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Epidemiology of Celiac Disease in The Netherlands

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Herein we provide an updated analysis of the membership records of the Dutch Coeliac Disease Society up to January 1, 1995, and the data on childhood celiac disease (CD) provided by the Dutch Paediatric Surveillance Unit (1993 to 1994), which enabled us to study the incidence of CD prospectively and on a national level.

METHODS

Epidemiological and socioeconomic data of the general Dutch population were obtained from the Netherlands Central Bureau for Statistics (1,2). Anonymity was guaranteed. The research project was approved by the appropriate ethical committee. Intergroup comparison was performed using the unpaired Student's *t* test and the chi-square test. Significance was accepted as $p < 0.05$ (two-sided).

Dutch Coeliac Disease Society

The records of members of the Dutch Coeliac Disease Society, with single biopsy-confirmed disease as of January 1, 1995, were analyzed and compared with data from January 1, 1990.

Dutch Paediatric Surveillance Unit

This unit was founded in 1992 under the auspices of the Dutch Society for Paediatrics, following the example of the British Paediatric Surveillance Unit. All pediatricians in clinical practice reported monthly to the unit whether they had diagnosed or suspected CD in a child throughout 1993-1994. The reported case was verified by means of a questionnaire sent to the concerned pediatrician. Inclusion criteria were that the patient had been born in the Netherlands, that the diagnosis of CD was based on at least one small-intestinal biopsy showing (sub)total villous atrophy between January 1, 1993, and January 1, 1995, and that the age at diagnosis was between 0 and 14 years. The data were ascertained by means of the Dutch Network and National Database of Pathology, in which all pathological specimens taken in the Netherlands are registered anonymously. The results were compared with those of a previous, retrospective study covering 1975 to 1990 (3).

RESULTS

Dutch Coeliac Disease Society

The mean prevalence rate (per 100,000 inhabitants) of CD in the Netherlands has increased from 7.9 on January 1, 1990, to 17.5 on January 1, 1995. The mean prevalence rate in the 20 largest cities with more than 100,000 inhabitants was 16.8. The mean prevalence rate in a selected group of 13 smaller (10,000 to 60,000 inhabitants), but prosperous cities (>13,000 Dutch guilders per year per socioeconomic unit) was 29.1, which is significantly higher than the mean national prevalence rate. This prevalence rate is also significantly higher than that found in a selected group of 13 comparable, but less prosperous cities (<12,500 Dutch guilders per year per socioeconomic unit)—15.2. The incidence rate (per 100,000 inhabitants) of CD increased from 0.49 in 1975 to 1.26 in 1995. The general Dutch population has increased by $0.6 \pm 0.2\%$ (mean \pm SD) per year. The overall female/male ratio is 2.12 ($n = 2,048$). CD became manifest in 34% before age 10, but in 63% it was diagnosed in adulthood.

Dutch Paediatric Surveillance Unit

All pediatricians throughout the Netherlands were contacted each month from 1993 through 1994. The average response rate of the pediatricians was 92%. The response to the questionnaire was 100%. The crude incidence rate of childhood CD was calculated using the new cases of CD as numerator and the number of live births in the study years as denominator, expressed per 1,000. The overall crude incidence rate was 0.49 per 1,000 live births. Compared with the incidence rates of 0.10 in 1976 and 0.32 in 1990, this trend is increasing in a linear fashion significantly.

Most of the 193 celiac patients (male/female ratio, 1:2.1) identified in the study period had classic CD: growth failure in height and/or weight in 89.7%, chronic diarrhea in 62.2%, and abdominal distension in 55.1%. The mean age at diagnosis was 3.1 ± 3.0 years, and 60.0% of the children were diagnosed under the age of 2 years. A total of 21 (10.9%) children had diseases associated with CD, among which are diabetes mellitus, Down syndrome, and selective IgA deficiency.

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Immunoserological tests were performed before small-bowel biopsy in the majority of cases. Antigliadin antibody determination in 98.3%, antireticulin antibodies in 27.0%, and anti-endomysium antibodies in 16.9%. Sugar absorption tests, such as the lactulose-mannitol test and the xylose test, were applied in 20.8% and 15.7%, respectively. From 1993 through 1994 a total of 1,712 small-intestinal biopsies were taken in children <15 years. Villous atrophy was found in 295 cases (ratio between biopsies with subtotal villous atrophy and the total number of biopsies, 1:5.8).

DISCUSSION

An analysis of the records of the Dutch Coeliac Disease Society provides what is thought to be accurate data on CD at a national level and gives only a slight underestimate of the real prevalence rate of CD in the Netherlands: 80% of children with CD are members of the society. On the other hand, the Dutch Paediatric Surveillance Unit also offers the unique possibility of studying the incidence of CD in children at a national level. The high response rate of the Dutch pediatricians and the method of ascertainment by means of the Dutch Network and National Database for Pathology lend reliability to the findings.

In the Netherlands the overall prevalence rate of CD is 17.5 per 100,000 individuals, which is low compared with the English prevalence estimate in 1980 of 61 per 100,000 inhabitants (4). It is remarkable that the Dutch prevalence estimate of 5.5 per 100,000 individuals in 1981 (5) has increased to 17.5 in 1995, probably due in part to correction for underdiagnosis in the past.

One might also conclude from this study that in the Netherlands prosperity and the number of recognized cases of CD are associated. High prevalence rates are found in a selected group of prosperous smaller cities, and these rates are significantly higher than those found in a comparably sized group of less prosperous cities. The tendency among some socioeconomic classes to seek a second or third medical opinion as well as the socioeconomically determined difference in dietary gluten intake may play a role (6). However, in Sweden the opposite has been found: childhood CD is more common in the lower social groups (7). These findings suggest a correlation between prevalence of CD and socioeconomic status, but the identity of this association is unclear.

A significant increase in the reported incidence of childhood CD in the Netherlands was seen: from 0.10 in 1976 and 0.32 in 1990 to 0.49/1,000 in 1993–1994. The question remains, however, whether the increases in incidence seen in adulthood and childhood are parallel. There is a possibility that the gap caused by nondiagnosis of CD in patients at a younger age is diminishing. Ten years is probably too short a period of time to assess

whether the number of nondiagnosed children is diminishing, which might ultimately result in fewer diagnoses of CD at older ages. Biemond et al. reported that about one third of patients with CD were diagnosed before the age of 10 in 1983 (5). In 1994 the same age distribution was found among the members of the Coeliac Disease Society. The lack of a shift in diagnosis toward a younger age over a period of more than 10 years suggests that CD is not being missed by pediatricians.

The increasing incidence of CD in the Netherlands could be explained by several mechanisms, such as underdiagnosis in the past, wider use of endoscopy and endoscopic-guided small biopsy capsules to take small-bowel biopsies, and greater awareness of the disease among Dutch physicians. However, the most likely explanation is the wider use of sensitive and specific immunological and functional tests in selecting individuals for small-intestinal biopsy.

In conclusion, epidemiological studies investigating the incidence and prevalence of CD in the Netherlands show impressive increases in recent years. These epidemiological shifts might at least in part be caused by the development of more sensitive screening tests (8), which allow for the recognition of subclinical forms and facilitate diagnosis earlier in the disease course and for less typical forms of disease. Increasing prevalence and incidence rates in the Netherlands, possibly as a consequence of underdiagnosis in the past, suggest increased awareness and improved diagnostic skills on the part of clinicians.

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DISCUSSION

Peña: I wonder whether the increase in adult CD found in Holland is due to the presence of Dr. Mulder, who is really doing a lot of diagnosing and influencing the general situation here. But we should not see the situation so superficially. Let me ask the view of Prof. Vandenbroucke from the University of Leiden, who is an epidemiologist in polygenic diseases and environmental effects.

Vandenbroucke: Hearing the first two presentations, I was reminded of an old story that epidemiologists like to tell. There was once an argument between two veteri-

nary schools about whether a certain disease in pigeons was environmental or genetic. One school thought that when new pigeons are brought to the stables, their descendants get the disease; thus it is genetic. The other school said that when the diet is changed, the pigeons get the disease; thus it is environmental. Finally it was found that the disease was based on susceptibility to certain food in genetically predisposed pigeons. If you always give the same food to your pigeons, then you think that it is a genetic trace. When you change the food, you see that a few pigeons become ill, and you assume that it is an environmental disease. I don't know whether this will be enlightening for further discussion.