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Alimentary Tract

The clinical presentation of coeliac disease in 1030 Swedish children: Changing features over the past four decades

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ABSTRACT

Background: The features of paediatric coeliac disease have changed in recent decades. We hypothesised that the age at diagnosis might continue to increase, whereas the severity of symptoms should decrease.
Methods: In the present study, filed data on 1030 paediatric patients diagnosed with coeliac disease between 1973 and 2013 were analysed. The information available covered 99.8% of small bowel biopsies and included information on sex, age and clinical symptoms.
Results: The age at diagnosis increased significantly, from a mean of 2.2 years during the first 10 years to 8.2 years in recent years. The proportion of children with severe symptoms declined from 92.8% to 78%, as did the proportion of biopsies characterised by severe pathology. In recent years, the monosymptomatic form of coeliac disease has been more common, and the number of patients detected at screening has increased. The frequency of patients with gastrointestinal symptoms, extra-intestinal symptoms, and failure to thrive and/or short stature at presentation decreased.
Conclusions: The mean age of newly diagnosed patients has increased over the last 15 years. Currently, coeliac disease shows a less severe picture in terms of symptoms and intestinal pathology. Younger children suffer primarily from gastrointestinal symptoms and growth failure, and adolescents from extra-intestinal manifestations.
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1. Introduction

Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy triggered and maintained by dietary gluten in genetically predisposed individuals [1]. The small intestinal biopsy was considered to be the gold standard for disease diagnosis in Europe in guidelines by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) from 1969 [2]. In 2012, the guidelines were revised, stating that biopsy could be omitted under specific circumstances [3].

In Sweden, there were reports of one of the highest observed prevalences of CD worldwide, i.e. 3%, among 12-year-olds born during what has been described as "the Swedish coeliac epidemic", 1984–1996, henceforth referred to as the coeliac epidemic [4].

Subjects suffering from the classical type of CD, traditionally most frequently encountered among younger children, may present various gastrointestinal symptoms and signs of malabsorption. By contrast, the non-classical type predominates in the older paediatric population, i.e. children of school age and adolescents [3,5,6]. The disease panorama also includes asymptomatic cases where the patients are detected through screening [5]. The sex distribution in CD patients has always shown a dominance of female subjects [7,8].

To our knowledge, there is no current standard method of global assessment of disease severity in CD, such as in other diseases, e.g. inflammatory bowel disease [9], and studies have employed different clinical, serological and pathological parameters to assess severity [10–15]. However, our impression from the clinical work is that the disease severity has changed, as has the age at presentation.

We hypothesised that the mean age at diagnosis of CD has continued to increase over the 41-year study period, and that disease severity, in terms of clinical symptoms and pathological findings, has decreased. Accordingly, we have tried to elucidate possible

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changes in the way the disease is presented in relation to the pre-epidemic, epidemic, and post-epidemic periods of CD in Sweden. Knowledge of presumed clinical features of coeliac disease at various ages is important for family doctors and paediatricians in caring for small children and adolescents who present with gastrointestinal and other potentially CD-related signs and symptoms.

2. Materials and methods

2.1. Data collection

Since 1973, a regional CD register was used, covering information about age at diagnosis, sex, clinical symptoms and the results of the biopsy examination. This information was filed when the biopsy was performed, i.e. on an occasion between 1973 and 2013. Analyses of the filed data were performed in 2014 and 2015, when some original charts were re-examined if information was missing or incomplete.

For this study, we have analysed material both for the whole period, 41 years, and for the three subperiods: pre-epidemic (1973–1983), epidemic (1984–1996) and post-epidemic (1997–2013).

2.2. Patients

The study was performed in the County of Östergötland, Sweden, with a catchment area of about 450,000 inhabitants (5% of the national population), of whom 20% are children under 18 years of age. The county is served by three paediatric clinics, in Linköping, Motala and Norrköping. Since 1973, a regional CD register has been kept with information about age at diagnosis, clinical symptoms and the results of the biopsy examination.

The inclusion criteria for the study were: age below 18 years at diagnosis, CD diagnosis based on the ESPGHAN criteria valid at the time of investigation, i.e. with a small intestinal biopsy revealing enteropathy compatible with CD until 2011, or diagnosis based on the revised criteria suggested by ESPGHAN after 2012.

The study comprised 1030 paediatric patients, diagnosed with CD between 1973 and 2013. Among them, 987 received a biopsy-confirmed diagnosis, and 43 were diagnosed according to the revised ESPGHAN criteria without small intestinal biopsy [3]. Detailed biopsy reports were available for 99.8% of the patients. The numbers of patients in each period were: pre-epidemic ($n = 98$), epidemic ($n = 319$) and post-epidemic ($n = 613$).

2.3. Age and symptoms at presentation

For each patient, the age at presentation was noted. The mean age at presentation for the whole period was determined in addition to the age in the three subperiods, pre-epidemic, epidemic and post-epidemic, to evaluate any possible changes over the period.

To assess the severity of the disease during the whole period and the subperiods, we studied both the clinical picture and the histopathological evaluations to see whether there were any differences as stated in the hypothesis.

The clinical picture of CD at presentation was divided into four groups: (i) gastrointestinal, (ii) extra-intestinal, (iii) failure to thrive (FTT) and/or short stature, and (iv) no obvious symptoms–detection by screening. The information was provided by the parents in the case of young children, whereas adolescents described their symptoms directly to the physician. FFT was defined as weight-for-age less than two standard deviations below the mean for age and short stature as standing height more than two standard deviations below the mean for boys and girls respectively. Screening was only used for patients who were deemed to be at increased risk of CD, e.g. children with diabetes type 1 or a family history of CD. Some of these subjects may eventually develop symptoms, mostly mild, between the two different screening occasions. Each patient could be assigned to more than one group. The frequencies of symptoms were described in relation to four different age groups at diagnosis, 0–1.9, 2–4.9, 5–14.9 and 15–17.9 years, and three different time periods in relation to the Swedish coeliac epidemic, pre-epidemic (1973–1983), epidemic (1984–1996) and post-epidemic (1997–2013) periods [4]. The clinical symptoms were assessed with a severity score: no symptoms, i.e. asymptomatic = 1, moderate symptoms = 2, severe symptoms = 3, based on information from the patients and/or their parents. In the case of multiple symptoms, the most intense one was chosen to characterise the severity. Patients with continuous constipation problems, daily abdominal pain, frequent loose stools per day, low haemoglobin, and/or weight loss were given a score of 3. Children with intermittent diarrhoea or constipation, mild abdominal pain, etc. were given a score of 2.

2.4. Histopathological evaluations

In total 985/987 pathology reports were retrieved from the patients' charts, which meant that pathology reports were available in 99.8% of the cases with biopsy-based diagnosis. Over the 41-year period, three different grading manuals have been used in Sweden for biopsy classification of mucosal enteropathy: the Alexander, the Marsh, and the Swedish KVAST assessment [16–18]. To facilitate comparisons, we reclassified the material as follows: biopsy score 1 if there was normal or almost normal mucosa (Alexander I, Marsh 0, and KVAST normal); biopsy score 2 for mild enteropathy (Alexander II, Marsh I and II, and KVAST borderline); and biopsy score 3 for severe enteropathy (Alexander III and IV, Marsh IIIa, IIIb, and IIIc, and KVAST partial or subtotal/total villous atrophy).

The study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences, Linköping University, Sweden. The families/parents provided consent to data collection.

2.5. Statistical analyses

Descriptive statistics were presented as means and 95% confidence interval (CI). Frequency comparisons were performed using the Chi-squared test. Differences between group means were determined by one-way ANOVA and confirmed by least significant difference (LSD) post hoc tests. Unpaired two-tailed Student's t-test was used to compare characteristics and the means of two different samples. A p-value less than 0.05 was considered statistically significant. Analyses were performed using SPSS software (SPSS Statistics for Windows, Version 22.0. IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographics

The mean age at CD diagnosis for the whole study group was 6 years (range, 5.7–6.3).

The mean age for the whole population, and for the male and female subgroups, increased gradually over the study period (Fig. 1). The pre-epidemic, epidemic and post-epidemic mean ages of the study population were 2.2 (1.6–2.8), 2.8 (2.4–3.2) and 8.2 (7.8–8.6) years respectively, and the male and female populations displayed similar results (Table 1). Further analyses of the data with post hoc LSD t-tests revealed a higher mean age in the post-epidemic period than in the pre-epidemic ($p < 0.001$) and epidemic ($p < 0.001$) periods. The female-to-male distribution in the study was 1.8:1.

The boys' mean age at diagnosis during the 41-year study period exceeded that of the girls in 25 out of 41 years; in contrast, the girls'

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