ORIGINAL PAPER

Available from: http://www.jgld.ro/wp/archive/y2016/n4/a5
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.254.gil

Celiac Disease in The Netherlands: Demographic Data of Members of the Dutch Celiac Society

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Received: 14.07.2016
Accepted: 13.09.2016

ABSTRACT

Background & Aims: Celiac 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 celiac disease. The aim of this study is to describe differences in gender and age at the time of celiac disease diagnosis in the Netherlands.

Methods: Data was obtained from a prospectively maintained database of members of the Dutch Celiac Society in whom celiac disease was diagnosed between 1980 and August 2015. Design: retrospective database study; Setting: database of members of the Dutch Celiac 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 celiac disease diagnosis ranged between 0 and 88 years; the minority (36%) were diagnosed in childhood. In children, the majority (52%) were diagnosed before the age of 4 years. Median age did not differ in children when compared for gender (3 years). In adults, median age differed between males (52 years, IQR 41-61) and females (44 years, IQR 32-56), $p<0.001$. Female to male ratio was 2.4:1.

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

Key words: Celiac disease – epidemiology – gender – age distribution – adult – child.

Abbreviations: CBS: Statistics Netherlands; CD: celiac disease; GFD: gluten-free diet; HLA: human leukocyte antigen; IQR: interquartile range.

INTRODUCTION

Celiac disease (CD) is an autoimmune 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 [2]. 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 regarding CD prevalence in Asia [5]. In the last years, there has been an increased awareness of (serological) testing of CD by clinicians in different countries [6]. Yet, screening studies have shown that still just one out of eight people with CD is diagnosed [3]. This underdiagnosis 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].

The literature has evidenced a predominance of females diagnosed with CD with a female to male ratio of 2-4:1 [5, 12-17]. This difference was not found in screening studies, suggesting an underdiagnosis in daily practice in males [18, 19]. Although some studies showed a different age of onset

of CD in males and females, there is still a lack of knowledge regarding age and gender distribution in CD.

The aim of our study was to describe the age and gender distribution of CD in the Dutch population.

METHODS

Data of a prospectively maintained database of members of the Dutch Celiac Society, including CD patients diagnosed between 1980 and August 2015, were used. The Dutch Celiac Society is the Dutch association for CD patients. These CD members completed a questionnaire during membership registration. This questionnaire included the date of biopsy and date of diagnosis. Date of biopsy and date of birth were used to calculate age at time of diagnosis. Because we only knew the year of biopsy, we used January 1st as the dummy date of biopsy to calculate age at diagnosis. If the date of biopsy was not available, we used date of diagnosis 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 the dummy date to calculate age at time of diagnosis for these persons.

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

Data were provided by the Dutch Celiac 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 the 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 Celiac 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: 5,546, males: 2,337, unknown: 3). Data showed no difference in the 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 (1.8:1), 16-30 years (6.0:1), 31-45 years (3.5:1), 46-60 years (2.1:1) and 60 years or older (1.7:1), $p<0.001$.

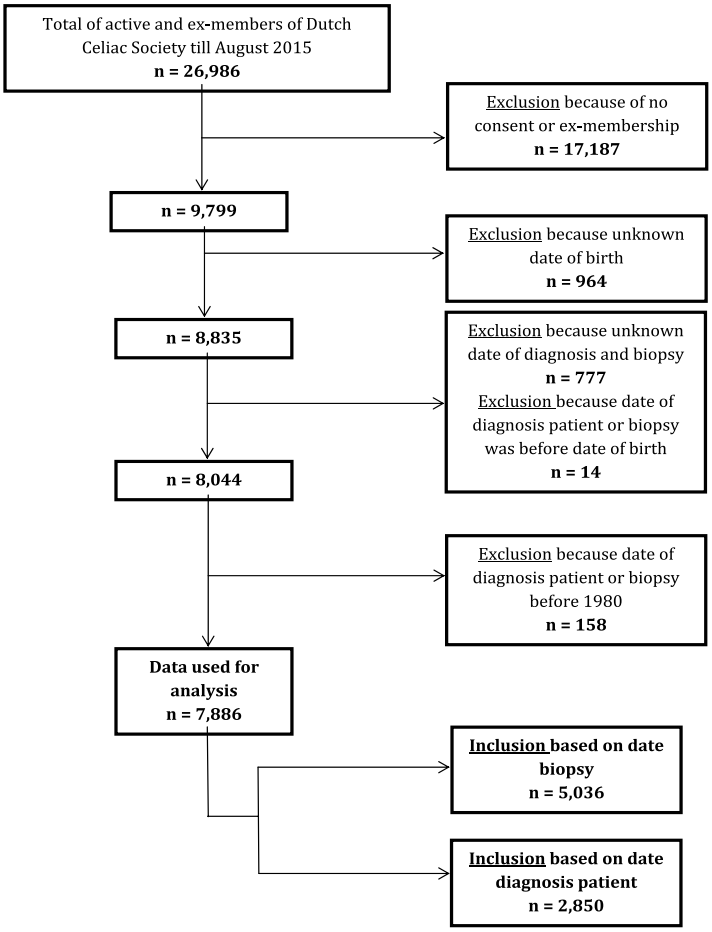

Fig. 1. Selection of the patients.

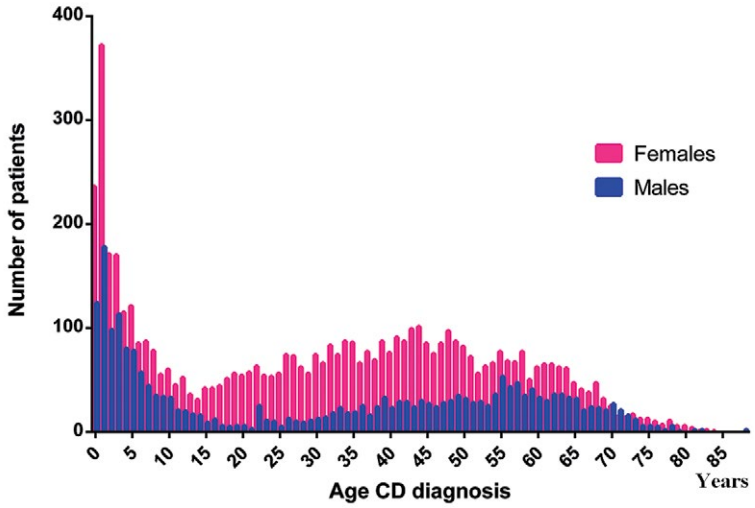

Fig. 2. Distribution of the age at time of diagnosis.

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% were diagnosed in childhood. Of the children diagnosed with CD, the majority (52%) were diagnosed before the age of 4 years. Median age at time of diagnosis in children did not significantly differ between males and females, with a median age of 3 years (IQR 1-7) in boys and also 3 years (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 (IQR 41-61) in males and 44 years (IQR 32-56) in females ($p<0.001$).

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 are diagnosed as adults. 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 [20] .

There are several hypotheses for the predominance of females in CD. Firstly, it is well known that females are more often diagnosed with other autoimmune 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]. Secondly, females have a 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 low number of young adult males diagnosed at the age of 16-30 years, as reported earlier [14]. Thirdly, females are considered to be more often symptomatic in CD than males [23].

In our study, we included members of the Dutch Celiac 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 members of patient groups in general (6% versus 5% of males) [24]. However, the Dutch Celiac Society might have 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 appears to be many advantages to being a member for both males and females. Another reason why we think that females do not frequently become members of the Dutch Celiac Society is that CD patients have a high treatment burden due to the GFD [25]. This has also a high impact burden on the whole family. These other family members seem to play an important role to stimulate CD patients to become members of the Dutch Celiac Society since they need clear information about 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. This might result in another approach of follow-up in these older patients rather than in children since these patients are more often presenting fatigue and are at risk for several complications such as osteoporosis, refractory CD 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) does not prevent children in high-risk families from developing CD [28]. This suggests that the moment of introduction of gluten in the diet 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 since the introduction of dietary gluten on developing CD at a 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 [28].

One study showed a correlation between HLA-DQ8 phenotype and the development of CD in adulthood [29]. 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 [30]. 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 are not performed. It has been suggested to test all idiopathic osteoporosis patients for CD since osteoporosis in untreated CD could cause osteoporotic fractures [31].

The limits of our study are that we had to work with dummy dates and that the data were provided by the members of the Dutch Celiac Society themselves, so we could not check whether they had the right diagnosis of CD based on histology or not.

CONCLUSION

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.

Conflicts of interest: There are no conflicts to declare.

Authors' contribution: T.G. drafted the manuscript, analyzed and interpreted data. B.R. collected data, reviewed the manuscript. G.B. interpreted data, revised the manuscript. C.J.J.M. designed the study, interpreted data, revised the manuscript.

Acknowledgements. We would like to thank the Dutch Celiac Society for providing the data used in this study.

REFERENCES

1. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013; 62: 43-52. doi: 10.1136/gutjnl-2011-301346
2. van Berge-Henegouwen GP, Mulder CJ. Pioneer in the gluten free diet: Willem-Karel Dicke 1905-1962, over 50 years of gluten free diet. Gut 1993; 34: 1473-1475. doi: 10.1136/gut.34.11.1473
3. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol 2012; 107: 1538-1544. doi: 10.1038/ajg.2012.219
4. Kang JY, Kang AH, Green A, Gwee KA, Ho KY. Systematic review: worldwide variation in the frequency of coeliac disease and changes over time. Aliment Pharmacol Ther 2013; 38: 226-245. doi: 10.1111/apt.12373
5. Singh P, Arora S, Singh A, Strand TA, Makharia GK. Prevalence of Celiac disease in Asia: A systematic review and meta-analysis. J Gastroenterol Hepatol 2016; 31: 1095-1101. doi: 10.1111/jgh.13270
6. Leja M, Kojalo U, Frickauss G, Bandere B, Gavars D, Boka V. Changing patterns of serological testing for celiac disease in Latvia. J Gastrointestin Liver Dis 2011; 20: 121-126.
7. Green PH, Cellier C. Celiac disease. N Engl J Med 2007;357: 1731-1743. doi: 10.1056/NEJMra071600
8. Biemond I, Pena AS, Groenland F, Mulder CJ, Tytgat GN. Coeliac disease in The Netherlands: demographic data of a patient survey among the members of the Dutch Coeliac Society. Neth J Med 1987; 31: 263-268.
9. Wierdsma NJ, van Bokhorst-de van der Schueren MA, Berkenpas M, Mulder CJ, van Bodegraven AA. Vitamin and mineral deficiencies are highly prevalent in newly diagnosed celiac disease patients. Nutrients 2013; 5: 3975-3992. doi: 10.3390/nu5103975
10. Tucker E, Rostami K, Prabhakaran S, Al Dulaimi D. Patients with coeliac disease are increasingly overweight or obese on presentation. J Gastrointestin Liver Dis 2012; 21: 11-15.
11. Ludvigsson JF, Card TR, Kaukinen K, et al. Screening for celiac disease in the general population and in high-risk groups. United European Gastroenterol J 2015; 3: 106-120. doi: 10.1177/2050640614561668
12. Burger JP, Roovers EA, Drenth JP, Meijer JW, Wahab PJ. Rising incidence of celiac disease in the Netherlands; an analysis of temporal trends from 1995 to 2010. Scand J Gastroenterol 2014; 49: 933-941. doi: 10.3109/00365521.2014.915054
13. Pratesi R, Gandolfi L, Garcia SG, et al. Prevalence of coeliac disease: unexplained age-related variation in the same population. Scand J Gastroenterol 2003; 38: 747-750.doi: 10.1080/00365520310003255
14. Dixit R, Lebwohl B, Ludvigsson JF, Lewis SK, Rizkalla-Reilly N, Green PH. Celiac disease is diagnosed less frequently in young adult males. Dig Dis Sci 2014; 59: 1509-1512. doi: 10.1007/s10620-014-3025-6
15. Llorente-Alonso MJ, Fernandez-Acenero MJ, Sebastian M. Gluten intolerance: sex and age-related features. Can J Gastroenterol 2006; 20: 719-722.
16. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, et al. Increasing incidence of celiac disease in a North American population. Am J Gastroenterol 2013; 108: 818-824. doi: 10.1038/ajg.2013.60
17. Dydensborg S, Toftedal P, Biaggi M, Lillevang ST, Hansen DG, Husby S. Increasing prevalence of coeliac disease in Denmark: a linkage study combining national registries. Acta Paediatr 2012; 101: 179-184. doi: 10.1111/j.1651-2227.2011.02392.x
18. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003; 163: 286-292.
19. Walker MM, Murray JA, Ronkainen J, et al. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. Gastroenterology 2010; 139: 112-119. doi: 10.1053/j.gastro.2010.04.007
20. Fuchs V, Kurppa K, Huhtala H, Collin P, Maki M, Kaukinen K. Factors associated with long diagnostic delay in celiac disease. Scand J Gastroenterol 2014; 49: 1304-1310. doi: 10.3109/00365521.2014.923502
21. Quintero OL, Amador-Patarroyo MJ, Montoya-Ortiz G, Rojas-Villarraga A, Anaya JM. Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. J Autoimmun 2012; 38: J109- J119. doi: 10.1016/j.jaut.2011.10.003
22. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. J Fam Pract 2000; 49: 147-152.
23. Ciacci C, Cirillo M, Sollazzo R, Savino G, Sabbatini F, Mazzacca G. Gender and clinical presentation in adult celiac disease. Scand J Gastroenterol 1995; 30: 1077-1081.doi: 10.3109/00365529509101610

24. Kloosterman R, Coumans M. Lidmaatschap en deelname verenigingen. Statistics Netherlands (CBS) 2014, 4. Available online http://www.cbs.nl/NR/rdonlyres/FF14DA26-9BEB-4E63-ACB0-8C232FC3F3DC/0/2014Lidmaatschapendeelnameverenigingenart.pdf
25. Shah S, Akbari M, Vanga R, et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. Am J Gastroenterol 2014; 109: 1304-1311. doi: 10.1038/ajg.2014.29
26. Mulder CJ, Wierdsma NJ, Berkenpas M, Jacobs MA, Bouma G. Preventing complications in celiac disease: our experience with managing adult celiac disease. Best Pract Res Clin Gastroenterol 2015; 29: 459-468. doi: 10.1016/j.bpg.2015.05.006
27. van Gils T, Nijeboer P, van Wanrooij RL, Bouma G, Mulder CJ. Mechanisms and management of refractory coeliac disease. Nat Rev Gastroenterol Hepatol 2015; 12: 572-579. doi: 10.1038/nrgastro.2015.155
28. Vriezinga SL, Auricchio R, Bravi E, et al. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med 2014; 371: 1304-1315. doi: 10.1056/NEJMoa1404172
29. Fernandez-Cavada-Pollo MJ, Alcala-Pena MI, Vargas-Perez ML, et al. Celiac disease and HLA-DQ genotype: diagnosis of different genetic risk profiles related to the age in Badajoz, southwestern Spain. Rev Esp Enferm Dig 2013; 105: 469-476.
30. Bandela V, Munagapati B, Karnati RK, Venkata GR, Nidudhur SR. Osteoporosis: Its Prosthodontic Considerations - A Review. J Clin Diagn Res 2015; 9: ZE01-ZE04. doi: 10.7860/JCDR/2015/14275.6874
31. Armagan O, Uz T, Tascioglu F, Colak O, Oner C, Akgun Y. Serological screening for celiac disease in premenopausal women with idiopathic osteoporosis. Clin Rheumatol 2005; 24: 239-243. doi: 10.1007/s10067-004-1011-7