High prevalence of coeliac disease: Need for increasing awareness among physicians

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Abstract

Background. Coeliac disease is a wheat gluten and related prolamin-induced disease with a prevalence that may be underestimated in many geographical regions and populations.

Aim. To investigate the prevalence of coeliac disease in a population of schoolchildren of Estonia using tissue transglutaminase antibodies for screening.

Subjects and methods. The study was designed as cross-sectional. Serum samples from 1160 randomly selected schoolchildren (636 female and 564 male, aged 9 or 15 years) were studied using a novel tissue transglutaminase antibody immunoassay (EliA® Celikey® IgA assay). Antibody-positive subjects were investigated for coeliac disease.

Results. A total of five subjects had antibodies. Four of them agreed for further investigations. By small-bowel biopsy they all were confirmed to have active coeliac disease, including three subjects with symptoms that were not considered by their family doctors. The prevalence of coeliac disease is at least 1 case per 290 (0.34% with CI 0.09–0.88%) in Estonia. It is much higher than that in our previous screening studies but is comparable with data from other European countries.

Conclusion. The prevalence of coeliac disease might have increased during the last decade in Estonia. This study clearly shows that the awareness of coeliac disease among physicians is low. Thus, there is a need for more epidemiological studies and education related to coeliac disease.

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1. Introduction

Coeliac disease (CD) is an immune-mediated disorder of the small bowel in which the ingestion of wheat gluten and related prolamin in genetically susceptible individuals (mostly with the human leucocyte antigen DQ2 allele) leads to chronic inflammation and damage of the small intestinal mucosa. The disease is characterised by various immune reactions, but the presence of IgA antibodies to tissue transglutaminase (TGA) is most characteristic [1]. Being rarely revealed earlier, CD not only has been detected today in up to 1.5% of the investigated populations of European ancestry [2] but is also common in the investigated children’s populations from Africa, Middle East, south Asia and Americas [3]. Such high prevalence makes CD one of the most common chronic diseases among children. The disease has specific and effective treatment—life-long gluten-free diet that not only stops the development of serious nutritional complications such as growth failure,
iron-deficiency anaemia, osteoporosis, delayed puberty, but may also reduce the risk of developing other autoimmune diseases and gastrointestinal lymphoma [1]. Therefore, the knowledge about the prevalence of CD as well as the timely diagnosis of CD is of great importance for every population.

Estonia is an east European country known so far as a country with low prevalence of CD [4,5]. The aim of this study was to find out, by screening of random schoolchildren population, whether the prevalence of CD has increased during last years in this country.

2. Materials and methods

The study is cross-sectional. Coded sera from 1160 randomly-selected Estonian schoolchildren (636 female and 564 male subjects) aged 9 or 15 years were obtained from the European Youth Heart Study sample collected in 1998/1999 in Tartu county. In the original study, 25 schools (44.6% of schools of the county) were randomly selected using probability proportional to school size. In every school, on the basis of the school register, children of appropriate age were sampled randomly using random number tables. Participation rate for blood sampling was 98.6% [6].

In 2004, these sera had been tested for TGA by a novel fully automated EliA™ Celikey® IgA assay (Pharmacia Diagnostics, Freiburg, Germany) according to the manufacturer’s instructions. This system uses ImmunoCAP technology where solid-phase antigen-coated monowells are utilised under fully automated system for quantitative detection of antibodies. To evaluate the test results, the response for patient samples was compared directly to the response for calibrators by fluorescence read-out. Antibody concentrations were automatically converted to EliA U/ml using the lot-specific conversion factor. The measurement range for EliA Celikey IgA was from 0.1 to more than >128 EliA U/ml. According to manufacturer’s suggestions, values of IgA-TGA of 10 EliA U/ml or more were considered positive, and values less than 7 EliA U/ml were considered negative.

When using this cut-off value, our own investigation on unslected hospital patients with biopsy-proven CD (18 females, 8 males; mean age 5 years at range 0.8–14 years) and normal small-bowel mucosa (5 females, 7 males, mean age 3.7 years at range 1–10 years) showed this assay to have 100% specificity and 92% sensitivity for CD. This is similar to corresponding parameters of the Varelisa™ IgA Celikey® assay that has been used earlier in CD screening [2]. Test results below the detection limit (“low RU”) were interpreted as IgA deficiency, and in these sera IgA levels were evaluated by turbidimetry and IgG TGA with were measured EliATM Celikey® IgG.

In spring 2005, all antibody-positive subjects were invited for confirming the findings of IgA-TGA investigations and, in the case of positive results, for an additional medical interview and small-bowel biopsy to categorise the intestinal mucosal state by the Marsh classification and to confirm the CD diagnosis. Here, type IIIa lesions represent partial villous atrophy, type IIIb sub-total villous atrophy and type IIIc total villous atrophy [7]. During follow-up, the genomic DNA of peripheral blood leucocytes was also extracted and the presence of the HLA-DQ2 allele was detected by the Dynal AS kit (Oslo, Norway). Parents and children gave their written consent. The study was approved by the Committee of Ethics at the University of Tartu.

3. Results

Five sera from the initial sample were positive for IgA-TGA (all above 99.7th percentile) that gave for antibody prevalence 1:232. The antibody-positive subjects were identified and were invited for follow-up. Four out of five, all non relatives, agreed to participate and were again IgA-TGA positives and had the HLA-DQ2 allele characteristic of CD. In all four, CD was confirmed by biopsy (Table 1). Three of them had clinical signs that might be attributable to CD but were not considered by their family doctors. All patients with CD were suggested to follow strict gluten-free diet. Five subjects from the whole sample had “low RU” (one with IgA deficiency), but no one had IgG-TGA.

4. Discussion

In this study, the prevalence of CD is at least 1 case per 290, i.e. 0.34% (95% exact binomial confidence interval 0.09–0.88%) in Estonia, which contrasts with our earlier finding obtained in the 90s—absence of CD cases in the screening of 1939 persons from general population including 1461 adults [4] and 478 schoolchildren [5]. Most probably,
in this sample the CD prevalence is actually 1 case per 232 whereas the person who had refused follow-up had had positive IgA-TGA test that has been shown in our laboratory to have 100% diagnostic specificity for CD. However, we could not exclude the presence of additional CD patients in our sample because this test works with lower than 100% sensitivity rate for CD. As a rule, negative IgA type TGA assay results are seen in CD patients with IgA deficiency or among children less than 2 years of age. In our study, the presence of negative test results from these causes were excluded because all sera with low IgA type TGA test responses were further analysed for IgG type TGA—a well-proven CD marker for IgA-deficient patients [8]. Also, our study sample did not include infants.

One could ask whether there has been an actual CD increase in Estonia, or whether the present result is caused by changing the screening method. Yet, the latter reason is unlikely as the combination of antigliadin and antireticulin antibody assays (used in our first studies) has been shown to be highly effective in detecting CD although somewhat inferior to IgA-TGA assay (used in this study) regarding sensitivity [1]. However, the comparison itself is not free from potential bias because both studies were not performed in the same geographical location. As seen from the recent study of Fowell et al., CD incidence may have tendency for clustering in some geographical regions because of differences in disease-modulating environmental factors [9].

Hence, we believe that the real prevalence of CD in Estonia appears to have increased during the last decade. A similar trend has followed in other populations of Europe; however, prevalence figures are still diverse from 1:67 to 1:250 [10]. Interestingly, the increase in some other immune mediated diseases, including allergy, has been described in several populations. Usually this increase is explained by changes in the microbial environment and by the so-called “hygiene hypothesis” [11]. In CD, however, increase in the intake of disease-inducing gluten and other prolamines is of crucial importance in the background population [1,10]. In a special study performed in 1994–1999 in Estonia, the 2.5-fold increase of cereal intake among 6-month-old children was demonstrated [12], and this trend has continued according our preliminary investigations till today. In addition, other environmental factors, most probably some micro-organisms [13], might play a significant role in the pathogenesis of CD. As all of these factors may have a different impact on different populations, they should be studied simultaneously in different geographical regions parallel with CD prevalence studies. The results may better elucidate different aspects of the pathogenesis of CD and may help work out novel tactics for prevention of CD. These studies could also answer the question, why screening studies with similar study protocols still give rather different CD prevalence rates in genetically similar populations. In this connection, the relatively low prevalence of CD (1:290) with exceptional predominance of females in our study as compared with a recent Italian study (CD prevalence 1:96 with female to men ratio about 3:1 [14]) deserves special attention.

However, in addition to these important basic results, a very important practical problem has arisen—the low awareness of CD among physicians. In Estonia, according to a recent survey covering the last 15 years, the incidence of clinical CD is 1.71 (CI: 0.29 to 3.24) per 100 000 children upto age 15 years [15]. Similar results about low awareness of CD were obtained in some other studies including a recent survey [16]. Therefore, all members of any medical community should pay much more attention to CD education among all physicians, especially among primary care providers. This is particularly needed in regions with low frequency of registered CD cases. Recent studies clearly show that CD may affect significant numbers of individuals of all ages from diverse regions of the world, even in areas where CD has not been suspected to occur so far [3,10]. It is extremely important to diagnose CD on time to prevent serious complications related to malabsorption of nutrients.

Practice points

- Coeliac disease has been detected today in up to 1.5% of the European population, being one of the most common chronic diseases in childhood.
- The low frequency of registered coeliac disease cases might be due to low awareness of coeliac disease among physicians.
- Increasing the awareness of coeliac disease is essential to diagnose coeliac disease in time and thereby prevent serious complications.

Research agenda

- To evaluate the impact of different environmental factors on the pathogenesis and increased prevalence of coeliac disease.

Conflict of interest statement

None declared.

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