Digestive and Liver Disease 46 (2014) 32–35

Contents lists available at ScienceDirect

Digestive and Liver Disease

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

Alimentary Tract

Case-finding for coeliac disease in secondary care: A prospective multicentre UK study

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ARTICLE INFO

Article history:
Received 1 May 2013
Accepted 6 August 2013
Available online 12 September 2013

Keywords:
Case-finding
Coeliac disease

ABSTRACT

Background: Coeliac disease affects 1% of the population. Despite this high prevalence, the majority of individuals are undetected. Many patients present with subtle symptoms which may also contribute to under diagnosis. Our aim was to determine the relative importance of different presenting characteristics.
Methods: Unselected gastroenterology patients referred to 4 hospitals in South Yorkshire were investigated for coeliac disease. Diagnosis was based on positive serology and the presence of villous atrophy. Odds ratios were calculated for presenting characteristics and multivariate analysis performed to identify independent risk factors.
Results: 4089 patients were assessed (41.5% male, mean age 55.8 ± 18.2 years); 129 had coeliac disease (3.2%, 95% CI 2.6–3.7%). Multivariate analysis of patients referred to secondary care showed family history of coeliac disease (OR 1.26, $p < 0.0001$), anaemia (OR 1.03, $p < 0.0001$) and osteoporosis (OR 1.1, $p = 0.006$) were independent risk factors for diagnosis of coeliac disease. When compared to population controls, diarrhoea (OR 4.1, $p < 0.0001$), weight loss (OR 2.7, $p = 0.02$), irritable bowel syndrome symptoms (OR 3.2, $p = 0.005$) thyroid disease (OR 4.4, $p = 0.01$) and diabetes (OR 3.0, $p = 0.05$) were also associated with increased coeliac disease risk.
Conclusions: Coeliac disease accounts for 1 in 31 referrals in secondary care to unselected gastroenterology clinics. A low threshold for coeliac disease testing should be adopted.

1. Introduction

Coeliac disease (CD) is a common condition arising from the ingestion of gluten-containing foods resulting in small bowel villous atrophy. Historically, CD was felt to be an uncommon entity presenting with malabsorption and weight loss [1]. With the advent of improved serological testing, contemporary epidemiological studies have estimated the prevalence in the European adult population of 1% [2,3]. Recent meta-analyses have shown that for every patient identified as having CD seven to eight individuals remain undiagnosed [4,5]. Untreated CD is associated with increased morbidity and mortality and may have a negative impact on an undetected individual's quality of life [6,7]. Early institution of a gluten free diet (GFD) may avoid these complications [8]. As a result mass population screening has been proposed [9–12]. However, this remains controversial particularly as the absolute risks of coeliac related complications in asymptomatic individuals remains to be elucidated.

Serological testing with anti-endomysial (EMA) and anti-tissue transglutaminase (tTGA) antibodies has been shown to have excellent sensitivity and specificity with negative predictive values approaching 100% [13,14]. In recent years, there has been increased awareness of serological testing, particularly for patients complaining of irritable bowels syndrome (IBS) type symptoms [15]. Despite this the rate of detection of CD remains suboptimal. In this study, we aimed to determine the relative importance of different presenting characteristics that are associated with CD. In doing so, we endeavoured to identify a case-finding strategy that can increase the detection of CD.

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1590-8658/$36.00
http://dx.doi.org/10.1016/j.dld.2013.08.127

2. Materials and methods

This was a multicentre, prospective study of patients in the South Yorkshire area (UK). All patients referred to the clinics of participating consultants within the South Yorkshire Luminal Gastroenterology Research Group (SYLGRG) for a gastroenterology opinion between January 2008 and December 2010 were invited to take part in the study. In the South Yorkshire region, there are 4 hospitals which includes the Royal Hallamshire Hospital, Northern General Hospital, Rotherham District General Hospital and Chesterfield and North Derbyshire Royal Hospital with a total catchment population of about 2,000,000. Each gastroenterology department sees in the region of 3000 new patients per year.

All patients attending unselected gastroenterology clinics were investigated for CD with anti-endomysial (EMA), anti-tissue transglutaminase (tTG) antibodies or a combination of the 2 tests depending on the protocols of the individual trusts. Patients were recruited consecutively and no patients declined to take part in the study. As EMA and tTG are both immunoglobulin A (IgA) based tests all patients also had their total IgA levels measured in line with local policy to rule out the possibility of deficiency leading to a false negative result. EMA was detected using direct immunofluorescence on primate oesophagus sections (Binding Site, Birmingham, UK). tTG were measured using commercially available enzyme linked immunosorbent assay kits (Aesku Diagnostics, Wendelsheim, Germany). A tTG titre of greater than 15 U/ml was regarded as positive. Total IgA was measured on a Behring BN2 nephelometer. Patients with IgA levels below the manufacturer's recommended lower range were regarded as having evidence of IgA deficiency.

Reason for referral, demographic data and co morbidities were noted at the time of referral. All patients with a positive tTG or EMA and patients with evidence of total IgA deficiency were offered duodenal biopsy. Duodenal biopsies were reviewed locally by gastrointestinal histopathologists. All biopsies were classified according to the Marsh criteria for CD. A diagnosis of CD was made on the basis of positive serology and histology comprising of elevated intra-epithelial lymphocytes, crypt hyperplasia and villous atrophy (Marsh grades 3a–3c). In those patients with evidence of villous atrophy (Marsh 3a–3c) but negative serological tests corroborative evidence of CD was sought (HLA, family history, histological improvement on GFD etc.).

2.1. Statistical analysis

The prevalence of CD within populations of patients in whom each presenting complaint and associated condition either was or was not present was calculated. A chi square test was then applied to assess the difference between these two groups and odds ratios were calculated. Multivariate regression analysis was then used to identify associated conditions and presenting complaints that were most significantly independently associated with a positive diagnosis of CD. The prevalence of CD in each group was also compared to our previous general practice cohort [16] to give an accurate estimation of the relevance of symptoms in the community. All statistical calculations were performed using SPSS (IBM) and all *P* values are 2 sided.

3. Results

A total of 4089 patients were prospectively recruited from the gastroenterology outpatient departments of the hospitals in the SYLGRG. The mean age of the population was 55.8 ± 18.2 years, range 16–99 and 1697 (41.5%) of patients referred were male; 3656 patients (89.4%) were found to be antibody negative and 2246 of these sero-negative patients underwent an endoscopy, either because of a high clinical suspicion of CD or for an alternative indication. Overall 1430 patients were not biopsied as negative serology was felt sufficient to exclude a diagnosis of CD and there was no other indication for an upper GI endoscopy. In total, 386 patients had a positive serological test: 14 were positive for EMA alone, 248 for tTG alone and 124 were positive for both EMA and tTG. A total of 129 patients were diagnosed with CD, giving a prevalence of CD within our cohort of 3.2% (2.7–3.8). The mean age of patients diagnosed with CD was significantly lower than those who did not have CD, 49.7 ± 3.0 (SD 17.0) vs. 56.0 ± 0.6) (SD 18.2) ($p = 0.0001$). Of the coeliac cohort 65.1% (84/129) were female compared to 58.2% (2308/3960) of the non-coeliac cohort. The sensitivity and specificity for EMA alone were 69.8% (61.0–77.4) and 98.2% (97.6–98.7), respectively. The sensitivity and specificity for tTG were 79.8% (61.7–86.1) and 91.4% (90.2–92.4), respectively. The combined EMA and tTG approach resulted in the best outcome for serological testing with a sensitivity of 78.1% (69.2–85.1), specificity 98.5% (98.0–99.0), positive predictive value 73.6% (64.6–81.0) and a negative predictive value of 98.9% (98.3–99.3).

The prevalence of coeliac disease, with associated odds ratios for associated conditions and presenting complaints are shown in Table 1. Unsurprisingly the presenting complaints that were most significantly associated with the presence of CD were those who had been referred for a gastrointestinal opinion based on the presence of positive coeliac serology or the need for a small bowel biopsy with odds ratios (OR) of 21.7 (14.2–33.3) and 3.8 (2.2–6.6), respectively. The presence of anaemia OR 2.0 (1.3–2.9), a history of autoimmunity OR 2.0 (1.0–4.3), osteoporosis OR 4.9 (1.4–16.9) and a family history of CD OR 11.9 (4.9–28.8) were also positively associated with the diagnosis of CD.

Interestingly, symptoms such as abdominal pain and bloating or symptoms of irritable bowel syndrome (IBS) that are commonly seen in CD were seen more commonly in patients without a diagnosis of CD with the symptoms of abdominal pain and reflux being significantly negatively associated with a positive diagnosis of CD with odds ratios of 0.4 (0.2–0.7) and 0.3 (0.1–0.9), respectively. However, when compared to our general population reference cohort patients with diarrhoea, IBS symptoms and weight loss were significantly more likely to be diagnosed with CD with ORs of 4.1 (2.0–8.3) 3.2 (1.4–7.1) and 2.7 (1.2–6.2), respectively. Although CD was more prevalent in patients with abdominal pain compared to the general population OR 1.6 (0.8–3.3) this didn't achieve

Table 1
Prevalence of coeliac disease for presenting complaints and associated conditions. Odds ratios for diagnosis of coeliac disease compared to other patients referred to secondary care.

Presenting complaint	*N* (%)	Coeliac disease prevalence % (95% CI)	OR for the presence of CD in secondary care (95% CI)	*p*-Value
Anaemia	676 (16.5)	5.3 (3.9–7.3)	2.0 (1.3–2.9)	0.0004
Diarrhoea	601 (14.7)	4.0 (2.7–5.9)	1.3 (0.9–2.1)	0.2
Irritable bowel syndrome symptoms	416 (10.2)	3.1 (1.6–5.0)	1.0 (0.6–1.8)	1.0
Weight loss	445 (10.9)	2.7 (1.5–4.7)	0.8 (0.5–1.5)	0.6
Dyspepsia	417 (10.2)	1.9 (0.9–3.8)	0.6 (0.3–1.2)	0.1
Abdo pain	1135 (27.8)	1.6 (0.9–2.5)	0.4 (0.2–0.7)	0.0004