Digestive and Liver Disease xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Risk of complications in coeliac patients depends on age at diagnosis and type of clinical presentation

Federico Biagi[a,*,1], Annalisa Schiepatti[a,1,2], Gregorio Maiorano[a], Giacomo Fraternale[a], Simona Agazzi[a], Fabiana Zingone[b], Carolina Ciacci[b], Umberto Volta[c], Giacomo Caio[c], Raffaella Tortora[d], Catherine Klersy[e], Gino R. Corazza[a]

[a] Coeliac Centre/First Dept. of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Italy
[b] Celiac Center at Gastrointestinal Unit, AOU S. Giovanni di Dio e Ruggi d'Aragona, University of Salerno, Italy
[c] Department of Medical and Surgical Sciences, University of Bologna, Italy
[d] Department of Clinical and Experimental Medicine, Unit of Gastroenterology, University of Naples Federico II, Naples, Italy
[e] Biometry and Clinical Epidemiology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Italy

ARTICLE INFO

Article history:
Received 13 September 2017
Received in revised form 7 November 2017
Accepted 3 December 2017
Available online xxx

Keywords:
Celiac disease/epidemiology
Gluten
Incidence
Prognosis
Risk assessment

ABSTRACT

Background: Coeliac disease is characterised by an increased mortality mostly due to its complications.
Aims: To study the risk of developing complications according to clinical presentation and age at diagnosis, a combined retrospective–prospective longitudinal study was performed in three Italian centres.
Methods: Incidence of complications and mortality rates were calculated using type and age at diagnosis of coeliac disease, sex, and centre of diagnosis as predictors. Patients referred after being found to suffer from coeliac disease elsewhere were excluded.
Results: Between 01/1999 and 06/2015, 2225 adult coeliac patients were directly diagnosed in our centres. 17 of them developed a complication and 29 died. In patients older than 60 years at diagnosis of coeliac disease, the risk of complication is 18 times higher than in patients diagnosed at 18–40 years and 9 times higher than in patients diagnosed at 40–60 years. Classical presentation increases the risk of complications by 7 times compared to non-classical presentation; in asymptomatic patients the risk of complication is virtually absent.
Conclusions: The risk of developing complications in coeliac patients is linked to age at diagnosis of coeliac disease and type of clinical presentation. Follow-up methods of coeliac patients should be tailored according to these parameters.

1. Introduction

Coeliac disease (CD) is a very common chronic gluten-induced enteropathy characterised by an increased mortality mostly due to its complications [1]. Although they are rare, these malignant conditions are burdened by a very bad prognosis [1,2]. This is the case of refractory CD (RCD, type 1 and 2), enteropathy associated T-cell lymphoma (EATL), small bowel carcinoma (SBC), B-cell lymphoma (BCL), and ulcerative jejunoileitis. While RCD type 1 has a 5-year survival rate of 80–96%, up to 50% of RCD type 2 patients can develop an overt EATL within 5 years of diagnosis. The 5-year survival rate of these last two conditions is between 40 and 58% and less than 20%, respectively [3–6]. SBC and B-cell lymphomas complicating CD also have a poor prognosis [2,7–9]. Given their malignant nature, the origin from the abdomen, the very similar clinical picture and the common underlying pathogenic mechanism of some of them [10], it is possible to consider these conditions all together as complicated forms of CD (CCD).

In the last 15 years it has emerged that the mortality of coeliac patients depends on several factors, strict adherence to a gluten-free diet, clinical type and age at diagnosis of CD being the most important ones [11]. Other factors such as a long diagnostic delay and male sex were initially described as risk factors for complications [11,12], but they were not subsequently confirmed [2,13]. Finally, HLA typing was shown to correlate with clinical types of CD and onset of complications [14].

* Corresponding author at: Coeliac Centre/1st Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, P.le Golgi, 19, I-27100 Pavia, Italy,
E-mail address: f.biagi@smatteo.pv.it (F. Biagi).
[1] These authors contributed equally to the work.
[2] Dr. Annalisa Schiepatti is attending the PhD course in Experimental Medicine at the University of Pavia, Italy.

https://doi.org/10.1016/j.dld.2017.12.001
1590-8658/

The aim of the present work was to investigate whether clinical parameters already present at the time of diagnosis of CD can enable early identification of those coeliac patients at higher risk of developing complications. This would be of great help in establishing the follow-up methods of CD patients which have not been standardised so far [15,16].

2. Patients and methods

2.1. Data collection

Between January and December 2015 a combined retrospective and prospective design longitudinal multicentre study based on collection of clinical data was carried out in three Italian referral centres for the study of adult CD and its complications, Pavia, Bologna, and Naples-Salerno.

Sex, age at diagnosis of CD, year of diagnosis, clinical type of CD, age at last outpatient clinic access or phone contact, age at onset and type of possible complication, age at death and cause of death were recorded for each adult CD patient directly diagnosed in our centres between January 1999 and June 2015. We must point out that, to avoid a selection bias, coeliac patients diagnosed elsewhere and seen in our centres to obtain a certificate entitling them to gluten-free products through the Italian National Health Service, for confirmation of the diagnosis, or for suspected CCD, were excluded.

For the purpose of the statistical analysis, clinical type of CD was divided into classical, non-classical and asymptomatic according to the Oslo criteria [17] and corresponding to major, minor and silent [11]; analogously, three age groups were defined on the basis of age at diagnosis of CD (18–40 years; 41–60 years; >60 years).

All the patients who had not attended our centres for regular follow-up in the six months before the time of data collection were contacted over the phone to ascertain whether they were still alive and had not developed complications. For those patients who could not be reached by phone, the local council services were contacted to know whether they were still alive (in this case, information about the potential onset of a complication was not available). Causes and dates of death were obtained through the Italian standard certificates of death.

Diagnosis of CD was always based on at least four correctly oriented duodenal biopsies showing a certain degree of villous atrophy and positive IgA tissue transglutaminase/endomysial antibodies while on a normal gluten-containing diet. Seronegative patients were excluded. Diagnosis of RCD was based on persistence or recurrence of malabsorption symptoms and persistence of villous atrophy despite at least 12 months of a strict gluten-free diet [3,15,16]. Identification of aberrant $CD3^{-}CD8^{-}CD103^{+}CD7^{+}$cytoplasmatic $CD3^{+}$ intraepithelial lymphocytes by flow cytometric analysis (>20%) and/or gamma chain T-cell monoclonal rearrangement by means of polymerase chain reaction allowed the diagnosis of RCD type 2 and the distinction from RCD type 1 [3,18]. Finally, the diagnoses of EATL, BCL, and SBC were based on histopathological criteria [6–9].

2.2. Statistics

Stata 14.2 (StataCorp, College Station, TX, USA) was used for computation. Data are reported as mean and standard deviation or as median and quartiles (25th–75th percentiles) if continuous and as counts and percent if categorical. Median follow-up (25th–75th) was computed with the inverse Kaplan–Meier methods. Clinical type of CD, sex, age at diagnosis of CD, year of diagnosis, and Centre where the diagnosis of CD was made were considered as predictors. Incidence of complications and overall mortality rate were calculated in each group. Survival and event-free survival were compared with the Cox model between groups of patients; hazard ratios (HR) and 95% confidence intervals (95%CI) were computed. The prognostic role of CCD was assessed with a time-dependent Cox model. Bivariable models were fitted to adjust for potential confounders in turn. The effect modification of each confounder was assessed with a test on interaction. If an interaction was found, separate models by subgroups were fitted. A p-value <0.05 was considered statistically significant. Bonferroni correction was applied for post-hoc comparisons.

2.3. Ethics

All patients signed informed consent before the biopsies, both for clinical and research purposes. After verifying the good quality of the data, the data were all irreversibly anonymized. None of the patients had signed against participation in anonymous studies. On 30th April 2014, the study was approved by the ethics committee of the Fondazione IRCCS Policlinico San Matteo according to the 1975 Declaration of Helsinki (6th revision, 2008).

3. Results

Between January 1999 and June 2015, 2225 adult coeliac patients (F 1660, mean age at diagnosis 36 ± 12 years) were directly diagnosed in our three centres. Between January and December 2015, 1899 of them (85.4%) were seen directly in our outpatient clinics or contacted over the phone to ascertain that they were still alive and had not developed complications. Only 326 patients (14.6%) could not be contacted or seen directly, so information on whether they were still alive or had died was provided by the respective local council services. Median follow-up was 79 months (25th–75th 37–125 months).

Seventeen out of 2225 patients (11 F; mean age at diagnosis of complication 56 ± 16 years) developed a complication (6 type 1 RCD, 4 EATL, 5 SBC, 2 abdominal BCL); mean age at diagnosis of CD was 52 ± 15 years (age was >60 years in 8 of them, between 41 and 60 in 4, and <40 in 5). Median time between diagnosis of CD and diagnosis of complication was 55 months (25th–75th 29–105 months); similar results were obtained in the three different age groups (44, 58, and 48 months). Fourteen of them had a classical presentation and 3 a non-classical one. The overall incidence of complication is therefore 11 per 10,000 persons/year (95% CI 6–17 per 10,000 persons/year). Five of these 17 patients with CCD died (3 F; mean age at death 63 ± 7 years; median time between diagnosis of CD and death 85 months, 25th–75th 68–111 months). Causes of death included 3 EATL, 1 type 1 RCD and 1 SBC.

Twenty-four of the 2208 patients who had not developed CCD had died (14 F; mean age at diagnosis of CD 57 ± 14 years; mean age at death 64 ± 14 years; median time between diagnosis of CD and death 91 months, 25th–75th 37–121 months). Causes of death in this group were very heterogeneous and included 6 cardiocerebrovascular causes and 4 cancers unrelated to CD. A more precise list of these causes of death is available on request.

The 326 patients for whom information was obtained from the local council services substantially had the same clinical and epidemiological characteristics of the remaining 85% of patients who were seen/contacted directly (268 F, mean age at diagnosis of CD 35 ± 11; classical presentation in 108, non-classical in 137, asymptomatic in 81).

Table 1 shows the results of predictors of complications at the time of diagnosis. Age at diagnosis of CD and clinical type of CD represent strong predictors of complications. More precisely, the risk of complications progressively increases with the increase in age at diagnosis of CD. While the incidence of complications is very low in CD patients diagnosed before the age of 40 years (1/2000 per-

Please cite this article in press as: Biagi F, et al. Risk of complications in coeliac patients depends on age at diagnosis and type of clinical presentation. Dig Liver Dis (2017), https://doi.org/10.1016/j.dld.2017.12.001