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Alimentary Tract

Increased rate of abdominal surgery both before and after diagnosis of celiac disease

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ABSTRACT

Background: The detection of celiac disease (CD) is suboptimal.
Aims: We hypothesized that misdiagnosis is leading to diagnostic delays, and examine this assertion by determining if patients have increased risk of abdominal surgery before CD diagnosis.
Methods: Through biopsy reports from Sweden's 28 pathology departments we identified all individuals with CD (Marsh stage 3; n = 29,096). Using hospital-based data on inpatient and outpatient surgery recorded in the Swedish Patient Register, we compared abdominal surgery (appendectomy, laparotomy, biliary tract surgery, and uterine surgery) with that in 144,522 controls matched for age, sex, county and calendar year. Conditional logistic regression estimated odds ratios (ORs).
Results: 4064 (14.0%) individuals with CD and 15,760 (10.9%) controls had a record of earlier abdominal surgery (OR = 1.36, 95% CI = 1.31–1.42). Risk estimates were highest in the first year after surgery (OR = 2.00; 95% CI = 1.79–2.22). Appendectomy, laparotomy, biliary tract surgery, and uterine surgery were all associated with having a later CD diagnosis. Of note, abdominal surgery was also more common after CD diagnosis (hazard ratio = 1.34; 95% CI = 1.29–1.39).
Conclusions: There is an increased risk of abdominal surgery both before and after CD diagnosis. Surgical complications associated with CD may best explain these outcomes. Medical nihilism and lack of CD awareness may be contributing to outcomes.

1. Introduction

Celiac disease (CD) is an immune mediated small bowel enteropathy, which affects 1 in 100 people [1,2]. It occurs in genetically susceptible individuals and is triggered by gluten, which is a protein found in wheat, barley and rye. The commonest age for diagnosis is between 40 and 60 years old, however it can occur at any age, with women 1.5–2 times more likely to develop the condition than men [3]. Diagnostic delays in CD have been widely reported, ranging between 10 and 13 years from symptom onset to diagnosis [4–8]. Recent reports from Finland, Sweden and the UK suggest these diagnostic delays are improving [4,9,10]. This is supported by improvements in CD detection, with the ratio of clinically diagnosed CD cases to undetected cases improving in the UK from 1 in 8 in 1999 to 1 in 4 in 2011 [11,12]. Although these findings are encouraging they are not universal, with data from the Canadian Celiac Health Survey showing no improvements in diagnostic delays over recent years [13].

These diagnostic delays can have significant consequences to patients. Individuals with CD have increased healthcare costs, higher usage rates of healthcare services and use more drugs before having a diagnosis of CD [14–16]. Health related quality of life (HRQoL) can also be affected, with a recent study from Sweden showing HRQoL in undiagnosed patients to be comparable to that of stroke patients [4,10]. Delays in diagnosis may also influence morbidity, and potentiate the development of celiac-related com-

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plications [6,17–20], however overall mortality does not appear to be influenced [21].

The protean clinical manifestations of CD may be responsible for the delays in diagnosis. Patients with CD can present to varying healthcare professionals, with an array of clinical symptoms and signs. These include gastrointestinal symptoms, weight loss, anemia, reduced bone mineral density, or in association with other autoimmune diseases [1]. Other individuals may present more insidiously for example with ataxia, or peripheral neuropathy or could be asymptomatic, having been identified through screening of high-risk population groups [22]. These diverse presentations create diagnostic challenges to clinicians, which could be influencing CD detection rates.

Alternative reasons as to why CD detection rates remain low are that clinicians do not consider the diagnosis of CD or ignore the diagnosis (medical nihilism). Collectively, this could be termed diagnostic inertia, which is a derivation of clinical inertia where a patient fulfills the diagnostic criteria for a particular disorder, but is not diagnosed by their physician as having the disorder [23,24]. Diagnostic inertia in CD has been shown to exist in both primary and secondary care settings [7,25]. The type of clinician the patient encounters also influences diagnostic outcomes, with gastroenterologists and more experienced physicians more likely to consider and diagnose CD [6,7,26]. Diagnostic inertia in CD has implications to patients, culminating in misdiagnosis, unnecessary interventions and potentially the prescription of inappropriate medications [5,27].

These concerns lead to our hypothesis that patients with CD have higher rates of abdominal surgery before their CD diagnosis as a consequence of diagnostic inertia. Our hypothesis is tested in this large population-based study by examining abdominal surgery and the risk of having a later diagnosis of CD.

2. Materials and methods

Through Sweden's 28 pathology departments we obtained data on CD through small intestinal biopsies with villus atrophy (Marsh III). We then used the Swedish personal identity number [28] to link biopsy data to surgery recorded in the Swedish Patient Register [29].

2.1. Exposure—surgery

We defined abdominal surgery as either of laparotomy, appendectomy, biliary tract surgery or uterine surgery according to relevant international classification of disease (ICD) code in the Swedish Patient Register (see Appendix in Supplementary material). We did not include uterine surgery that was specifically carried out for infertility reasons, as it has been suggested that patients with CD have a decreased fertility [30], although this has been debated [31]. We have previously examined CD and appendectomy [32], but that paper was restricted to individuals with an inpatient diagnosis with CD, and we have since found that risk estimates based on biopsy data on CD can be substantially different [33,34].

The Swedish Patient Register started in 1964. It became nationwide in 1987, adding day-surgery data in 1997, and hospital-based outpatient care in 2001. The positive predictive value of most diagnoses in this registry is between 85% and 95% [29].

2.2. Outcome measure—celiac disease

IT personnel at Sweden's 28 pathology departments identified individuals with small intestinal villus atrophy (VA; histopathology stage Marsh 3 [35]) from computerized biopsy reports. The data collection took place in 2006–2008 but the biopsies themselves had been performed in 1969–2008. Data on personal identity number, topography (duodenum and jejunum), morphology (according to SnoMed histopathology codes, for a list see our earlier publication [36]), and date of biopsy were delivered to the researchers. We then reviewed the patient charts of 114 randomly selected individuals with VA and 108 (95%) had CD. The biopsy reports were based on average of three tissue specimen [37], which should, according to Pais et al., detect 95% of all CD [38]. Throughout the study period, biopsy was requested for CD diagnosis in Sweden.

2.3. Controls

Each patient with CD was matched with up to five controls by *Statistics Sweden* using the Swedish Total population register [39]. Matching criteria were sex, age, county, and calendar year. Removal of data irregularities and duplicates left us with 29,096 individuals with CD and 144,522 matched controls, i.e., an identical data-set as in our earlier paper on mortality in CD [40].

2.4. Statistics

We calculated odds ratios (ORs) for later CD in patients undergoing abdominal surgery using conditional logistic regression (thereby comparing strata with one CD patients and his/her matched controls). Through the conditional approach we automatically considered age, sex, county and calendar year. Of note, uterine surgery calculations were only performed in women (18,005 with CD and 89,544 controls).

A priori we decided to examine the association between abdominal surgery (and its components) according to age at CD ($\leq$19 years; 20–39 years; 40–59 years; $\geq$60 years), sex, and calendar period (1997–2004; 2005–2008). We also examined the risk of CD according to time since abdominal surgery (<1, 1–4, and $\geq$5 years). In a separate analysis we adjusted for country of birth (Nordic vs. not Nordic) and education using four a priori-defined categories [41]. Four percent of study participants lacked data on education and were fitted into a separate fifth category in the multivariate analysis.

Finally we examined the temporal relationship between abdominal surgery and CD and used Cox regression to calculate the risk of abdominal surgery *after* CD. This analysis was based on individuals without a prior record of abdominal surgery at date of CD diagnosis (and corresponding date in matched controls): CD: n = 25,030; controls: n = 120,610.

We used SPSS 22 (SPSS, Inc., Chicago, IL, USA) for the statistics. ORs with 95% confidence intervals that did not include one were regarded as statistically significant.

2.5. Ethics

Our study was approved by the Ethics Review board of Stockholm, Sweden. According to the board's decision no study participant was contacted as the study is strictly register-based [42].

3. Results

3.1. Background data

Almost two thirds of our study participants were female (Table 1), and some 41% had received their diagnosis in childhood (Table 1). The median year of CD diagnosis (and entry year of study for the participants) was 1998 (range: 1969–2008). The median age at CD diagnosis was 30 years (range: 0–95). More than 90% of the study participants were born in the Nordic countries.