Inova Diagnostics) and to confirm the EMA and hTTG-IgA titres. As a third step, individuals in whom the disease was suspected after the first tests and confirmed by the later test were advised to undergo a small intestinal mucosal biopsy under general anaesthesia (fig. 1). Patients with asymptomatic CD were recommended to adopt a gluten-free diet. Three months after the beginning of dietary treatment the subjective evaluation of dietary effects and dietary compliance were assessed by telephone interview.

Statistics

The SPSS program was used to calculate sample size. Taking into account a 5% estimated prevalence of asymptomatic CD, a 1% known prevalence of symptomatic CD, an expected power of 80% and a confidence interval of 95%, the required sample size was 1,400 volunteers. Mann-Whitney U test was used to compare groups with ordinal and Fisher’s exact test to compare groups with categorical data (Statview program). All results are given with a 95% confidence interval.

Results

Screening was carried out in 17 participating schools (19 invited), attended by 6,073 students aged 12–18, between September 1999 and June 2000. The participation rate was 27.5%, with 1,675 volunteers (235 = 14% of non-Swiss nationality). Finally, 1,450 students (23.8%; 579 [39.9%] male, 871 [60.1%] female) were available for blood tests on the prearranged day. A total of 253 (14%) of the participating volunteers (present for blood tests 214 = 14.7%) were citizens of countries other than Switzerland, chiefly Eastern Europe (55.3%), Southern Europe (20%), Near East countries (11.9%), Asia (3.7%), as well as two black and 3 Singalese adolescents. Students of school years higher than the tenth were mainly of Swiss origin.

Eleven students (two of Yugoslav origin), one male and ten females, had positive EMA and/or TTG. In ten of the 11 individuals with elevated autoantibody titres for EMA, we also measured hTTG, AGG and AGA in venous blood, confirming the results of the first test in each case (fig. 1). One female student refused any further tests. Nine of the ten students with positive autoantibodies subsequently underwent biopsy of the small intestinal mucosa. Eight of the nine had enteropathy of type III according to Marsh’s criteria, the other exhibiting normal mucosal histology (table 1). Given the heightened specificity and sensitivity of combined testing for coeliac disease using EMA and TTG [10, 11], we included the two positive individuals who did not undergo biopsy in our prevalence calculation as well as the student with normal mucosal histology, calling it latent coeliac disease [14, 15]. Calculated prevalence was 0.75% or 1 in 132 adolescents.

All capillary blood samples were first tested for TTG using guinea pig antigen, but as there were a number of low positive results all the samples were retested for TTG using human recombinant antigen. This was carried out to establish the final results. Ten students with asymptomatic CD were recommended to go on a gluten-free diet. Three months after beginning they were interviewed by telephone about how they felt on a gluten-free diet and about their compliance. All of them reported non-specific improvement of physical condition.
but were not willing to continue on a gluten-free diet.

We found no difference in height or weight between students with or without asymptomatic coeliac disease (table 2). No abdominal pain (other than during menstruation) and no stool irregularities (constipation, diarrhoea) were mentioned in either group.

In 49 students (3.4%) anti-TTG autoantibody levels within the same serum sample were found to be elevated when using guinea pig antigen but normal when using recombinant human antigen. None of these students had an elevated EMA level. Venous blood samples from six of the 11 students with moderately elevated levels of TTG were retested for AGA, AGG, EMA and hTTG, and none of these had elevated autoantibody titres. The other five refused to take any further tests, and, along with the remaining 38 students, were considered CD negative.

Total IgA was <0.2 g/l in nine students, and four of these students consented to AGG testing. None of them had elevated AGG levels.

53 students (3.1%) of the 1,675 who volunteered had family members with known coeliac disease. Of these 53 students, 38 (2.6%) had given blood samples and all of them had normal EMA/TTG and total IgA. None of the 11 students with asymptomatic CD was aware of a family member with CD.

**Discussion**

The primary aim of this study was to assess the prevalence of oligo- and/or asymptomatic CD among adolescents in a rural region with a low migration rate. Tests for EMA, hTTG and total serum-IgA [16, 17] indicated a prevalence of 0.75% or 1 in 132 adolescents. This type of antibody-testing was chosen because of the additive high sensitivity and specificity of EMA and TTG, thereby avoiding many false positive results. The prevalence found in this study is similar to that

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**Table 1**

Individuals with asymptomatic coeliac disease.

<table>
<thead>
<tr>
<th>Sex</th>
<th>age (yr)</th>
<th>height (cm)/weight (kg)</th>
<th>EMA 1/2</th>
<th>TTG 1/2</th>
<th>AGAg/l</th>
<th>AGA</th>
<th>AGG</th>
<th>histology jejunal</th>
<th>z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>14.5</td>
<td>157/65</td>
<td>&gt;20/20</td>
<td>44/32</td>
<td>2.37</td>
<td>38</td>
<td>24</td>
<td>Marsh III</td>
<td>z = –1/2</td>
</tr>
<tr>
<td>F</td>
<td>14.3</td>
<td>155/44</td>
<td>&gt;80/5</td>
<td>26/59</td>
<td>1.73</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>normal histology</td>
<td>z = –1.7/–1</td>
</tr>
<tr>
<td>F</td>
<td>16.7</td>
<td>166/67</td>
<td>&gt;20</td>
<td>&gt;100</td>
<td>1.2</td>
<td>nd</td>
<td>nd</td>
<td>no biopsy</td>
<td>z = 2/1</td>
</tr>
<tr>
<td>F</td>
<td>14.5</td>
<td>180/63</td>
<td>&gt;5/20</td>
<td>6</td>
<td>2.3</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>Marsh III</td>
<td>z = –1.7/–1</td>
</tr>
<tr>
<td>F</td>
<td>13.6</td>
<td>153/38</td>
<td>&gt;5/10</td>
<td>9</td>
<td>1.26</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>Marsh III</td>
<td>z = –1.7/–1</td>
</tr>
<tr>
<td>F</td>
<td>16.0</td>
<td>167/59</td>
<td>&gt;5/5</td>
<td>12/92</td>
<td>1.4</td>
<td>46</td>
<td>158</td>
<td>Marsh III</td>
<td>z = 1/1</td>
</tr>
<tr>
<td>F</td>
<td>14.6</td>
<td>168/52</td>
<td>&gt;20/20</td>
<td>&gt;244/131</td>
<td>1.61</td>
<td>&gt;161</td>
<td>55</td>
<td>Marsh III</td>
<td>z = 1/2</td>
</tr>
<tr>
<td>F</td>
<td>14.5</td>
<td>130/38</td>
<td>&gt;5/5</td>
<td>&gt;195/131</td>
<td>0.95</td>
<td>&lt;20</td>
<td>20</td>
<td>Marsh III</td>
<td>z = 1/2</td>
</tr>
<tr>
<td>F</td>
<td>16.8</td>
<td>164/45</td>
<td>160/160</td>
<td>&gt;217</td>
<td>2.2</td>
<td>36</td>
<td>140</td>
<td>Marsh III</td>
<td>z = 1/2</td>
</tr>
<tr>
<td>F</td>
<td>17.3</td>
<td>164/64</td>
<td>80/20</td>
<td>185</td>
<td>2.26</td>
<td>62</td>
<td>26</td>
<td>Marsh III</td>
<td>z = 1.7/1</td>
</tr>
<tr>
<td>M</td>
<td>17.4</td>
<td>176/64</td>
<td>7/5</td>
<td>23/11</td>
<td>2.85</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>no biopsy</td>
<td>z = 1/1</td>
</tr>
</tbody>
</table>

Normal values: EMA <5, AGG + AGA <20, TTG <5

**Table 2**

Height and weight z-scores and gender of students with and without CD.

<table>
<thead>
<tr>
<th></th>
<th>students with CD (n = 11)</th>
<th>students without CD (n = 1439)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight: z-score (median + range)</td>
<td>+ 1.7 (–2 – +3)</td>
<td>+ 1 (–2.6 – + 4.4)</td>
<td>ns*</td>
</tr>
<tr>
<td>Height: z-score (median + range)</td>
<td>+ 1.35 (–2 – +2)</td>
<td>– 1 (–2.65 – + 3.06)</td>
<td>ns*</td>
</tr>
<tr>
<td>Gender</td>
<td>10 female, 1 male</td>
<td>861 female, 578 male</td>
<td>0.059**</td>
</tr>
</tbody>
</table>

* Mann Whitney U test; ** Fishers exact test
found in Scandinavian countries (up to 2%) [11, 18, 19], Ireland (0.8%) [20], Italy (0.03–1.06%) [7, 21] and North America (0.4%) [22]. Thus, about 1% of the adolescent population of those countries has CD. The reasons for this alarmingly high prevalence are not known, nor do we know whether this is an old problem that has only now come to light or indeed an entirely new phenomenon.

The relatively low participation rate of 24% was mainly due to the blood test, which many students were afraid of. Additionally, the participation rate was strongly influenced by classroom peer pressure and the motivation provided or authority wielded by individual teachers.

We included all the students with both elevated TTG and EMA in the CD group, even though two of them refused small intestinal biopsy and one student had normal histology. The two without small intestinal histology should be considered to have at least latent (elevated autoantibody titres without histological abnormalities) or silent (no symptoms, but histological abnormalities) coeliac disease [14, 15], as should the student with normal histology. It is widely acknowledged that a patient can be autoantibody-positive for months before enteropathy is histologically visible [23, 24].

Individuals with newly diagnosed CD went on a gluten-free diet for a three-month trial period and felt subjectively better during that time. However, this improvement was not felt to be great enough to motivate them to continue the diet, even though the importance of a lifelong gluten-free diet was explained to them. The most significant reason for giving up the diet was the fact that gluten-free products are both expensive and difficult to obtain. They were therefore informed of the risks inherent in untreated CD and advised to consult their family doctor whenever symptoms appeared.

There was no difference in height, weight, stool habits or abdominal pain episodes between students with elevated and those with normal autoantibody titres, but in students with asymptomatic CD there was a female predominance which approached statistical significance (table 2). However, larger studies are necessary to determine whether female gender is a more important risk factor for asymptomatic CD than for autoimmune disease in general [25].

None of the students with asymptomatic CD had family members with known CD, whereas 2.6% of participants with normal autoantibodies had. Given that Auricchio found that 10% of first-year schoolchildren related to CD patients have coeliac disease [26], that Catassi [21] established a ratio of one known case to every seven undiagnosed cases of CD in Italy, and that the mean family size in the Canton of St. Gallen is between four and five persons, we did not expect to find that the only students who had known family members with CD did not themselves have asymptomatic CD, and that those 11 students who had asymptomatic CD diagnosed for the first time by the study did not have any known family members with the disease. Wider screening studies will be necessary to ascertain whether CD occurring in families and asymptomatic CD are different manifestations of the same disease, possibly dependent on genetic factors other than HLA class II haplotypes, as was found to be the case for dermatitis herpetiformis [27].

We found a number of falsely elevated anti-TTG-IgA titres when using guinea pig antigen, whereas anti-hTTG-IgA positivity correlated well with anti-EMA-IgA positivity. This good correlation using hTTG has also been established by other groups [28–30] and has been attributed to the purity of the antigen used both in screening studies and in groups with known coeliac disease.

In conclusion, we found a high prevalence of asymptomatic CD in adolescents of Canton St. Gallen. This unexpectedly high prevalence raises the question of population screening. However, CD can appear at any age and thus there is no time-point for autoantibody screening. Inclusion of HLA-DQ2 [31] in newborn screening is controversial, since only positive individuals develop CD. However, ethical and economic considerations argue against this type of screening. Further research for risk factors is therefore necessary.

Acknowledgement: The participating schools played a major organising role and made rooms available for blood sampling.
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