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PEDIATRIC DISEASE

The Swedish coeliac disease epidemic with a prevailing twofold higher risk in girls compared to boys may reflect gender specific risk factors

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Abstract. In the mid 1980s the incidence of coeliac disease in Swedish children below 2 years of age increased threefold within a few years, and after a 10-year high incidence period returned equally rapidly to the previous level. Analysing the epidemic with respect to any change in female to male ratio over time, or shift in age at diagnosis, may increase the understanding of coeliac disease aetiology. In a population-based incidence study of childhood coeliac disease, 2151 cases (811 boys/1340 girls) were diagnosed from 1973 to 1997. Incidence rates and relative risks (RRs) were calculated by gender, age at diagnosis and calendar time. Cumulative incidences by age and gender were calculated for different birth cohorts. A twofold higher risk (RR: 1.9, 95% confidence interval (CI) 1.7–2.1) for coeliac disease in girls as compared to boys prevailed throughout the epidemic. Further, during the post-epidemic period there was an upward shift in age at diagnosis. So far, however, a majority of the cases diagnosed at older ages belong to birth cohorts of the epidemic period, i.e. cohorts that already had a high coeliac disease risk before 2 years of age. Our results suggest that girls as compared to boys may be genetically more vulnerable to environmental exposures influencing the immunological processes towards coeliac disease. Further, an increased risk for coeliac disease during the first years of life due to, for example, unfavourable infant dietary habits, may result in an increased total childhood risk for coeliac disease. A longer follow-up, even into adulthood, is needed to determine whether or not the lifetime risk has changed.

Key words: Aetiology, Coeliac disease, Gender, Genetic, Incidence, Relative risk

Introduction

Coeliac disease is characterised by a gluten-dependent enteropathy and has been considered mainly a gastrointestinal disease, although it is now recognised as an immunological disease that may affect many different organs [1, 2]. Intolerance to gluten is lifelong. If, however, wheat gluten and related proteins from rye and barley are excluded from the diet, the disease processes resolve.

Family clustering indicates a strong genetic influence. So does the fact that females seem more vulnerable to coeliac disease than males, although this is not considered in current models. Human leukocyte antigen (HLA)-DQ2 is carried by more than 90% of coeliac patients, as compared to 20–30% of healthy controls. Non-HLA genes may be even more influential, but so far no unambiguous candidate genes have been identified.

Models for coeliac disease pathogenesis have been proposed, although they are still incomplete [3, 4]. In the currently favoured model, DQ2 molecules of antigen-presenting cells present gluten peptides, or digests thereof, to T-cells (CD4+), thus activating these to produce cytokines of a predominantly T_H1-pattern. It has been suggested that tissue transglutaminase is a major autoantigen [5], and also that it deamidates certain gliadin peptides, producing an enhanced T-cell response [6]. In active coeliac disease antibodies are produced against gliadins and endomysium components (including transglutaminase), perhaps as a consequence of an interaction between gliadin and tissue transglutaminase. Furthermore, efforts have been made to define which epitope(s) of the gluten proteins are crucial for triggering the immunopathological processes [7–9].

Coeliac disease most likely has a multifactorial aetiology [3], with interplay between several genetic and environmental factors. Thus, environmental exposures – in addition to ingestion of gluten proteins – are likely to contribute. Infection with adenovirus (serotype 12) has been suggested to contribute through its immunological cross reactivity with A-gliadin [10], but the relevance of this has been questioned. The possible role of infant feeding practices has also been explored, with varying conclusions [11–17]. Our recent results do, however, support a protective effect of introducing gluten-containing foods into the infant diet in small amounts while breastfeeding is still ongoing [18–20]. Other environmental

exposures could also be of importance, but are thus far essentially unexplored.

Early screening studies on coeliac disease revealed a prevalence of around 4 per 1000 in several populations [21–23]. However, Estonia constitutes an exception, without a single case identified in a well-performed population screening [24], as does the prevalence of 56 per 1000 recently found among Saharawi children in Algeria [25]. Thus, the prevalence of coeliac disease clearly varies among different populations. The extent to which this variation results from differences in genetic susceptibility and/or environmental exposures is thus far merely a matter of speculation.

In the mid 1980s the incidence of coeliac disease in Swedish children below 2 years of age increased threefold within a few years, and after a 10-year high incidence period returned equally rapidly to the previous level [18]. Since the population is genetically fairly stable, this indicates changes in causal environmental exposures. It is not yet clear whether these changes in incidence constitute the first sign of an upward shift in age at diagnosis [26, 27], similar to what has been reported from some other countries [28, 29].

Most studies on coeliac disease, both studies on clinical series of patients and screening studies, report a predominance of females as compared to males [29–35]. This suggests that gender specific genetic factors are pre-disposing for females and/or protective for males. Such genetic factors might contribute through interaction with environmental exposures. To our knowledge, no studies have explored this issue.

Revealing the extent to which the Swedish epidemic of coeliac disease affected girls as compared to boys might contribute to an increased understanding of the interaction between genetic pre-disposition and environmental exposures in coeliac disease aetiology. We therefore decided to analyse the epidemic further by means of two main questions: (1) To what extent did the epidemic affect boys and girls, respectively? and (2) Is the epidemic followed by an upward shift in age at diagnosis?

Methods

Case ascertainment

Sweden's national child health program – with almost complete coverage (>99%) – is implemented through child health clinics and school health services throughout the country. When coeliac disease is suspected, the child is referred to the closest paediatric department for further examination.

A central register of coeliac disease cases in children below 15 years of age was organised based on reporting from paediatric departments throughout the country. At five departments, information on all coeliac disease cases diagnosed from 1973 to 1990 was excerpted from local registers. These as well as an additional nine departments prospectively reported all incident cases from 1991 to 1997. The retrospective and prospective parts of the register cover 15 and 40%, respectively, of all children in the country [18].

A total of 2151 cases (811 boys and 1340 girls) fulfilled the diagnostic criteria for coeliac disease according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [36] (Table 1), which are based on assessment of the morphology of the small intestinal mucosa. All information reported by 31 December 1998 was considered.

Population data

Population data were obtained from Statistics Sweden (Table 1). The national population register is complete, and each paediatric department has a well-defined geographical catchment area. The number of children living in the study area on 31 December for two consecutive years, divided by two, was used to estimate the number of person-years of follow-up. Exact figures were available for the number of births each year.

In 1973 the study area comprised 258,683 children (five clinics) and in 1991 there were 623,439 children (14 clinics), including all children below fifteen years

Table 1. Number of coeliac disease cases and population size by time period, age at diagnosis and gender

	Time period			
Characteristics	1973–84 N (%)	1985–95 N (%)	1996–97 N (%)	1973–97 N (%)
No. of cases				
0–1.9 years				
Boys	82 (33)	450 (36)	53 (43)	585 (36)
Girls	168 (67)	810 (64)	71 (57)	1049 (64)
Total	250	1260	124	1634
2.0–14.9 years				
Boys	15 (35)	148 (46)	63 (41)	226 (44)
Girls	28 (65)	173 (54)	90 (59)	291 (56)
Total	43	321	153	517
*Population * 1000*				
0–1.9 years				
Boys	196	343	82	621
Girls	186	326	77	589
Total	382	669	159	1210
2.0–14.9 years				
Boys	1348	2009	592	3949
Girls	1280	1909	561	3750
Total	2628	3918	1153	7699
*No. of births * 1000*				
Boys	104	174	38	316
Girls	98	166	36	300
Total	202	340	74	616

of age. This resulted in a study base of 4,408,816 and 4,500,685 person-years for the retrospective and prospective parts of the study, respectively, taking the variation in population over the years and the follow-up period into account.

Definitions

The words gender and sex are used synonymously. Age at diagnosis was defined as the age when the first small intestinal biopsy was performed. Children were divided into the age groups 0–1.9 and 2.0–14.9 years at diagnosis, mainly because the epidemic of coeliac disease only affected children below 2 years of age.

Based on variations in incidence rates over time in children below 2 years of age, the study period was divided into: (1) the *pre-epidemic period*, i.e. the low incidence period from 1973 to 1984, (2) the *epidemic period*, i.e. the high incidence period from 1985 to 1995, and (3) the *post-epidemic period*, i.e. the medium to low incidence period from 1996 to 1997 (Figure 1).

Statistical analyses

Incidence rates of coeliac disease were calculated by dividing the number of new cases diagnosed by the number of person-years of follow-up, reported per 100,000 person-years. This was done separately for boys and girls, age groups (0–1.9 and 2.0–14.9 years), calendar year at diagnosis (1973, 1974, ..., 1997), and time period at diagnosis (1973–1984, 1985–1995, 1996–1997).

Poisson regression models were used to estimate the relative risk (RR) of developing coeliac disease considering these characteristics. Bivariate analyses were followed by multivariate analyses, keeping interaction terms with a p-value < 0.1 in the final model.

The cumulative incidence of coeliac disease was calculated by dividing the number of cases diagnosed up to a certain age by the number of births in each cohort, reported per 1000 births. This was done separately for the birth cohorts of 1973–1996, and for boys and girls.

Statistical significance was defined as RRs with a 95% confidence interval (CI) excluding 1.0. EXCEL [37] and SPSS [38] were used for basic calculations, and EGRET [39] for Poisson regression analyses.

Ethics

The Swedish Data Inspection Board and the Research Ethics Committees of all Swedish Medical Faculties approved the study. Informed consent was obtained from the families.

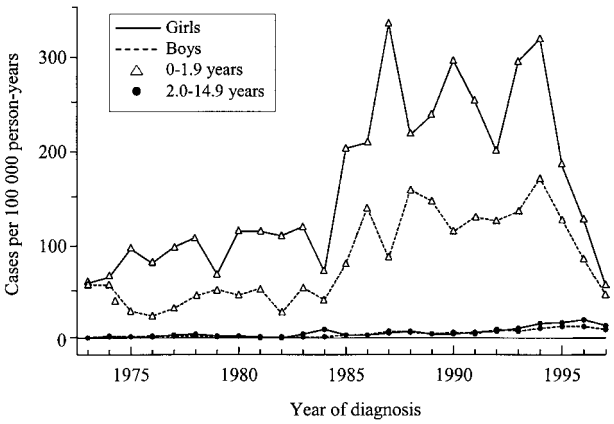

Figure 1. Annual incidence rate of coeliac disease by gender and age group from 1973 to 1997.

Results

The epidemic

In the mid 1980s the incidence rate of coeliac disease in Swedish children below 2 years of age increased threefold within a few years, and after a 10-year high incidence period it returned equally rapidly to the previous level (Figure 1) [18]. During the whole study period from 1973 to 1997, the incidence rate in children between 2 and 15 years of age slowly increased, although it remained at a considerably lower level than in the younger age group (Figure 1).

Gender as a risk factor

The incidence rate of coeliac disease was about twice as high in girls as compared to boys (Figure 1), also illustrated by a RR of 1.9 (95% CI: 1.7–2.1) (Table 2). This gender difference was less pronounced in children diagnosed after 2 years of age (Figure 2a and b), as illustrated by a significant interaction between the variables gender and age group (RR: 0.72) (Table 2).

The twofold higher risk for girls as compared to boys was largely constant over the pre-epidemic period, the epidemic period and the post-epidemic period, as illustrated by the absence of significant interaction between the variables gender and time period (Table 2). Thus, when the epidemic started the increase in incidence rate was larger in girls as compared to boys, as was the decrease during the post-epidemic period (Figure 2a and b).

Variation in incidence between birth cohorts

In all the birth cohorts of 1973 to 1995, the cumulative incidence increased most rapidly until 2 years of age. The level reached at this age was, however, considerably higher during the epidemic period as compared to the pre-epidemic period (Figure 3a and b). Furthermore, the cumulative incidence also continued to increase after 2 years of age in all the cohorts, including those that had already reached a

Table 2. Risk for coeliac disease by gender, age at diagnosis and time period. Poisson regression analyses based on 2151 cases and 8,909,501 person-years of follow-up

Independent variables	Bivariate analyses RR (95% CI)[b]	Multivariate analysis[a] RR (95% CI)
Gender		
Boys	1.0	1.0
Girls	1.7 (1.6, 1.9)	1.9 (1.7, 2.1)
Age group		
0–1.9 years	1.0	1.0
2–14.9 years	0.050 (0.045, 0.055)	0.031 (0.022, 0.043)
Time period		
1973–1984	1.0	1.0
1985–1995	3.5 (3.1, 4.0)	2.9 (2.5, 3.3)
1996–1997	2.2 (1.8, 2.6)	1.2 (0.97, 1.5)
[Gender * age group][c]		
0–1.9 years		1.0
2–14.9 years		0.72 (0.59, 0.88)
[Age group * time period]		
1973–1984		1.0
1985–1995		1.7 (1.2, 2.5)
1996–1997		6.8 (4.5, 10)

[a] Likelihood ratio statistics (LRS) on 8 degrees of freedom (DF) = 17.2, $p < 0.001$. The interaction term [gender * time period] was excluded from the model as it was non-significant [gender * 1973–1984, RR: 1.0; 1985–1995, RR: 0.83, 95% CI: 0.64–1.1; and 1996–1997, RR: 0.78, 95% CI: 0.55–1.1].
[b] Relative risk (95% confidence interval).
[c] Interaction term.

comparatively high level at that age. For the cohorts born during the post-epidemic period, a longer follow-up is needed to evaluate the coeliac disease risk within the age interval 2 to 15 years. At present the majority of coeliac disease cases diagnosed within this age interval originate from cohorts born during the epidemic.

Cohort effects by gender

When a cohort of 100,000 boys and 100,000 girls borne in the 1970s (1973–1977) reached 15 years of age, there were 81 coeliac disease cases among boys and 208 coeliac disease cases among girls (Figure 3a and b). In the beginning of the 1990s, during the peak years of the epidemic (e.g. 1993), a cohort of the same size had, at 4 years of age, 374 cases among boys and 635 cases among girls. The 1993 cohort had, at 2 years of age, generated 324 of these cases in boys and 556 in girls. This should be compared with the cohort of 1995, which at 2 years of age had only 133 cases among boys and 201 cases among girls (Figure 3a and b). Thus, consecutive birth cohorts at comparable ages first had an increased number of cases in both boys and girls, after which a decrease was noted in both sexes.

Discussion

A major finding in the present study was a twofold higher risk for coeliac disease in girls as compared to boys that was largely constant over time, in spite of an epidemic incidence pattern indicating changes in causal environmental exposures. Furthermore, during the end of the study period the yearly number of diagnosed coeliac disease cases decreased, and there was an upward shift in age at diagnosis. It is important to note that a majority of the cases diagnosed at an older age originate from birth cohorts of the epidemic period, and consequently also had a high risk of coeliac disease before 2 years of age.

This is the first study on coeliac disease that explores any changes in the female to male ratio over decades and that also considers possible cohort effects. We are confident that virtually all diagnosed cases of coeliac disease in children in the study area were reported to the register [18]. Diagnostic criteria were based on evaluation of the small intestinal mucosa [36] and were largely unchanged during the study period. Moreover, there is no reason to expect differences in reporting to the register or in evaluation of the mucosal specimens with respect to gender. The incidence register was based on coeliac disease cases diagnosed in clinical practice, and did not encompass a general screening.

Our finding of an increased risk for coeliac disease in girls as compared to boys confirms previous reports from several populations [29–35]. However, in this paper we extend the previous observations to show that the twofold higher risk for girls as compared to boys was largely constant over a period of decades, in spite of a three fold difference in incidence rates over time indicating large variations in causal

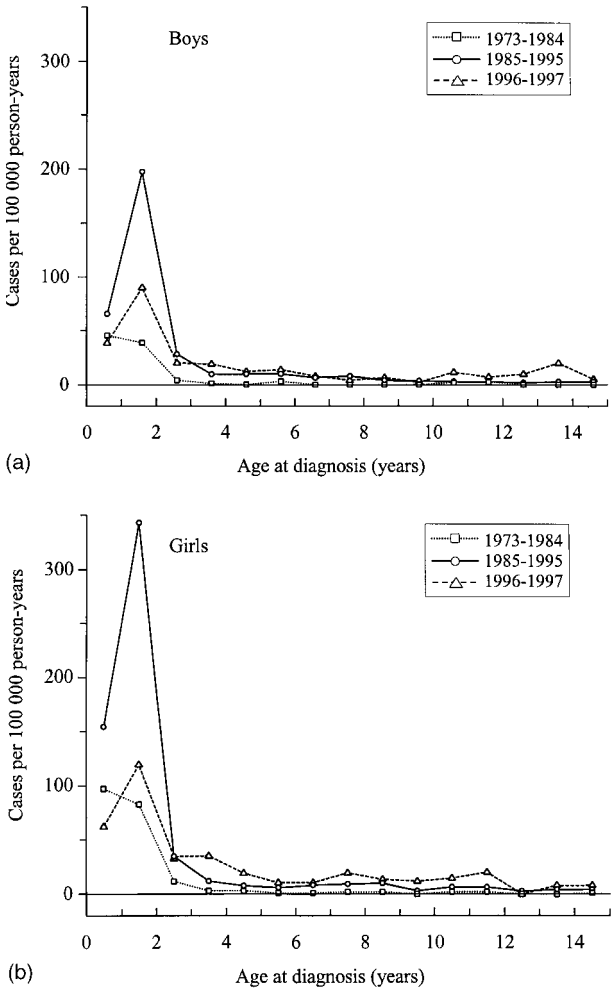

Figure 2. Average incidence rate of coeliac disease by age at diagnosis for boys (a) and girls (b) during the pre-epidemic period (1973–1984), the epidemic period (1985–1995) and the post-epidemic period (1996–1997).

environmental exposures. This implies that when the epidemic started, the increase in incidence rates was larger in girls as compared to boys, as was the decrease during the post-epidemic period. The constant, twofold higher risk for girls as compared to boys was further supported by analyses of coeliac disease risk in different birth cohorts. Thus, it may be that girls as compared to boys are genetically more vulnerable to environmental exposures influencing the immunological processes towards coeliac disease. It cannot, however, be completely excluded that differences between the life conditions of boys and girls that lead to different environmental exposures also contribute.

The gender difference in incidence was larger in children below than above 2 years of age at diagnosis. In a previous study we showed that infant dietary exposures were important with respect to coeliac disease risk in the age group below 2 years of age, while in older children they were of no – or only minor – importance [19]. These findings suggest that the aetiology of coeliac disease might differ somewhat between younger and older children.

Coeliac disease has many similarities with so-called autoimmune diseases; however, one crucial difference is that the immunological process in coeliac disease is dependent on exposure to dietary gluten. Thus, in coeliac disease the immunological process can be turned on by introduction of gluten-containing foods, and shut off by exclusion of these foods. Coeliac disease patients also have an increased risk for other autoimmune diseases, a risk that seems to increase with the number of years on a gluten-containing diet [40]. Like coeliac disease, most autoimmune diseases are more common in females than in males [41]. In multiple sclerosis and rheumatoid arthritis the female to male ratio is between 2:1 and 3:1, and in systemic lupus erythematosus it is as high as 9:1. The reasons for this gender difference are not very clear. There are, however, indications that clinically distinct autoimmune diseases share genetic risk factors [42], and that many of these loci are gender influenced [43].

During recent years there have been numerous reports on the changing clinical presentation of coeliac disease in childhood, with a shift from infants and young children with classical symptoms of malabsorption to older children with mild and atypical symptoms [28, 29]. In Sweden, the former group has continued to be predominant. However, a change has taken place during the post-epidemic period, with an upward shift in age at diagnosis. So far, however, a majority of the cases diagnosed at older ages belong to birth cohorts of the epidemic period, i.e. cohorts that already had a high coeliac disease risk before 2 years of age. Thus, it may be that as a consequence of unfavourable exposures during their first years of life, the birth cohorts of the epidemic years also carry an excess risk for coeliac disease later in life. If so, the cohorts of the post-epidemic period might have a decreased risk for coeliac disease later in life as well. So far these cohorts actually have a lower cumulative incidence at comparable ages than the cohorts of the epidemic period. However, a longer follow-up, preferably extending into adulthood, is necessary to determine the extent to which this lower risk remains. Thus, it is not yet proven that the lifetime risk has changed.

In summary, our results suggest that girls as compared to boys may be genetically more vulnerable to environmental exposures that influence the immunological processes towards coeliac disease. Thus, studies of coeliac disease – irrespective of type, e.g. clinical, epidemiological, or experimental – ought to be stratified for gender in order to contribute even further to the understanding of coeliac disease aetiology. Moreover, the Swedish epidemic of coeliac disease was followed by an upward shift in age at diagnosis. So far, however, children diagnosed at an older age originate from birth cohorts of the epidemic period. Thus, our findings are compatible with the possibility – although they do not prove it – that an increased risk for coeliac disease during the first years

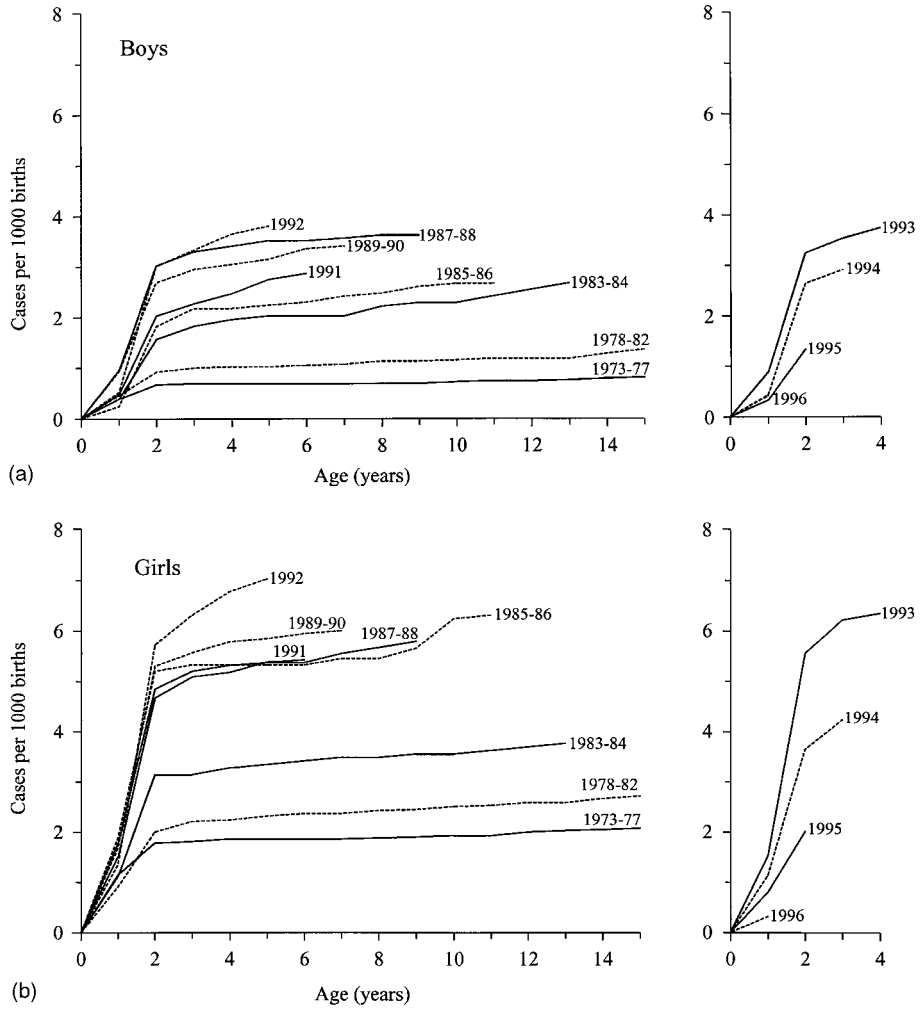

Figure 3. Cumulative incidence of coeliac disease by age for boys (a) and girls (b) from the birth cohorts of 1973–1996.

of life due to, for example, unfavourable infant dietary habits, may result in an increased total childhood risk for coeliac disease. A longer follow-up, extending into adulthood, is needed to determine whether or not the lifetime risk has changed.

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