Diagnostic delay in adult coeliac disease: an Italian multicentre study

Running title: Diagnostic delay in coeliac disease

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Abbreviations: CD, coeliac disease; GFD, gluten-free diet; IBS, irritable bowel syndrome.

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Abstract

Background: There are few data regarding the diagnostic delay and its predisposing factors in coeliac disease (CD). **Aims**: To investigate the overall, the patient-dependant, and the physician-dependant diagnostic delays in CD. **Methods**: CD adult patients were retrospectively enrolled at 19 Italian CD outpatient clinics (2011-2021). Overall, patient-dependant, and physician-dependant diagnostic delays were assessed. Extreme diagnostic, i.e., lying above the third quartile of our population, was also analysed. Multivariable regression models for factors affecting the delay were fitted. **Results**: Overall, 2362 CD patients (median age at diagnosis 38 years, IQR 27-46; M:F ratio=1:3) were included. The median overall diagnostic delay was 8 months (IQR 5-14), while patient- and physician-dependant delays were 3 (IQR 2-6) and 4 (IQR 2-6) months, respectively. Previous misdiagnosis was associated with greater physician-dependant (1.076, p=0.005) and overall (0.659, p=0.001) diagnostic delays. Neurological symptoms (odds ratio 2.311, p=0.005) and a previous misdiagnosis (coefficient 9.807, p=0.000) were associated with a greater extreme physician-dependant delay. Gastrointestinal symptoms (OR 1.880, p=0.004), neurological symptoms (OR 2.313, p=0.042), and previous misdiagnosis (OR 4.265, p=0.000) were associated with increased extreme overall diagnostic delay. **Conclusion**: We identified some factors that hamper CD diagnosis. A proper screening strategy for CD should be implemented.

Keywords: diagnosis; enteropathy; gluten; malabsorption; villi.

Introduction

Coeliac disease (CD) is an immune-mediated enteropathy which is triggered by the ingestion of gluten in genetically susceptible individuals [1]. While on a gluten-containing diet, CD diagnosis in the adult relies on the presence of CD-specific serum autoantibodies, such as anti-tissue transglutaminase (TTG) IgA and/or anti-endomysial IgA antibodies (EMA), and on the evidence of villous atrophy [1]. CD is characterised by proteiform manifestations, spacing from being asymptomatic to having a malabsorption syndrome. Sometimes CD may only present with isolated alterations, including osteoporosis, micronutrient deficiencies, or growth retardation making its clinical diagnosis even more challenging [1]. This broad clinical spectrum often leads to a delayed diagnosis which is associated with reduced quality of life [2,3], slow improvement of symptoms after commencing a gluten-free diet (GFD) [4,5], and increased mortality [6]. The reduction of the diagnostic delay in CD should therefore be considered as a priority.

According to the medical literature looking at this issue in adult CD (Table 1), the median diagnostic delay varies depending on the year of patient inclusion, the geographical area, and the clinical setting [2,6-15]. A trend towards a reduction of the diagnostic delay over the years is apparent, although it still remains long [2,16-18]. Additionally, most of the previous studies are either based on administrative data, included a limited number of patients, or are poorly generalisable. Finally, the predisposing factors to diagnostic delay are not well defined, and the literature on the matter is conflicting.

To reduce the diagnostic delay, CD should be recognised as a public health problem [4,10,16,17]. A consistent screening of patients at risk for CD would also potentially allow to reduce the diagnostic delay [16]. For this reason, a mass screening has been raised as a possible public health measure [10,17,19].

Starting from these premises, the main aim of our study was to investigate the overall, the patient-dependant, and the physician-dependant diagnostic delays, and to evaluate a wide range of potential factors affecting the delay.

Materials and methods

Patient population and study design

This was a retrospective and multicentre study. It involved 19 Italian gastroenterological, secondary or tertiary referral, outpatient clinics. The 19 participating centres are located throughout Italy, thus providing a broad, although specialistic, overview of CD diagnosis in the whole country.

In 2021, the study coordinators (MVL and ADS), before study inception, exchanged mails and phone calls with the other centres to establish the overall structure of the study and to determine the relevant variables to be included. At first, 21 centres were invited and 19 decided to take part to the project. A multiple round, modified Delphi process [20] was applied in 2021, and a final study protocol was eventually approved. The study is based on all the adult patients diagnosed with CD (age >18 years) between 2011 and 2021. We included only patients diagnosed in the last decade to avoid potential biases due to the improvement of CD-specific antibody detection, the availability of novel

guidelines, and the increasing awareness of CD. The diagnosis was based and confirmed in each centre according to internationally-agreed guidelines [21]. In details, the diagnosis of overt CD was performed in case of (i) positive serology for CD-specific autoantibodies (i.e., TTG IgA and/or EMA IgA, in the absence of IgA deficiency; TTG IgG and/or EMA IgG, in case of IgA deficiency), and (ii) presence of typical CD histological alterations on duodenal biopsy (Marsh classification based on increased intraepithelial lymphocytosis, crypt hyperplasia/hypertrophy and villous atrophy). In case of common variable immunodeficiency, a definitive diagnosis of CD was made on the basis of an HLA-DQ2 or -DQ8 and a duodenal histological response to a GFD [22,23]. Patients with potential CD (i.e., a positive CD serology with Marsh 0 or 1 duodenal lesions) and uncertain histological diagnosis were excluded.

The pseudo-anonymised medical records of the patients were extracted in each centre. An attempt to recover missing data was performed through phone calls with the patients or next of kin, or through outpatient assessment. This also includes the information about the beginning of symptoms, or the occurrence of signs or other clues related to CD diagnosis. Patients in whom the quantification of the diagnostic delay was missing (i.e., the precise onset of symptoms, signs laboratory alterations or the occurrence of other clues), those missing more than 50% of the collected data, and those that had not been followed-up for at least one year by the enrolling centre, were eventually excluded from the analysis.

The data incorporated in the study were (i) the time lapse between the first onset of manifestations clearly related to CD (either symptoms, signs, or laboratory alterations) or other clues related to CD diagnosis (i.e., first degree family history

of CD or occurrence of other autoimmune disorders with a known association with CD) and the definitive CD diagnosis, which was defined as the overall diagnostic delay; (ii) the time lapse between the onset of clues clearly related to CD (either symptoms, signs, or laboratory alterations) and seeking medical care, which was defined as patient-dependant diagnostic delay; (iii) the time lapse between the first medical consultation and the definitive diagnosis of CD, which was defined as physician-dependant diagnostic delay; (iv) the number of specialists by which the patient was assessed before the diagnosis was reached (i.e., even before the patient was assessed by each referral centre), and the specialisation of the physician which performed the final diagnosis; (v) the socioeconomic characteristics of the patients, including marital status, level of education, and exemption from the payment of hospital taxes; (vi) the presence of autoimmune comorbidities, a family history of CD, osteoporosis, iron deficiency anaemia, infertility or recurrent miscarriages, dermatitis herpetiform, selective IgA deficiency, common variable immunodeficiency, and Down syndrome; (vii) all the previous misdiagnoses, before a formal diagnosis of CD was made. The patients were then classified according to the clinical presentation [1] as having major (i.e., malabsorption syndrome, with diarrhoea, weight loss, nutrient and micronutrient deficiencies), minor (i.e., only isolated symptoms and single alterations, such as isolated iron deficiency anaemia, unexplained osteoporosis, etc…), or silent CD (i.e., completely asymptomatic and with no laboratory alterations). In the category “other” we included those patients in whom the clinical presentation evolved over time and we could not classify them into a single category.

The ethics committee of Pavia authorized the study protocol (30th September 2014) and all patients included in the study signed a written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. All the findings of the study conform to the STROBE standards for quality control [24]. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Endpoints and statistical analysis

The primary endpoint was the estimation of patient-dependant, physician-dependant, and overall diagnostic delay. The secondary endpoint consisted in assessing potential correlations of socioeconomic and clinical factors with the diagnostic delays. As a tertiary endpoint we analysed the “extreme” diagnostic delays in relation to the clinical presentation of CD (minor, major and silent). Extreme patient-dependant, extreme physician-dependant and extreme overall diagnostic delay were defined as the subgroups of patients with diagnostic delays lying above the third quartile of our population.

The software used for computations was Stata 17 (StataCorp, College Station, TX, USA). We used median and interquartile range (IQR, i.e., 25th-75th percentiles) to describe continuous data, while categorical data were described with counts and percent. We considered as statistically significant 2-sided p-values of <0.05. Bonferroni correction was applied for *post-hoc* comparisons, when applicable. We fitted linear regression models to the log of diagnostic delay (overall, patient-dependant, and physician-dependant). The difference in log-time

between categories of patients and its 95% confidence interval (95% CI) was then derived from these models. We included the non-collinear variables with a p-value <0.2 at the univariable analysis into a multivariable model for factors affecting the diagnostic delay. An additional multivariable analysis for factors affecting the extreme delay (i.e., a delay above the1.5*75° percentile) was fitted. We computed Huber White robust standard errors to account for intra-centre correlation of measures.

Results

Demographic data and quantification of the diagnostic delay

Data of 3137 adult CD patients were collected in the participating centres between 2011 and 2021. However, 775 patients were excluded due to the absence of relevant information in their clinical record as per protocol design (689, 88.9%) and/or because they had not been followed up for at least one year in the enrolling centre (86, 11.1%). Consequently, the analysis included 2362 patients (median age at diagnosis 38 years, IQR 27-46; F:M ratio 3:1). Table 2 shows the sociodemographic characteristics of the patients included in the study. The median overall diagnostic delay was 8 months (IQR 5-14), the median patient-dependant diagnostic delay was 3 months (IQR 2-6), and the median physician-dependant diagnostic delay was 4 months (IQR 2-6). No differences regarding the diagnostic delay between the period 2011-2016 and 2017-2021 were noticed (p not significant).

Clinical aspects related to the diagnostic delay

Table 3 reports the clinical manifestations (i.e., symptoms, signs, and laboratory alterations) that were related to the diagnosis of CD. Gastrointestinal symptoms were, collectively, the most reported manifestation. About 70% of the included patients had at least one gastroenterological symptom, the most common being abdominal pain. The second most common manifestation of CD was red blood cell count alterations, among which microcytic anaemia was the most frequent. Fatigue was the single most common manifestation of CD and it was found in about 40% of the cases. According to the clinical presentation, 51.7% of the patients were classified as having major CD, 35.7% as having minor CD, and 11.1% as having silent CD. About 28% of the patients had at least one associated autoimmune disease, Hashimoto's thyroiditis being the most common. Family history of CD was present in 22.2% of patients. In 80% of the cases the diagnostic process was initiated due to the presence of a clinical picture suspicious for CD, while 14% of our patients were screened with coeliac specific antibodies due to the presence of risk factors associated with CD. In 5.3% of the cases the diagnosis was accidental. Also, 398 patients (17.5%) received at least one previous misdiagnosis before the correct diagnosis of CD was made. Supplementary Table 1 shows that the most common misdiagnosis was irritable bowel syndrome (IBS), accounting for about 43% of the misdiagnoses.

Correlates of the diagnostic delay

Tables 4, 5, and 6 report the multivariable analyses for factors affecting the patient-dependant, physician-dependant, and overall diagnostic delay,

respectively. The presence of a previous misdiagnosis was significantly associated with physician-dependant (p=0.005) and overall (p=0.001) diagnostic delay. On the other hand, a family history of CD was not correlated with either patient-dependant, physician-dependant, and overall diagnostic delay. Silent CD was associated with a significantly lower patient-dependant, physician-dependant, and overall diagnostic delay in respect to major or minor CD in all sub-groups of delay. Finally, socioeconomic factors, including level of education and marital status, did not affect the diagnostic delay.

Correlates of the extreme diagnostic delay

Supplementary tables 2, 3, and 4 show the multivariable analyses for factors affecting the extreme patient-dependant, physician-dependant, and overall diagnostic delay, respectively. The presence of gastrointestinal symptoms was associated with significant extreme overall diagnostic delay (p=0.004), while neurological symptoms were associated with significant extreme physician-dependant (p=0.005), and extreme overall (p=0.042) diagnostic delay. The presence of a previous misdiagnosis was significantly associated with extreme physician-dependant (p=0.000) and extreme overall (p=0.000) diagnostic delay. The type of clinical presentation (i.e., minor, major, and silent) was not associated with a significant increase in extreme patient-dependant, extreme physician-dependant, or extreme overall diagnostic delay.

Discussion

By including 19 Italian secondary or tertiary referral centres and 2362 adult CD patients, our multicentre study provides a population size significantly larger than the populations of other previously published studies having as a primary endpoint the diagnostic delay in CD (Table 1). Importantly, our study was based on hospital records, whereas most of the previous studies were based on less reliable methods, such as questionnaires or the use of administrative data.

Our estimates are in line with the previously published studies that reveal a trend towards a reduction of the diagnostic delay over the last decade (Table 1). Several different reasons can explain this phenomenon such as the wide spread of more and more accurate CD-specific autoantibodies. This trend started from the 1980s, led to a progressive lowering of the threshold for CD investigation, resulting in a significant reduction of the diagnostic delay, in an increased disease prevalence, and in the broad recognition of CD's subtle and multi-organ manifestations [1,25,26]. Minimising the diagnostic delay should be considered as key for several reasons. In particular, previous research has revealed that the quality of life before CD diagnosis is often significantly reduced, but it returns to standard levels after a diagnosis is made and after shifting to a GFD [2,3]. Diagnostic delay has also been associated with significantly slower improvement of symptoms after a GFD [4,5], and the standardised mortality ratio increases with increased delay in diagnosis [6]. The increase in mortality is partly due to the increased likelihood of developing threatening complications such as refractory CD and enteropathy-associated T-cell lymphoma [6]. Even patients with mild symptoms are at risk of developing complications, when undiagnosed for a long period of time [6].

The medical literature looking at predisposing factors for the diagnostic delay in CD is conflicting. For instance, Paez et al. reported a significantly prolonged diagnostic delay in patients without gastroenterological symptoms compared to those with gastroenterological symptoms [2], while Fuchs et al. reported that diarrhoea, abdominal pain, and malabsorption were associated with a significantly prolonged diagnostic delay [16]. Riznik et al. concluded that the type of clinical presentation had no significant effect on the diagnostic delay [27]. The differences among these studies could derive from the specific expertise of the centre in which data were collected.

In our study, gastrointestinal symptoms were not associated with any significant change in diagnostic delay. Anyway, considering the quartile of patients who experienced the highest diagnostic delay, a significant association between gastrointestinal symptoms and increased overall diagnostic delay emerged. It is likely that most of the patients who went undiagnosed for a prolonged time experienced just mild unspecific symptoms which are easily overlooked.

Similarly, neurological symptoms were not associated with diagnostic delay when considering the whole population; anyhow, considering just the quartile of patients with the highest diagnostic delay, neurological symptoms were correlated with a significant increase in physician-dependant and overall diagnostic delays. In our population 10% of patients presented at least one neurological symptom, the most common was paraesthesia, other manifestations being headache, mood changes, and behavioural changes. All these manifestations in a clinical setting are not easily related with CD.

Also, 17.5% of our population received at least one previous misdiagnosis before the correct diagnosis was formulated. Unsurprisingly, the presence of a previous misdiagnosis was correlated with increased physician-dependant and overall diagnostic delay both across the whole population and in the extreme delay subgroups. Indeed, misdiagnoses tend to stick to patients for long periods of time due to the so-called “anchoring bias”, which is defined as the tendency to consider correct the diagnosis already formulated despite contrary evidence [28]. Notably, misdiagnoses were found to be strictly correlated to the diagnostic delay of other immune-mediated gastrointestinal diseases, including inflammatory bowel disease (median overall delay of 3 months) [29], autoimmune atrophic gastritis (median overall delay of 14 months) [30], and eosinophilic esophagitis (median overall delay of 36 months) [31]. In all those conditions, the most commonly reported misdiagnosis was that of a benign or a functional condition the diagnosis of which does not depend on gastrointestinal endoscopy, including IBS, functional dyspepsia, and gastroesophageal reflux disease, respectively. Consistently, the most common misdiagnosis in our series was IBS, accounting for 43% of all misdiagnoses. Vast medical literature confirms that misdiagnosis of CD with IBS is frequent [4,8], and this occurs because CD often mimics typical IBS symptoms. For this reason, current guidelines [21] recommend assessing CD-specific antibodies when a diagnosis of IBS is suspected. A negative serology allows to reasonably exclude a diagnosis of CD and avoid misdiagnosis. To note, the widespread of self-reported non-coeliac gluten sensitivity [32] a condition where gluten ingestion triggers intestinal and/or extra-intestinal symptoms in the absence of either CD or wheat allergy [33], could greatly contribute to the

diagnostic delay of CD, as many patients would start a GFD prior to serological testing for CD.

Regarding the clinical presentation of CD, we found that silent CD, i.e., patients diagnosed with a screening strategy for either a first-degree family history of CD or autoimmune associations, was associated with a significantly lower diagnostic delay when compared to either major or minor CD in all sub-groups of delay. This result is not novel and has already been reported by Corazza et al. [8] nearly 30 years ago. Corazza et al. postulated that a previous misdiagnosis of IBS could have represented the main confounding factor in this setting, and hence IBS represents a high-risk category that should be screened for CD. Indeed, our data confirm this previous finding.

Finally, our study did not show a significant association between first-degree family history and a reduced delayed diagnosis [16]. Anyhow, screening asymptomatic patients with a first-degree relative affected by CD is recommend by guidelines because it has been demonstrated to be effective in reducing diagnostic delay [21]. Probably our study could not demonstrate the association between family history of CD and reduced diagnostic delay because screening is not implemented as it should. National guidelines encouraging consistent application of this indication would probably result in a reduction of diagnostic delay in this subgroup of patients. Mass screening for CD has been raised as a possible option [17,19]. Although CD fulfils many of the WHO criteria for a medical mass screening, as for now it is not recommended by guidelines [21]. Further studies are needed to assess the cost-effectiveness of CD mass screening in both children and adults [19,34,35].

Our study has some limitations. First, there may be a selection bias derived from the involvement of only gastrointestinal secondary or tertiary referral centres, all having a peculiar interest and expertise in the management of CD. Additionally, these centres may also have some heterogeneity. It is likely that our population contains a higher prevalence of complex patients, while patients encountered in general practice may be underrepresented. Also, the heterogeneous time for referral from the primary care setting may strongly influence the diagnostic delay. Another limitation is that data collection took place retrospectively. Indeed, the retrospective nature is a major limitation of all studies investigating diagnostic delay, and this could explain the heterogeneous and conflicting results in the available literature dealing with this issue. Finally, as in other studies aimed at estimating diagnostic delay [29-31] it was not possible to discern with certainty whether specific symptoms were a direct consequence of CD and to determine exactly the disease onset, and the limits of patient-dependant and physician-dependant delays. To minimise these issues, we excluded 775 patients lacking complete medical reports. Indeed, the entity of the diagnostic delay in still undiagnosed CD patients and in those who were excluded due to missing data is yet to be defined.

To conclude, as demonstrated by our evidence, an important cause of diagnostic delay in CD is the disease's broad clinical spectrum which can result in overlooking CD symptoms or in CD misdiagnosis. Increased awareness of the protean manifestations of CD is the chief factor demanding improvement [4,16,17]. Although improvements have been made over the last decades, the current overall diagnostic delay of 8 months still remains long. Increased clinical

awareness of CD and consistent application of guidelines are necessary to reduce the diagnostic delay.

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Table 1. Diagnostic delay of adult patients with coeliac disease according to the available, retrospective, studies focusing on this issue as a primary endpoint.

Authors	Publication year	Country	N. patients	Data collection	Overall DD (years)	Main findings
Gregory et al.	1983	UK	40	Questionnaire	Median 7.0	CD DD is common and substantial
Corazza et al.	1996	Italy	419	Medical record	Mean 12.9 (previous misdiagnosis); mean 8 (no previous misdiagnosis)	Antibody testing for CD in patients with diarrhoea might reduce the risk of misdiagnosis and DD
Corrao et al.	2001	Italy	1072	Medical record	Median 1.4	Prompt and strict dietary treatment ad reduced DD decrease mortality in CD
Gasbarrini et al.	2001	Italy	1353	Questionnaire	Mean 14 in adults <65y; mean 17 in the elderly ≥65y	In spite of classical CD manifestations, the DD in the elderly is particularly prolonged compared to adults
Norström et al.	2011	Sweden	1031	Questionnaire	Median 4,	Reduction of DD may improve quality of life
Pulido et al.	2013	Canada	5912	Questionnaire	Mean 12.6	CD DD is substantially long in Canada despite the available screening tests
Fuchs et al.	2014	Finland	825	Phone interview	>10 in 32% of patients	Female gender, neurological/musculoskeletal disorders, diarrhoea, abdominal pain, malabsorption were associated with prolonged DD; male gender, diagnosis after the Current Care Guidelines (1997), being diagnosed by serological screening, and a family history of CD were associated with lower DD
Paez et al.	2017	US	101	Medical record	Median 0.2 (GI symptoms); 3.5 (non-GI symptoms)	DD in patients without GI symptoms remains prolonged
Fuchs et al.	2018	Finland	611	Questionnaire	Median 3.0	Being a student or homemaker, but not gender, marital or occupational status, site of diagnosis and place of residence, were associated with DD; DD predisposes to reduced well-being
Tan et al.	2021	The Netherlands	211	Questionnaire	>3 in 33% of patients	Non-classical CD presentation is more prevalent in males
Mansueto et al.	2021	Italy	369	Medical record	Mean 9.0	Frequent use of unrecommended tests before CD diagnosis
Zingone et al.	2021	Italy	110	Interview	Median 1.7 (GI symptoms); 1.4 (non-GI symptoms)	CD symptoms at diagnosis, DD, and sex may affect quality of life

Abbreviations: coeliac disease, CD; diagnostic delay, DD; gastrointestinal, GI.

Table 2. Sociodemographic characteristics of the 2362 patients with coeliac disease.

	N (%)
Sex	
Female	1786 (75.6)
Male	576 (24.4)
Age at diagnosis	
≤38 years	1243 (52.7)
>38 years	1118 (47.4)
Smoking status	
Never smoker	1702 (75.5)
Current smoker	423 (18.8)
Former smoker	127 (5.6)
Ethnicity	
Caucasian	2301 (99.5)
Hispanic	4 (0.2)
Arabic	3 (0.1)
Asian	2 (0.1)
Black	0 (0)
Years of education	
≤5 years	26 (1.2)
8 years	426 (20.0)
13 years	757 (35.6)
>13 years	918 (43.2)
Marital status	
Single	612 (31.4)
Married	1032 (53.0)
Widow/er	26 (1.3)
Partner	278 (14.3)
Exemption from healthcare taxes	
Yes	343 (37.5)
No	571 (62.5)

Table 3. Symptoms, alterations, or clues that could have prompted further work-up for confirming coeliac disease.

	N (%)
Gastroenterological symptoms (at least one)	1634 (69.2)
>1 symptom	662 (28.1)
Abdominal pain	238 (10.1)
Weight loss	207 (8.8)
Bloating	188 (8.0)
Dyspepsia	140 (6.0)
Diarrhoea	120 (5.1)
GERD	30 (1.3)
Vomiting	19 (0.8)
Anorexia	3 (0.1)
Red blood cell count alteration (at least one)	1031 (44.2)
Microcytic anaemia	866 (37.1)
Normocytic anaemia	122 (5.2)
Macrocytic anaemia	38 (1.6)
Thrombocytopenia	4 (0.2)
Pancytopenia	1 (0.1)
Fatigue	948 (40.3)
Associated autoimmune disorders (at least one)	668 (28.3)
Hashimoto's thyroiditis	417 (17.8)
>1 autoimmune disorder	69 (2.9)
Psoriasis	61 (2.6)
Type 1 diabetes mellitus	28 (1.2)
Vitiligo	26 (1.1)
Rheumatoid arthritis	23 (1.0)
Connective tissue disease	22 (0.9)
Addison's disease	1 (0.1)
Family history of CD	519 (22.2)
Osteoporosis	365 (16.2)
Infertility or recurrent miscarriage (at least one)	294 (14.1)
Recurrent miscarriage	170 (8.1)
Delayed menarche	97 (4.6)
Infertility	38 (1.8)
Neuropsychiatric symptoms (at least one)	229 (9.7)
Others	121 (5.1)
Paraesthesia	70 (3.0)
Neuropsychiatric symptoms*	26 (1.1)
Dermatitis herpetiformis	75 (3.2)

Selective IgA deficiency	24 (1.0)
Common variable immunodeficiency	1 (0.1)
Down syndrome	2 (0.1)

Abbreviations: CD, coeliac disease; GERD, gastro-esophageal reflux disease

*This includes mood changes, confusion, memory loss, depression, persecutory delusions, psychosis.

Table 4. Multivariable analysis for factors affecting patient-dependant diagnostic delay. The diagnostic delay is log-transformed.

		Multivariable analysis	**Model p<0.001 R^2 0.09**
Patient DD	**Median DD**	**Coefficient (95%CI)**	**p-value**
Sex			
Female	3 (2-6)	0	
Male	3 (2-6)	-0.128 (-0.311 to 0.054)	0.157
Age			
≤38	2 (3-6)	0	
>38	2 (4-6)	0.106 (-0.117 to 0.328)	0.330
Neurological symptoms			
No	3 (2-6)	0	
Yes	5 (2-12)	0.133 (-0.229 to 0.494)	0.450
Family history of CD			
No	4 (2-6)	0	
Yes	3 (1-6)	-0.207 (-0.497 to 0.084)	0.152
N. of specialist physicians			
1	3 (2-6)	0	
≥2	3 (2-6)	0.143 (-0.137 to 0.424)	0.295
Classification			<0.001
Major	4 (2-6)	0	
Minor	3 (2-6)	-0.089 (-0.254 to 0.075)	0.268
Silent	1 (0-6)	-1.119 (-1.579 to -0.660)	0.000
Other	4 (3-12)	0.071 (-0.662 to 0.804)	0.840

Abbreviations: coeliac disease, CD; confidence interval, CI; diagnostic delay, DD.

Table 5. Multivariable analysis for factors affecting physician-dependant diagnostic delay. The diagnostic delay is log-transformed

		Multivariable analysis	**Model p<0.001, R^2=0.21**
Physician DD	**Median DD**	**Coefficient (95%CI)**	**p-value**
Sex			
Female	4 (2-7)	0	
Male	4 (2-6)	-0.033 (-0.187 to 0.122)	0.660
Age			
≤38	4 (2-6)	0	
>38	4 (2-7)	0.156 (-0.071 to 0.383)	0.164
Diagnosis made by a gastroenterologist			
No	4 (2-7)	0	
Yes	4 (2-6)	0.261 (-0.025 to 0.547)	0.071
GI symptoms			
No	4 (2-7)	0	
Yes	4 (2-6)	-0.207 (-0.442 to 0.028)	0.081
Neurological symptoms			
No	4 (2-6)	0	
Yes	6 (2-12)	0.190 (-0.044 to 0.423)	0.104
Asthenia			
No	3 (2-6)	0	
Yes	4 (2-7)	0.131 (-0.060 to 0.323)	0.166
Family history of CD			
No	4 (2-7)	0	
Yes	3 (1-6)	-0.221 (-0.470 to 0.028)	0.079
Previous misdiagnosis			
No	3 (2-6)	0	
Yes	7 (4.5-24)	1.076 (0.376 to 1.776)	0.005
Classification			<0.001
Major	4 (2-6)	0	0
Minor	5 (3-7)	0.100 (-0.068 to 0.267)	0.225
Silent	2 (0-5)	-0.896 (-1.472 to -0.319)	0.005
Other	6 (3-12)	-0.116 (-0.823 to 0.591)	0.732

Abbreviations: coeliac disease, CD; confidence interval, CI; diagnostic delay, DD; gastrointestinal, GI.

Table 6. Multivariable analysis for factors affecting overall diagnostic delay.

The diagnostic delay is log-transformed.

		Multivariable analysis	**Model p<0.001 R^2 0.19**
Overall DD	**Median DD**	**Coefficient (95%CI)**	**p-value**
Sex			
Female	8 (5-14)	0	
Male	8 (4-13)	-0.141 (-0.325 to 0.044)	0.125
Age			
≤38	8 (5-13)	0	
>38	8.5 (5-15)	0.119 (-0.093 to 0.330)	0.251
GI symptoms			
No	7 (4-12)	0	
Yes	9 (6-16)	0.162 (-0.112 to 0.436)	0.229
Neurological symptoms			
No	8 (5-13)	0	
Yes	12 (6-36)	0.220 (-0.109 to 0.550)	0.176
Asthenia			
No	8 (4-13)	0	
Yes	9 (6-17.5)	0.045 (-0.175 to 0.265)	0.671
Family history of CD			
No	9 (5-14)	0	
Yes	7 (3-14)	-0.192 (-0.409 to 0.025)	0.079
Previous misdiagnosis			
No	7 (5-12)	0	
Yes	15 (9-38)	0.659 (0.297 to 1.020)	0.001
N. of specialist physicians			
1	7 (4-12)	0	
≥2	9 (6-16)	0.326 (-0.034 to 0.686)	0.073
Classification			
Major	8 (5-14)	0	0.014
Minor	9 (6-15)	-0.042 (-0.181 to 0.097)	0.530
Silent	4 (1-12)	-0.852 (-1.371 to -0.332)	0.003
Other	12 (6-26.5)	-0.348 (-1.057 to 0.361)	0.314

Abbreviations: coeliac disease, CD; confidence interval, CI; diagnostic delay, DD; gastrointestinal, GI.

Supplementary Table 1. Previous 398 misdiagnoses in patients with coeliac disease, or confounding conditions leading to a delayed diagnosis.

	N (%)
Irritable bowel syndrome	173 (43.0)
Anaemia, allegedly attributed to other causes	53 (13.2)
Food intolerance	25 (6.2)
Gastroesophageal reflux disease	24 (6.0)
Functional dyspepsia	21 (5.2)
Gastrointestinal motility disorder	16 (4.0)
Chronic gastritis	15 (3.7)
Colitis (other than inflammatory bowel disease)	11 (2.7)
Anxiety and/or depression	10 (2.5)
Small intestine bacterial overgrowth	10 (2.5)
Stress and anxiety	8 (2.0)
Neuropathy of unknown cause	7 (1.7)
Gastroenteritis	5 (1.2)
Inflammatory bowel disease	5 (1.2)
Dermatitis of unknown cause	4 (1.0)
Thyroid disorder	3 (0.7)
Food allergy	3 (0.7)
Non-alcoholic steatohepatitis	2 (0.5)
Chronic constipation	2 (0.5)
Eating disorder	2 (0.5)
Migraine	1 (0.2)
Peptic ulcer disease	1 (0.2)
Fibromyalgia	1 (0.2)

Supplementary Table 2. Multivariable analysis for factors affecting extreme patient-dependant diagnostic delay.

	Multivariable analysis	**Model p=0.235 AUC ROC=0.57**
Patient DD	**Odds ratio (95%CI)**	**p-value**
Sex		
Female	1.0	
Male	0.837 (0.664 to 1.054)	0.130
Age		
≤35	1.0	
>35	1.122 (0.630 to 2.001)	0.695
Neurological symptoms		
No	1.0	
Yes	2.261 (0.985 to 5.189)	0.054
Family history of CD		
No	1.0	
Yes	1.073 (0.673 to 1.710)	0.766
N. of specialist physicians		
1	1.0	
≥2	1.065 (0.647 to 1.752)	0.806
Classification		0.235
Major	1.0	0
Minor	0.789 (0.584 to 1.065)	0.122
Silent	1.015 (0.432 to 2.383)	0.973
Other	1.256 (0.582 to 2.546)	0.519

Supplementary Table 3. Multivariable analysis for factors affecting extreme physician-dependant diagnostic delay.

	Multivariable analysis	**Model p<0.001, AUC-ROC=0.76**
Physician DD	**Odds ratio (95%CI)**	**p-value**
Sex		
Female	1.0	
Male	1.046 (0.736 to 1.485)	0.803
Age		
≤35	1.0	
>35	2.004 (0.744 to 5.396)	0.169
Diagnosis made by a gastroenterologist		
No	1.0	
Yes	1.073 (0.552 to 2.086)	0.835
GI symptoms		
No	1.0	
Yes	0.789 (0.544 to 1.146)	0.213
Neurological symptoms		
No	1.0	
Yes	2.311 (1.280 to 4.170)	0.005
Asthenia		
No	1.0	
Yes	1.203 (0.837 to 1.729)	0.318
Family history of CD		
No	1.0	
Yes	0.995 (0.687 to 1.441)	0.978
Previous misdiagnosis		
No	1.0	
Yes	9.807 (6.230 to 15.440)	0.000
Classification		0.3161
Major	1.0	0
Minor	1.094 (0.801 to 1.493)	0.572
Silent	1.648 (0.920 to 2.951)	0.093
other	1.884 (0.247 to 14.365)	0.541

Supplementary Table 4. Multivariable analysis for factors affecting extreme overall diagnostic delay.

	Multivariable analysis	**Model p<0.001 AUC ROC=0.72**
Overall DD	**Odds ratio (95%CI)**	**p-value**
Sex		
Female	1.0	
Male	0.775 (0.580 to 1.038)	0.087
Age		
≤35	1.0	
>35	1.285 (0.679 to 2.432)	0.441
GI symptoms		
No	1.0	
Yes	1.880 (1.220 to 2.896)	0.004
Neurological symptoms		
No	1.0	
Yes	2.313 (1.033 to 5.180)	0.042
Asthenia		
No	1.0	
Yes	1.055 (0.662 to 1.683)	0.822
Family history of CD		
No	1.0	
Yes	1.228 (0.758 to 1.989)	0.405
Previous misdiagnosis		
No	1.0	
Yes	4.265 (2.351 to 7.737)	0.000
N. of specialist physicians		
1	1.0	
≥2	1.341 (0.799 to 2.251)	0.266
Classification		0.777
Major	1.0	0
Minor	0.903 (0.594 to 1.374)	0.635
Silent	1.387 (0.626 to 3.074)	0.420
Other	1.044 (0.184 to 5.922)	0.961