Coeliac disease in the Netherlands: demographic data of members of the Dutch Coeliac Society

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Gender and age at CD diagnosis

INTRODUCTION

Coeliac disease (CD) is an auto-immune mediated enteropathy\(^1\). In the 1940s, Willem-Karel Dicke was the first to conclude that gluten is the factor responsible for what we now call CD\(^1\). Grains containing gluten include wheat, barley, and rye. The prevalence of CD is 0.5-1% in the western population and only slightly differs between countries\(^3\). The prevalence of CD in North Africa, the Middle East, and the Indian subcontinent is comparable to the prevalence in western countries\(^4\). However, there still is a lack of knowledge about CD prevalence in Asia\(^5\). The last years, there is an increased awareness of (serological) testing of CD by clinicians in different countries\(^6\). Yet, screening studies showed that still just one out of eight people with CD is diagnosed\(^3\). This underdiagnosing is probably due to the different forms of presentation of CD. Classic CD symptoms in children are diarrhea, bloating and failure to thrive. In adults, besides loss of weight and intestinal symptoms, both overweight and other extra-intestinal symptoms such as tiredness and osteoporosis are more common\(^7-10\). Remarkably, even CD patients who had not reported symptoms at the time of diagnosis, for example screened because of a family history of CD, benefit from a gluten-free diet (GFD)\(^11\).

Literature showed a predominance of females diagnosed CD with a female to male ratio of 2-4:1\(^5, 12-17\). This difference was not recognized in serological mass screening studies. Limited data are available on gender and age distribution in the daily clinical practice of coeliac disease. The aim of this article is to describe differences in gender and age at the time of coeliac disease diagnosis in the Netherlands.

METHODS

Data was obtained from a prospectively maintained database of members of the Dutch Coeliac Society in whom celiac disease was diagnosed between 1980 and August 2015.

Setting

Database of members of the Dutch Coeliac Society

Participants

Out of the total number of 26,986 current and ex-members, the data of 7,886 members could be used for analysis.

Results

Age at coeliac disease diagnosis ranged between 0-88 years old, the minority (36%) was diagnosed in childhood. In children, the majority (52%) was diagnosed before the age of 4 years old. Median age did not differ in children when compared for gender (3 years old). In adults, median age differed between males (52 years old, IQR 41-61) and females (44 years old, IQR 32-56), p<0.001. Female to male ratio was 2.4:1.

Conclusion

The majority of coeliac disease patients are diagnosed during adulthood, with males diagnosed at an older age. Only one-third of the patients was diagnosed at childhood. Coeliac disease is less frequently diagnosed in young adult males.

ABSTRACT

Background & Aims

Coeliac disease is an autoimmune disease induced by the intake of gluten with a female to male ratio of 2-4:1. Female predominance has not been recognized in serological mass screening studies. Limited data are available on gender and age distribution in the daily clinical practice of coeliac disease. The aim of this article is to describe differences in gender and age at the time of coeliac disease diagnosis in the Netherlands.

Methods

Data was obtained from a prospectively maintained database of members of the Dutch Coeliac Society in whom celiac disease was diagnosed between 1980 and August 2015.

Design

Retrospective database study

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Database of members of the Dutch Coeliac Society

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Age at coeliac disease diagnosis ranged between 0-88 years old, the minority (36%) was diagnosed in childhood. In children, the majority (52%) was diagnosed before the age of 4 years old. Median age did not differ in children when compared for gender (3 years old). In adults, median age differed between males (52 years old, IQR 41-61) and females (44 years old, IQR 32-56), p<0.001. Female to male ratio was 2.4:1.

Conclusion

The majority of coeliac disease patients are diagnosed during adulthood, with males diagnosed at an older age. Only one-third of the patients was diagnosed at childhood. Coeliac disease is less frequently diagnosed in young adult males.
as stated by the patient. Because only both the month and year of diagnosis were known the first day of that month was set as dummy date to calculate age at time of diagnosis for these persons.

Childhood was defined as any age between 0-17 years old. Adults were defined as aged 18 years and over.

Data were provided by the Dutch Coeliac Society. We only used data of members who gave consent for the use of their data for scientific purposes at initial registration after data anonymization.

**Statistical analysis**

Statistical analysis was performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois, USA). Categorical variables were summarized by descriptive statistics, including total numbers and percentages with significant differences analyzed using the Pearson Chi-Square test. Continuous data were summarized by median, interquartile range (IQR) and range with significant differences between two groups analyzed using the Mann-Whitney U test. A p-value of less than 0.05 was considered as statistically significant.

**RESULTS**

**Selection of patients**

The Dutch Coeliac Society had 26,986 current and ex-members in August 2015. For analysis, 7,886 members could be reviewed. For 64% of these members, the date of biopsy was available. Figure 1 shows the patient selection process.

**Gender**

The overall female to male ratio was 2.4:1 (females; n=5,546, males; n=2,337, unknown; n=3). Data showed no difference in distribution of gender between the years of CD diagnosis. The female to male ratio differs when dividing the patients in 5 different age groups: 0-15 years old (1.8:1), 16-30 years old (6.0:1), 31-45 years old (3.5:1), 46-60 years old (2.1:1) and 60 years or older (1.7:1), p<0.001.

**Age at time of diagnosis**

Age of CD diagnosis ranged between 0-88 years. Figure 2 shows age and gender distribution of CD diagnosis. Out of all patients, only 36% was diagnosed in childhood. Of the children diagnosed with CD, the majority (52%) was diagnosed before the age of 4 years old. Median age at time of diagnosis in children did not significantly differ between males and females, with a median age of 3 years old (IQR 1-7) in boys and also 3 years old (IQR 1-8) in girls. Median age at time of diagnosis in adults did differ significantly between males and females, with a median of 52 years old (IQR 41-61) in males and 44 years old (IQR 32-56) in females, p<0.001.

**Figure 1. Selection of patients**

| Total of active and ex-members of Dutch Celiac Society till August 2015 n = 26,986 |
| Exclusion because of no consent or ex-members n = 17,187 |
| n = 9,799 |
| Exclusion because unknown date of birth n = 964 |
| n = 8,835 |
| Exclusion because unknown date of diagnosis and biopsy n = 777 |
| Exclusion because date of diagnosis patient or biopsy was before date of birth n = 14 |
| n = 8,044 |
| Exclusion because date of diagnosis patient or biopsy before 1980 n = 158 |
| Data used for analysis n = 7,886 |
| Inclusion based on date biopsy n = 5,036 |
| Inclusion based on date diagnosis patient n = 2,850 |
DISCUSSION

This study showed a female to male ratio and age distribution of CD comparable with other studies. Although in the past CD was considered a disease only diagnosed in children, our study showed that the majority of CD patients is diagnosed as adult. The question remains whether these patients had CD since their childhood or developed CD at a later age. This is of particular importance because of the observed diagnostic delay of more than a decade in some CD patients 19.

There are several hypotheses for the predominance of females in CD. First, it is well known that females are more often diagnosed with other auto-immune diseases such as rheumatoid arthritis, multiple sclerosis, and autoimmune thyroid disease. This higher prevalence could be explained by multiple factors such as hormones, genetics (the Y chromosome might have a protective role) and pregnancy-related factors 21. Second, females have higher medical care service utilization than men and therefore are more likely to meet a doctor who will perform CD diagnostic tests 22. This could also explain the lower number of young adult males diagnosed between 16-30 years old, as reported earlier 14. Third, females are considered to be more often symptomatic in CD than males 23.

In our study, we included members of the Dutch Coeliac Society. A recent report of Statistics Netherlands (CBS), a Dutch organization which publishes reliable and coherent statistical information responding to the needs of Dutch society, showed that females are slightly more often a member of patient groups in general (6% versus 5% of males) 24. However, the Dutch Coeliac Society might has a special place due to its information about GFD and the issuing of warnings about supposedly GFD products which are not really gluten free. This information is crucial for CD patients, so there seem many advantages to being a member for both males and females. Another reason why we think that females do not frequently become member of the Dutch Coeliac Society is that CD patients have a high treatment burden due to the GFD 25. This has also an high impact burden on the whole family. These other family members seem to play an important role to stimulate CD patient to become member of the Dutch Coeliac Society since they need clear information about a GFD.

This study showed that the majority of CD patients are diagnosed during adulthood with males diagnosed at an older age. This could probably be due to health care service utilization or hormonal differences between genders. Forty percent of all CD patients were diagnosed above the age of 40 years old. This might results in another approach of follow-up in these older patients than in children since these patients are more often fatigue and at risk for several complications such as osteoporosis, refractory coeliac disease and enteropathy associated T-cell lymphoma 26, 27.

The first peak of CD in young children could be due to the introduction of dietary gluten. However, it has been reported that the introduction of gluten at a younger age (16-24 weeks old) does not prevent children in high-risk families from developing CD 28. This suggests that the moment of introduction of gluten does not play the most important role in triggering CD. It is noticeable that the primary outcome of that study was biopsy confirmed CD at the age of 3 years, so the effect of time of the introduction of dietary gluten in developing CD at later age is not known. Human Leukocyte Antigen (HLA)-DQ2 homozygosity contributes to the risk of developing CD in early childhood and could be another explanation of the large peak of young children diagnosed with CD 29.

One study showed a correlation between HLA-DQ8 phenotype and the development of CD in adulthood 30. An explanation of this finding was that the affinity of HLA-DQ8 to gluten is lower than the affinity of HLA-DQ2. Other environmental factors are probably necessary to trigger CD. These factors, such as infections, together with a diagnostic delay could explain the large number of CD patients diagnosed at an older age.
Osteoporosis is a common issue in postmenopausal females\textsuperscript{122}. We think that, despite the second peak of CD in postmenopausal females, CD is still underdiagnosed in patients with “idiopathic” osteoporosis. This underdiagnosis might be due to the conviction of clinicians that the postmenopausal phase is the cause of osteoporosis, so serological CD tests will not be performed. It has been suggested to test all idiopathic osteoporosis patients for CD since osteoporosis in untreated CD could cause osteoporotic fractures\textsuperscript{13}. Disadvantages of our study were that we had to work with dummy dates and that the data were provided by the members of the Dutch Coeliac Society themselves, so we could not check whether they had the right diagnosis of CD based on histology or not.

This study showed that the majority of CD patients are diagnosed during adulthood with a different distribution of age at CD diagnosis between genders. This has consequences for the CD work-up and follow-up in daily clinical practice.

REFERENCES


