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Alimentary Tract

Low incidence but poor prognosis of complicated coeliac disease: A retrospective multicentre study☆

Federico Biagi[a,*], Paolo Gobbi[a], Alessandra Marchese[a], Edoardo Borsotti[a], Fabiana Zingone[b], Carolina Ciacci[b], Umberto Volta[c], Giacomo Caio[c], Antonio Carroccio[d], Giuseppe Ambrosiano[e], Pasquale Mansueto[e], Gino R. Corazza[a]

[a] Coeliac Centre/First Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Italy
[b] Department of Medicine and Surgery, Gastrointestinal Immune Diseases Centre, University of Salerno, Italy
[c] Coeliac Centre/Department of Clinical Medicine, St. Orsola-Malpighi University Hospital, Bologna, Italy
[d] UO di Medicina, Ospedali Civili Riuniti di Sciacca, University of Palermo, Italy
[e] Internal Medicine, University of Palermo, Italy

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ABSTRACT

Background: Coeliac disease is a chronic enteropathy characterized by an increased mortality caused by its complications, mainly refractory coeliac disease, small bowel carcinoma and abdominal lymphoma. Aim of the study was to study the epidemiology of complications in patients with coeliac disease.
Methods: Retrospective multicenter case–control study based on collection of clinical and laboratory data. The incidence of complicated coeliac disease was studied among coeliac patients directly diagnosed in four Italian centres. Patients referred to these centres after a diagnosis of coeliac disease and/or complicated coeliac disease in other hospitals were therefore excluded.
Results: Between 1/1999 and 10/2011, 1840 adult coeliac patients were followed up for 7364.3 person-years. Fourteen developed complications. Since five patients died, at the end of the observation period (10/2011), the prevalence of complicated coeliac disease was 9/1835 (1/204, 0.49%, 95% CI 0.2–0.9%). The annual incidence of complicated coeliac disease in the study period was 14/7364 (0.2%, 95% CI 0.1–0.31%). Although complications tend to occur soon after the diagnosis of coeliac disease, Kaplan–Meier curve analysis showed that they can actually occur at any time after the diagnosis of coeliac disease.
Conclusions: Complications of coeliac disease in our cohort were quite rare, though characterised by a very high mortality.

1. Introduction

Coeliac disease (CD), a chronic enteropathy due, in genetically predisposed individuals, to the intake of gluten, is well known as being characterized by both a high prevalence and an increased mortality [1,2]. Although in the great majority of patients the prognosis of this disease is excellent, and most coeliac patients die for causes unrelated to CD, some of these patients may develop a series of serious complications, such as refractory CD type 1 and type 2 (RCD1 and RCD2), ulcerative jejunoileitis (UJI), enteropathy-associated T-cell lymphoma (EATL), abdominal B cell lymphoma (ABL), and small bowel carcinoma (SBC), which dramatically reduce the prognosis [3–7]. In particular, the five-year survival rate is between 80% and 96% in patients with RCD1, between 40% and 58% in patients with RCD2 and drops to less than 20% in patients with CD complicated by EATL [8–13].

The first papers on the molecular diagnosis of complicated CD (CCD) were published more than 10 years ago [14], and since then several papers were published on this subject [4–19]. Despite these achievements, the literature still provides only minor and insufficient indications on the incidence of these conditions in patients with CD [8,15–19]. The reason for this lack of data can probably be attributed to the fact that most patients with CCD are sent to large referral centres. Similarly, a considerable number of patients with non-complicated CD are also referred to these centres. While sending all these patients to such referral centres certainly makes it easier to study the disease, it also introduces an inevitable selection bias and thus makes an epidemiological study of CCD extremely difficult.

Our aim was to resolve this bias by studying how many patients with CD diagnosed directly in a single centre subsequently develop a complicated form of CD.

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* Corresponding author at: Coeliac Centre/1st Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, P.le Golgi, 19, I-27100 Pavia, Italy. Tel.: +39 0382 502973; fax: +39 0382 502618.
E-mail address: f.biagi@smatteo.pv.it (F. Biagi).

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2. Patients and methods

A retrospective multicenter case–control study based on collection of clinical and laboratory data was carried out in four Italian referral centres for the study of CD and its complications. In each of these centres it was calculated how many patients with CD were diagnosed directly in the centre between January 1999 and October 2011. The patients were diagnosed on the basis of a duodenal biopsy showing a certain degree of villous atrophy and of positive anti-transglutaminase/antiendomysial antibodies. This means that all patients with CD that were seen at the centre to obtain a certificate entitling them to gluten-free products through the Italian National Health Service, for confirmation of a diagnosis made elsewhere or for suspected CCD, were excluded. Among all the remaining patients, those whose malabsorption symptoms persisted despite at least 12 months of a gluten-free diet and in whom a diagnosis of complicated CD was made were selected. More specifically, the diagnosis of RCD2 was based on a flat duodenal mucosa not responding to 12 months on a gluten-free diet and evidence of an aberrant intraepithelial lymphocyte population and/or gamma chain T cell monoclonal rearrangement; diagnosis of RCD1 was based on a flat duodenal mucosa not responding to 12 months on a gluten-free diet but without the diagnostic criteria for RCD2; finally, the diagnoses of EATL, ABL, UJI, and SBC were based on morphological criteria [9–12]. For all these patients, the following information was collected: sex, date of birth, date of diagnosis of CD, date of the last examination at the centre, date of diagnosis of complications of CD, if applicable, and date of death, if applicable. In this article, the term "cases" indicates patients with CD who subsequent developed a complication while the term "controls" indicates patients with CD who did not subsequently develop a complication.

The study was approved by the ethics committee of the Fondazione IRCCS Policlinico San Matteo.

3. Statistics

The incidence of complication was evaluated both on the whole patient population and on the subsets from each of the four referral Centres. Differences of incidence were analysed with $2 \times K$ contingency tables, applying Fisher's exact test in cases of too small numbers [19]. The 95% confidence intervals were calculated according to Poisson's exact test.

Curves of duration of follow-up and complication-free survival were calculated according to the Kaplan–Meier technique and, when applicable, differences were analysed with the log-rank test [20,21].

The complication-free survival was further analysed through univariate and bivariate regressions applied to the proportional hazards model [22], with sex and age at diagnosis of CD as covariates. The relative risk, related to the adequacy of the model and calculated per single measurement unit of the covariate, was derived from the natural exponential of the partial regression coefficient.

The analyses were performed using the Stat View 5.0 software package (Abacus Concepts, Berkeley, California, 1995) for Macintosh.

4. Results

Between January 1999 and October 2011, a total of 2071 adult patients with CD were diagnosed in the four centres participating in the study. Two-hundred and thirty-one of them were not seen after the initial diagnosis of CD and were considered to be lost to follow-up. The remaining 1840 (1390 F, mean age 37.0 years ± 11.9) had a cumulative follow-up of 7364.3 person-years (mean follow-up 48.0 months, 95% CI 0.03–160.5). During this period, 14 of these 1840 patients developed a CD-related complication (11 F, mean age at diagnosis of CCD 61.1 years ± 12.2; 5 cases of RCD1, 3 SBC, 2 RCD2, 2UJI, 1 EATL, 1 ABL). All 14 had severe malabsorption symptoms and 5 of them died (3 F, mean age at death 69.6 years ± 8.2; 3 cases of RCD1, 1 EATL, 1 SBC). Since none of the 1826 controls (1379 F, mean age at diagnosis of CD 35.4 years ± 11.4) died, at the end of the observation period (October 2011), the prevalence of CCD in our population of patients with CD was therefore 9/1835 (1/204, 0.49%, 95% CI 0.2–0.9%). The annual incidence of CCD in our study period was 1/526.3 (0.2%, 95% CI 0.1–0.31%).

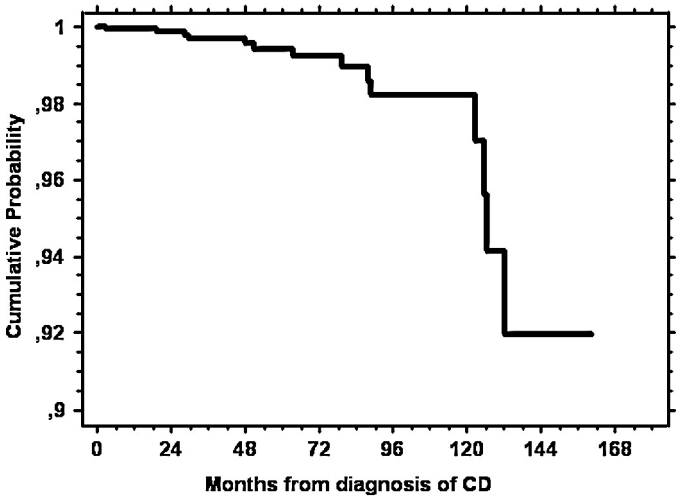

Fig. 1. Kaplan–Meier curve showing the complication-free survival in patients with coeliac disease. The onset of complications is a rare event but can occur even many years after the diagnosis of coeliac disease.

Fig. 1 shows the Kaplan–Meier curve for complication-free cumulative survival. This analysis confirms that the onset of complications is fortunately a rare event that can, however, also occur many years after the diagnosis of CD.

Age at diagnosis of CD in the cases was significantly higher compared with age at diagnosis of CD in the controls (59.2 ± 12.2 years vs. 36.8 ± 12.4; $p < 0.0001$). Fig. 2 shows that a value of age at diagnosis of CD between the two means (48 years) discriminates the complication-free survival very well. The analysis according to the proportional risks model shows that the age at diagnosis

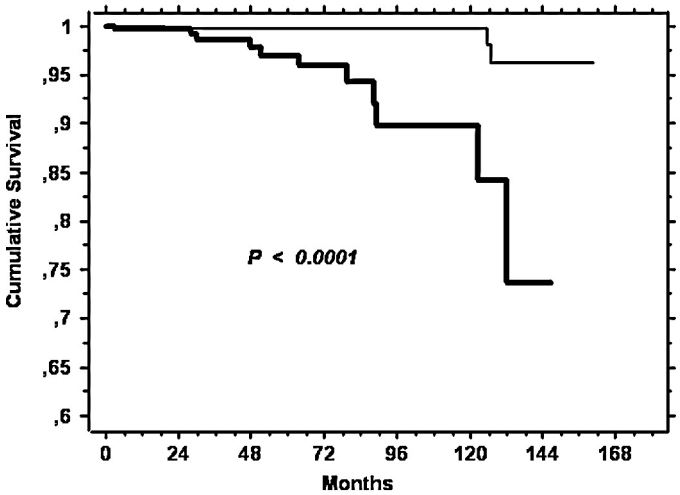

Fig. 2. Complication-free survival according to age at diagnosis of coeliac disease. Thick line > 48 years; thin line ≤ 48 years.