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Original article

Non-classical clinical presentation at diagnosis by male celiac disease patients of older age

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ABSTRACT

Background: . In a biopsy-proven adult celiac disease (CeD) cohort from the Netherlands, male patients were diagnosed with CeD at significantly older ages than female patients.
Objectives: To identify which factors contribute to diagnosis later in life and whether diagnostic delay influences improvement of symptoms after starting a gluten-free diet (GFD).
Methods: . We performed a questionnaire study in 211 CeD patients (67:144, male:female) with median age at diagnosis of 41.8 years (interquartile range: 25–58) and at least Marsh 2 histology.
Results: . Classical symptoms (diarrhea, fatigue, abdominal pain and/or weight loss) were more frequent in women than men, but sex was not significantly associated with age at diagnosis. In a multivariate analysis, a non-classical presentation (without any classical symptoms) and a negative family history of CeD were significant predictors of older age at diagnosis (coefficients of 8 and 12 years, respectively). A delay of >3 years between first symptom and diagnosis was associated with slower improvement of symptoms after start of GFD, but not with sex, presentation of classical symptoms or age at diagnosis.
Conclusion: . Non-classical CeD presentation is more prevalent in men and is associated with a diagnosis of CeD later in life. Recognizing CeD sooner after onset of symptoms is important because a long diagnostic delay is associated with a slower improvement of symptoms after starting a GFD.

1. Introduction

Celiac disease (CeD) is a complex immune-mediated disease that occurs in 1–2% of the Caucasian population [1]. In patients with CeD, ingestion of gluten peptides that are present in barley, wheat and rye activates the innate and adaptive immune system, eventually leading to the development of villous atrophy in the small intestine. The human leukocyte antigen (HLA) subtypes HLA-DQ2 and HLA-DQ8 are strongly associated with CeD and are necessary for the development of disease, as they are the molecules that present gluten peptides to the immune system. CeD presents with a wide variety of presenting clinical symptoms, from classical symptoms (diarrhea, weight loss, abdominal pain and/or fatigue) to a non-classical phenotype without classical symptoms but with symptoms like constipation and gastro-oesophageal reflux or anemia [2,3].

In a Dutch CeD cohort of >400 histopathologically proven adult CeD patients, we observed that men were diagnosed at significantly older ages than women [3]. This correlation had been reported previously for other cohorts, including in a large Dutch study (n = 7886) on demographic data of patients who are members of the Dutch Celiac Society [4–7]. One hypothesis put forward to explain why women are diagnosed at younger ages was that they are more likely to seek medical care than men [5,6]. However, two other studies (n = 1689 and n = 800) reported a longer diagnostic delay in women compared to men [8,9]. The authors of both these studies proposed that this could result from a higher proportion of male patients being diagnosed based on serological screening of high-risk individuals, or from differences in physicians' and patients' awareness of CeD between sexes. As there is limited data available on the clinical factors associated with age at diagnosis in histopathologically proven CeD patients, we carried out a questionnaire study to complement our previously published medical case record study in a Dutch cohort.

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Table 1
Descriptive characteristics.

	Total cohort(n = 211)	Men(n = 67)	Women(n = 144)	P-value(males vs females)	Test
Age of participants at time of questionnaire (years)	51.2 (33.2–67.0)	64.3 (45.0–69.4)	45.9 (31.3–62.7)	$P = 3.75\times10^{-4}$	#
Age at diagnosis CeD (years)	41.8 (25.2–57.6)	52.4 (36.9–61.7)	36.8 (23.4–52.3)	$P = 0.001$	#
Time between diagnosis and questionnaire completion (years)	8.02 (4.61–11.9)	7.37 (4.61–12.1)	8.09 (4.59–11.7)	$P = 0.880$	#
Marsh classification				$P = 0.610$	++
Marsh 2/3	5 (2.4%)	2 (3.0%)	3 (2.1%)		
Marsh 2	11 (5.2%)	2 (3.0%)	9 (6.3%)		
Marsh 3	195 (92.4%)	63 (94.0%)	132 (91.7%)		
Gluten-free diet				$P>0.99$	++
Yes	200 (94.8%)	64 (95.5%)	136 (94.4%)		
No	11 (5.2%)	3 (4.5%)	8 (5.6%)		
Hospital of diagnosis				$P = 0.747$	+
University	134 (63.5%)	41 (61.2%)	93 (64.6%)		
Non-university	77 (36.5%)	26 (38.8%)	51 (35.4%)		
Ethnicity				$P = 0.549$	+
Caucasian	194 (91.9%)	60 (89.6%)	134 (93.1%)		
Other	17 (8.1%)	7 (10.4%)	10 (6.9%)		

Displayed as: number (percentage) or median (interquartile range).
[#] MWU.
[++] Fisher's exact test.
[+] χ^2.

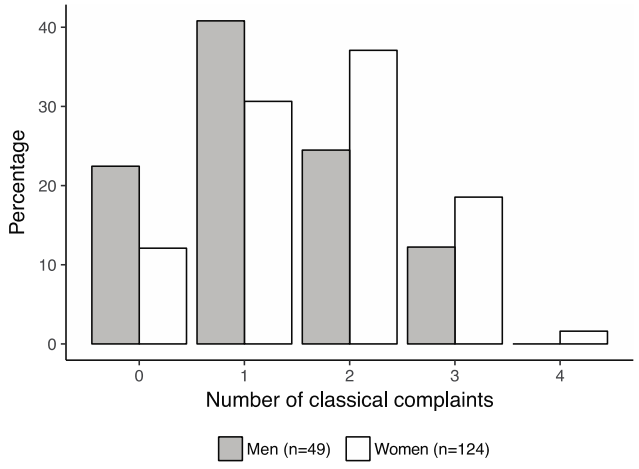

Fig. 1. Within the group of symptomatic patients with CeD, men report significantly fewer (P = 0.013) classical symptoms (diarrhea, weight loss, abdominal pain and fatigue) compared to women.

The aim of the present study was to gain insight into the clinical factors associated with age at diagnosis. The clinical factors investigated are: symptoms, diagnostic delay and family history of CeD and other immune-mediated diseases. We also investigated factors that influence the improvement of symptoms after the start of a gluten-free diet (GFD).

2. Materials and methods

2.1. Data collection

Questionnaires (n = 380) were sent to a cohort in the Netherlands consisting of adult, histopathologically proven CeD patients who were diagnosed in either a university medical center (University Medical Center Groningen) or a non-university medical center (Medisch Spectrum Twente (Enschede)). The questionnaires were sent by mail in 2015. Three questionnaires could not be linked to the patient's medical records and were excluded from further analyses. We only contacted patients included in the histopathologically proven CeD cohort and did not contact any of their family members with CeD. The methods of data collection from medical case records of the same patients cohort were reported previously [3]. After digitalization of the questionnaires, data was coded before further analyses. This questionnaire-based research did not fall under the scope of the Dutch Law on Medical Scientific Research involving Human Beings (WMO), and therefore did not need a full ethical review of the Institutional Review Board.

The questionnaire (see Table S1) contained questions about the participant's symptoms at the time of CeD diagnosis, the time interval from first symptom to diagnosis (diagnostic delay), the improvement of symptoms after starting a GFD and the occurrence of immune-mediated diseases in the participant and their family members. Patients who are asymptomatic at diagnosis did not have to fill out questions on type of symptoms, diagnostic delay and improvement of symptoms after start of the GFD. Fig. S1 shows how many patients in the total questionnaire cohort answered the questions on symptoms, diagnostic delay and improvement of symptoms after start of the GFD.

The questionnaire also contained an open question about what symptoms the participants experienced at the time of diagnosis. Answers to this open question were subsequently grouped (as shown in Table S2) by three of the authors (MCV, RKW and ILT). To reflect the current classical presentation of CeD, the four symptoms that were most frequently reported in medical records in our earlier study [3] - diarrhea, abdominal pain, fatigue and/or weight loss - were considered as "classical symptoms" here. These include classical symptoms that are part of the Oslo criteria (diarrhea, weight loss and abdominal pain) [10–12].

The following numeric variables were grouped into ordinal variables: diagnostic delay (<1 year, 1–3 years or >3 years between first symptom and diagnosis), time interval between the start of the GFD and the start of improvement of the symptoms (≤2 months or >2 months) and the time interval between the start of GFD and the maximum improvement of symptoms (≤6 months or >6 months). Participants were asked to indicate the diseases that are present in their family members from a table with 30 different immune-mediated diseases. One disease, "Cardiomyopathy", was removed from further analyses because the questionnaire did not state clearly that only auto-immune cardiomyopathy should be scored here. Additional diseases could be entered in a blank form, but were not considered in the analysis.

2.2. Statistical analysis

R (version 3.5.1) was used to perform statistical analyses. Throughout the study, we used complete case statistical analysis. The normality of the data was determined using the Shapiro-Wilks test, and the following statistical tests were used in the univariate analyses

Table 2
Age at diagnosis.

	n	Age at diagnosisYearsMedian (IQR)	UnivariateP-value	Test	Multivariate linear regression P-value*	Coefficient(SE) in years**
Sex	211		$P = 0.001$	#	$P = 0.070$	4.7 (2.6)
Men	67	52.4 (36.9–61.7)				
Women	144	36.8 (23.4–52.3)				
Classical complaints	173		$P = 3.84\times10^{-06}$	#	$P = 5.51\times10^{-4}$	−11.7 (3.3)
Yes	147	38.0 (23.0–51.5)				
No	26	59.7 (51.7–64.5)				
Positive family history CeD	211		$P = 0.174$	#	$P = 0.005$	−7.9 (2.8)
Yes	62	37.7 (25.2–51.5)				
No	149	42.8 (25.4–59.6)				
Positive family history immune-mediated diseases (including CeD)	211		$P = 0.010$	#	Not selected	–
Yes	154	38.7y (24.1–55.8)				
No	57	51.2 (28.0–61.7)				
Concomitant immune-mediated diseases	211		$P = 0.064$	#	Not selected	–
Yes	95	46.4 (27.3–59.32)				
No	116	37.7 (24.11–37.67)				
Diagnostic delay	175		$P = 0.709$	±	–	–
<1 year	60	41.0 (24.8–57.2)				
1–3 year	45	39.4 (23.0–55.8)				
>3 year	70	43.2 (27.2–56.7)				

* Age at diagnosis is the outcome variable in the multivariate model. The starting model for the step-wise linear regression model contained the variables in this table with *P*-value <0.25, family size and the total number of complaints. The *P*-values and coefficients selected for the final model (after combined backward and forward selection) are shown in this table, adjusted for family size. The final model has an adjusted R-squared (R^2) of 0.4013.

** Coefficients are for the first level of factors (male, classical complaints, positive family history).

MWU.

± Kruskal–Wallis test.

depending on the normality of the data: independent sample *t*-test, one-way Analysis of Variance (ANOVA), Mann–Whitney *U* (MWU), Kruskal–Wallis, Chi-square (χ^2), or Fisher's exact or Spearman's correlation. An agreement score (Cohen's Kappa value) was calculated between the information retrieved from case records and the information from the questionnaires for the occurrence of immune-mediated diseases and family history of CeD.

The lm- and glm-functions of the R-package “stat” (v3.5.1) were used to perform the multivariate regression analyses, either linear regression (age at diagnosis) or logistic regression (time until maximum improvement of symptoms after start of GFD). To select relevant predictors of the outcome variables (age at diagnosis and improvement of symptoms after start of GFD), all potential predictors of the outcome variable with a $P < 0.25$ in the univariate analyses were used as input for a combined backward and forward stepwise multivariate regression approach using the Akaike An Information Criterion (AIC) method. This method uses combined backward and forward selection to narrow-down relevant predictors in the final multivariate regression models and was carried out using the stepAIC function of the R-package “MASS” (v7.3-50).

3. Results

3.1. Response rate

In total, 211 out of the 380 questionnaires sent out were completed and returned, for an overall response rate of 56%. CeD patients treated in the university medical center had significantly ($P = 0.028$) higher response rates (61%; $n = 136/222$) than patients treated in the non-university medical center (49%; $n = 78/158$).

3.2. Descriptive characteristics of participants

Descriptive characteristics of responding participants are displayed in Table 1. The age at diagnosis (median 41.8 years (interquartile range (IQR): 25–58 years), sex distribution (female:male ratio of 2:1) and distribution between hospitals (63% seen at the university medical hospital) of the respondents are comparable to the previously published cohort ($n = 412$)[3]. The median time between diagnosis and completion of the questionnaire was 8 years (IQR 5–12 years) and did not differ between men and women (Table 1). More than one third (35%; $n = 74/211$) of CeD patients reported that they do not see their medical specialist on an annual basis.

There is a significant correlation between the number of symptoms and number of classical symptoms that were previously retrieved from medical case records and those reported by the questionnaires (symptoms: Spearman's rho = 0.19, $P = 0.006$; classical symptoms: Spearman's rho = 0.27, $P = 3.799\times10^{-4}$). Significant agreement scores (Cohen's Kappa value) were found between the information retrieved from case records and the information from the questionnaire for the occurrence of concomitant immune-mediated diseases and family history of CeD (Supplementary Results).

3.3. Symptoms at the time of diagnosis

Information was collected for the 193 CeD patients on the symptoms they experienced at the time of diagnosis, and 173 filled out which specific symptoms they experienced at that time (see Fig. S1). The frequencies of these symptoms are summarized in Table S4. The majority of the patients (76%; $n = 146/193$) reported two or more clinical symptoms at time of diagnosis, with men ($n = 57$) reporting significantly fewer symptoms (median: 2 (IQR: 1–3)) than women ($n = 136$) (median 3 (IQR 2–4), $P = 0.003$ (MWU)).

Twenty-six of the 173 participants with symptoms (15% overall; 12% of women; 22% of men) did not report any of the classical CeD symptoms (diarrhea, abdominal pain, fatigue and/or weight loss), and anemia was the most frequently reported symptom in this group ($n = 8/26$, 31%). Hemoglobin levels at time of diagnosis were retrievable from case records for 152 patients and showed that laboratory-confirmed anemia was present in a significantly higher proportion of patients without any classical symptoms (61%; $n = 9/23$) compared to participants who reported classical symptoms (32.6%; $n = 42/129$), $P = 0.018$ (MWU)).

Of the 173 symptomatic participants, men reported fewer classical

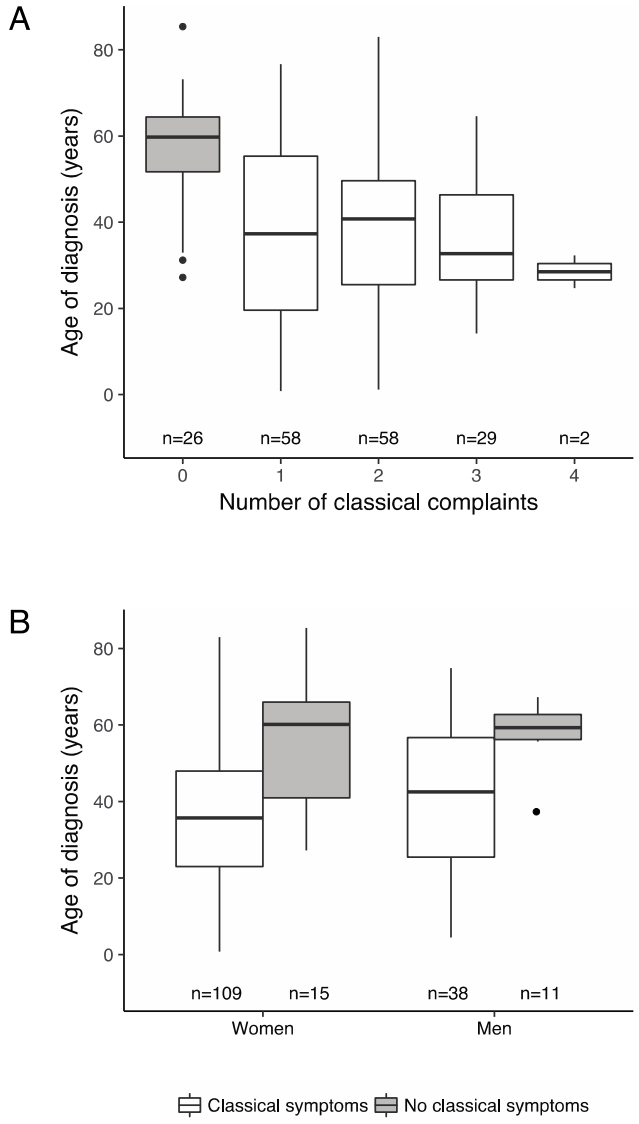

Fig. 2. Patients with CeD, both male and female, who did not report any classical symptoms were diagnosed later in life than patients with classical symptoms.

symptoms (median: 1 (IQR: 0–2)) than women (median 1 (IQR: 1–2), $P = 0.014$ (MWU)). The difference in number of reported classical symptoms between men and women is visualized in Fig. 1.

3.4. Clinical factors associated with age at diagnosis

We next investigated which clinical factors were associated with age at diagnosis (Table 2). Male participants were diagnosed at a significantly older ages than female participants ($n = 211$). Within the group of symptomatic participants ($n = 173$), those with a non-classical presentation (i.e. without any of the classical symptoms) were diagnosed at a significantly older age than those with classical symptoms ($P = 3.84 \times 10^{-06}$ (MWU)) (Fig. 2). In a univariate analysis, the presence of CeD in the family was not significantly associated with age at diagnosis (Table 2).

As family size increases significantly with age (Spearman's rho = 0.59, $P < 2.2 \times 10^{-16}$), the number of individuals at risk of a disease also increases. After correcting 'family history of CeD' for family size, a positive family history was significantly associated with age of diagnosis ($P = 6.98 \times 10^{-4}$, coefficient of a positive family history of CeD: −9.8 years (SE 2.8 years)). The frequencies of immune-mediated diseases in participants and their family members are displayed in Table S5.

The occurrence of concomitant immune-mediated diseases or a positive family history of immune-mediated diseases were not significantly associated with the age at diagnosis (Table 2). After the stepwise linear regression analysis using age at diagnosis as the outcome variable, we included sex, classical symptoms, family history of CeD and family size in the final multivariate regression model. The model identified occurrence of classical symptoms at time of diagnosis ($P = 5.51 \times 10^{-4}$) and family history of CeD ($P = 5.10 \times 10^{-3}$) as significant independent predictors of age at diagnosis. Non-classical CeD without any of the classical symptoms and a negative family history of CeD had coefficients of 8- and 12-year later diagnosis, respectively (Table 2).

3.5. Improvement of symptoms after start of GFD

Ten out of 189 participants (5%) reported no improvement of symptoms after starting a GFD (Table S3). These ten patients reported more classical symptoms at time of diagnosis than those who responded to a GFD (median = 3, IQR: 1–3 versus 1 (1–2); $P = 0.017$ (MWU)), and two (20%, 2/10) reported having stopped their GFD, a significantly higher drop-out than the 2% in the GFD responder group (3/176) ($P = 0.023$, Fisher's Exact).

Several clinical factors were found to contribute to the time between start of the GFD and maximal improvement of symptoms (≤6 months versus >6 months) (Table 3). There was a significant association between diagnostic delay and time until maximal improvement of symptoms ($P < 0.001$ (Kruskal–Wallis)) (Table 3 and Fig. S2). Moreover, having a higher number of reported symptoms at diagnosis was associated with a longer time until the symptoms maximally improved after start of GFD. After stepwise selection of prediction variables, the total number of symptoms and diagnostic delay were found to be significant predictors for the time to maximal improvement of symptoms after start of the GFD in the multivariate logistic regression model (Table 3).

We also observed a significant association between the diagnostic delay and the start of reduction of symptom severity after starting a GFD ($P = 0.001$ (Kruskal–Wallis)). To illustrate this, of the participants who had symptoms <1 year before diagnosis, 70% ($n = 38/54$) reported that these symptoms started to improve within 2 months of starting a GFD, while only 37% ($n = 23/63$) reported that improvement of symptoms started within 2 months the group of participants who had symptoms for >3 years prior to diagnosis.

4. Discussion

This questionnaire study complements an earlier medical case record study by our group in the largest cohort of histopathologically proven adult CeD patients in the Netherlands. Our results provide insights into the clinical factors associated with age at diagnosis and the clinical factors associated with the time between the start of the GFD and maximum improvement of symptoms. We conclude that male CeD patients are diagnosed later because they present with a subtype of CeD with non-classical symptoms and that arises later in life. Furthermore, we show that a longer diagnostic delay is associated with slower improvement of symptoms, which emphasizes the importance of rapid diagnosis after onset of symptoms.

One of the strengths of this study is the combination of questionnaire data and case records, which allowed us to check the concordance between the two data sources, a factor that was lacking in previous studies that investigated the factors associated with age at diagnosis, diagnostic delay and recovery of symptoms upon start of the GFD [9,13].

In line with observations in the full cohort of 412 patients, in the 211 participants included in this questionnaire study, men were diagnosed at a significantly older ages compared to women (median 52

Table 3
Maximal improvement of symptoms after start of the GFD.

	n	≤6 months*n* = 100*	>6 months*n* = 65*	Univariate	Test	Multivariate logistic regression*	Adjusted odds ratio (95% CI)
Age at diagnosis (years)	165	46.5 (32.3–59.6)	34.7 (23.9–49.3)	$P = 0.008$	#	Not selected	
Sex	165			$P = 0.105$	+	Not selected	
Men		38 (38.0%)	16 (24.6%)				
Women		62 (62.0%)	49 (75.4%)				
Total number of complaints at diagnosis	165	2.00 (1.00–3.00)	3.00 (2.00–5.00)	$P<0.001$	#	$P = 0.002$	1.4 (1.1- 1.8)
Classical complaints	150			$P = 0.145$	+	Not selected	
Yes		73 (82.0%)	56 (91.8%)				
No		16 (18.0%)	5 (8.20%)				
Concomitant immune-mediated diseases	165			$P = 0.622$	+	–	
Yes		41 (41.0%)	30 (46.2%)				
No		59 (59.0%)	35 (53.8%)				
Diagnostic delay	153			$P<0.001$	+		
<1 year		44 (48.4%)	11 (17.7%)				
1–3 year		21 (23.1%)	18 (29.0%)			$P = 0.098$	2.3 (0.9–6.3)
>3 year		26 (28.6%)	33 (53.2%)			$P = 8.41\times10^{-4}$	4.7 (1.9- 1.7)
Time between diagnosis and questionnaire completion (years)	165	8.32 (4.78–12.4)	7.56 (4.07;11.5)	$P = 0.562$	#	–	

* Maximal recovery of symptoms after start of the GFD is the outcome variable in the multivariate model. The starting model for the stepwise linear regression model contained the variables in this table with a *P*-value <0.25. The *P*-values and adjusted odds ratio of the variables included in the final model (after combined backward/forward selection) are shown.
# MWU.
+ χ^2.

years vs 37 years). Using a combined backward and forward stepwise linear regression analysis approach, the occurrence of classical symptoms at time of diagnosis and a positive family history of CeD were identified as significant independent predictors of age at time of diagnosis (Table 2), while sex was not. The length of diagnostic delay and total number of symptoms were not significantly associated with age at diagnosis.

Our observations suggest that male CeD patients are not diagnosed at older ages than female patients because of a longer diagnostic delay after onset of symptoms. This observation is in line with questionnaire studies that reported no difference between sexes, or even a longer delay between onset of symptoms and eventual diagnosis in women [8,9,13]. It appears that, even though men utilize medical care services less than women, women are not diagnosed more quickly after onset of symptoms [5,6].

Having at least one of the classical symptoms (diarrhea, abdominal pain, fatigue and/or weight loss) was associated with a significantly younger age at diagnosis, whereas sex was not. In the group with symptoms, fewer men reported classical symptoms. These results support the hypothesis that men are more prone to a subtype of CeD with a later onset and fewer classical symptoms. The chance that the lower frequency of the classical CeD picture in men is caused by recall bias is limited as the time between diagnosis and filling out the questionnaire did not differ between men and women in our cohort.

There are several other cohorts in which men were diagnosed at an older age compared to women and also reported fewer clinical symptoms at time of diagnosis [6,7]. However, these studies did not assess whether clinical presentation or sex were better predictors of age of diagnosis. The results from our multivariate analysis suggests that men more often presented with less pronounced CeD symptoms associated to a diagnosis later in life. This observation supports evidence from existing literature that the clinical spectrum of CeD changes with the age of presentation, although these earlier studies mainly focused on the difference between children and adults [12,14–17].

Recognizing and treating CeD that manifests late in life is important because it can reduce the chance of complications such as osteoporosis, and its concomitant risk of fractures, even with the high treatment burden a GFD [18]. For example, in a previous cohort, male sex and older age were significant independent risk factors for osteoporosis in CeD (anemia: OR = 2.5, adjusted $P = 0.002$; Male: OR = 2.2, $P = 0.2$; increasing age at diagnosis (years): OR 1.04, $P<0.001$) [19]. Moreover, a recent Italian cohort study ($n = 214$) found similar associations between sex, age at diagnosis and risk of osteoporosis.

A substantial percentage of the participants in this study (40%) reported a long diagnostic delay of >3 years from onset of the symptoms to eventual diagnosis. It is striking that 40% of participants had a diagnostic delay >3 years even though 29% had a positive family history of CeD. Previous studies have shown contradictory results when relating family history to diagnostic delay [8,9]. Our finding that it takes longer in patients with a long diagnostic delay (>3 years) before the symptoms start to improve upon GFD (>2 months) and before a maximum improvement of symptoms is reached (>6 months) highlights that this long delay in diagnosis has consequences in the clinical response to the GFD. In addition to the length of diagnostic delay, a higher number of symptoms is also associated with a slower improvement of symptoms with a GFD. Our observations are consistent with previous studies [9,13,20,21] and highlight the importance of rapid diagnosis after onset of symptoms.

Both doctors and patients will benefit from the knowledge that, in the majority of patients with a diagnostic delay >3 years, it takes more than two months before the symptoms start to improve. Only a limited number of previous studies had investigated the start of the improvement of symptoms after initiation of a GFD. While textbooks and guidelines cite very quick responses (within days to up to two weeks) [22–26], our results suggest that many CeD patients experience otherwise. This is important information to share with patients to prevent them from stopping their GFD, a phenomenon we found to be occurring in 20% of the unresponsive group, possibly because they did not notice a beneficial effect on the expected timescale.

Future studies should examine the pathophysiological mechanisms underlying the differences in clinical presentation and treatment response between men and women and, maybe even more relevant, the difference between a pronounced classical presentation and a more non-classical phenotype. Efforts to study the mechanisms underlying CeD heterogeneity are still scarce in current literature, but examples of factors that might influence heterogeneity within CeD include the impact of genetic factors [15,27,28] and gut microbial composition [29]. Future studies could also reveal whether the extent of mucosal damage might influence the clinical presentation and/or treatment response by using developments in non-invasive endoscopy techniques [30,31].

Identifying relevant pathways that play a role in (subsets of patients with) CeD could ultimately help to develop new personalized drug targets that could be used as safe adjuvant treatment to relieve the burden of a GFD [32].

In conclusion, this combined questionnaire and case record study of 211 histologically confirmed CeD cases underscores that CeD that manifests later in life occurs more often in men and is accompanied by a less pronounced non-classical clinical phenotype. Physicians should be aware of the symptoms that accompany CeD presenting at an older age, particularly because 40% of patients have a diagnostic delay >3 years between the onset of symptoms and diagnosis. This is important because a longer delay prior to diagnosis is associated with a slower improvement of symptoms upon start of a GFD, whereas age at diagnosis is not associated with how quickly the symptoms resolve upon GFD.

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Declaration of Competing Interest

The Author(s) declare(s) that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.09.020.

References

[1] Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:823–36. .e2.
[2] Lindfors K, Ciacci C, Kurppa K, et al. Coeliac disease. Nat Rev Dis Prim 2019;5:1–18.
[3] Spijkerman M, Tan IL, Kolkman JJ, et al. A large variety of clinical features and concomitant disorders in celiac disease–a cohort study in the Netherlands. Dig Liver Dis 2016;48:499–505.
[4] Thomas HJ, Ahmad T, Rajaguru C, et al. Contribution of histological, serological, and genetic factors to the clinical heterogeneity of adult-onset coeliac disease. Scand J Gastroenterol 2009;44:1076–83.
[5] Van Gils T, Rootsaert B, Bouma G, et al. Celiac disease in the Netherlands: demographic data of members of the dutch celiac society. J Gastrointest Liver Dis 2016;25:441–5.
[6] Dominguez Castro P, Harkin G, Hussey M, et al. Changes in presentation of celiac disease in Ireland from the 1960s to 2015. Clin Gastroenterol Hepatol 2017;15:864–71. .e3.
[7] Ciacci C, Cirillo M, Sollazzo R, et al. Gender and clinical presentation in adult celiac disease. Scand J Gastroenterol 1995;30:1077–81.
[8] Fuchs V, Kurppa K, Huhtala H, et al. Factors associated with long diagnostic delay in celiac disease. Scand J Gastroenterol 2014;49:1304–10.
[9] Vavricka SR, Vadasz N, Stotz M, et al. Celiac disease diagnosis still significantly delayed–doctor's but not patients' delay responsive for the increased total delay in women. Dig Liver Dis 2016;48:1148–54.
[10] Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013;62:43–52.
[11] Di Sabatino A, Corazza GR. Some clarification is necessary on the Oslo definitions for coeliac disease-related terms. Gut 2013;62:182.
[12] Kelly CP, Bai JC, Liu E, et al. Advances in diagnosis and management of celiac disease. Gastroenterology 2015;148:1175–86.
[13] Fuchs V, Kurppa K, Huhtala H, et al. Delayed celiac disease diagnosis predisposes to reduced quality of life and incremental use of health care services and medicines: a prospective nationwide study. United Eur Gastroenterol J 2018;6:567–75.
[14] Bardella MT, Fredella C, Saladino V, et al. Gluten intolerance: gender- and age-related differences in symptoms. Scand J Gastroenterol 2005;40:15–9.
[15] Senapati S, Sood A, Midha V, et al. Shared and unique common genetic determinants between pediatric and adult celiac disease. BMC Med Genom 2016;9:44.
[16] Vivas S, Ruiz De Morales JM, Fernandez M, et al. Age-related clinical, serological, and histopathological features of celiac disease. Am J Gastroenterol 2008;103:2360–5.
[17] van Kalleveen MW, de Meij T, Plötz FB. Paediatric coeliac disease: increasing incidence or increased awareness? J Pediatr Gastroenterol Nutr 2018;67:e42.
[18] Galli G, Lahner E, Conti L, et al. Risk factors associated with osteoporosis in a cohort of prospectively diagnosed adult coeliac patients. United Eur Gastroenterol J 2018;6:1161–8.
[19] Abu Daya H, Lebwohl B, Lewis SK, et al. Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. Clin Gastroenterol Hepatol 2013;11:1472–7.
[20] Paarlahti P, Kurppa K, Ukkola A, et al. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study. BMC Gastroenterol 2013;13:75.
[21] Pulido O, Zarkadas M, Dubois S, et al. Clinical features anmptovery on a gluten-free diet in Canadian adults with celiac disease. Can J Gastroenterol 2013;27:449–53.
[22] Pink IJ, Creamer B. Response to a gluten-free diet of patients with the coeliac syndrome. Lancet 1967;1:300–4.
[23] Murray JA, Watson T, Clearman B, et al. Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease. Am J Clin Nutr 2004;79:669–73.
[24] Daum S, Cellier C, Mulder CJJ. Refractory coeliac disease. Best Pract Res Clin Gastroenterol 2005;19:413–24.
[25] Kumar P, Clark CM. Clark's clinical medicine. Kumar & Clark's clinical medicine. Elsevier; 2012. p. 264–6.
[26] Houwen, R.*Richtlijn 'Coeliakie en dermatitis herpetiformis'*. 2010.
[27] Elli L, Poggiali E, Tomba C, et al. Does TMPRSS6 RS855791 polymorphism contribute to iron deficiency in treated celiac disease. Am J Gastroenterol 2015;110:200–2.
[28] Bajor J, Szakács Z, Farkas N, et al. Classical celiac disease is more frequent with a double dose of HLA-DQB102: a systematic review with meta-analysis. PLoS ONE 2019;14:e0212329.
[29] Wacklin P, Laurikka P, Lindfors K, et al. Altered Duodenal microbiota composition in celiac disease patients suffering from persistent symptoms on a long-term gluten-free diet. Am J Gastroenterol 2014;109:1933–41.
[30] Ludvigsson JF, Ciacci C, Green PHR, et al. Outcome measures in coeliac disease trials: the Tampere recommendations. Gut 2018;67:1410–24.
[31] Murray JA, Rubio-tapia A, Van Dyke CT, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. Clin Gastroenterol Hepatol 2008;6:186–93.
[32] 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;109:1304–11.