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Increased rate of abdominal surgery both before and after diagnosis of Celiac Disease

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Abbreviations: CD, Celiac disease; CI, Confidence Interval; OR, Odds Ratio; VA, Villous atrophy

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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: 4,064 (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.

Keywords: appendix, autoimmunity, celiac, gall bladder, inflammation, surgery

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 to 2 times more likely to develop the condition than men.[3] Diagnostic delays in CD have been widely reported, ranging between 10-13 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 complications [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, anaemia, 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 fulfils 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.

MATERIALS AND METHODS

Through Sweden's 28 pathology departments we obtained data on CD through small intestinal biopsies with villous 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]

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). 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]

Outcome measure - Celiac disease

IT personnel at Sweden's 28 pathology departments identified individuals with small intestinal villous atrophy (VA; histopathology stage Marsh 3 [35]) from computerized biopsy reports. The data collection took place in 2006-08 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.

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]

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 (≤19 years; 20-39 years; 40-59 years; ≥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 ≥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.

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]

RESULTS

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.

Main findings

Of 29,096 individuals with CD, 4,064 (14.0%) had undergone abdominal surgery prior to celiac diagnosis, compared to 15,760/144,522 (10.9%) of matched controls. This corresponded to an OR of 1.36 (95%CI=1.31-1.42). Adding level of education and country of origin to our model did not influence our risk estimates (1.35; 1.30-1.40). CD was more common in the first year after abdominal surgery (OR=2.00; 95%CI=1.79-2.22), than after 1-4 years (OR=1.31; 95%CI=1.22-1.42) or after 5 years or more (OR=1.23; 95%CI=1.18-1.29).

Stratified analyses found increased risk of CD after abdominal surgery in both males and females, in all age groups and in all calendar periods although risk estimates varied (results and interaction tests are presented in Table 2).

Specific conditions

A laparotomy was associated with a 58% increased risk of later CD (95% CI 1.48-1.69). Similarly we found a positive association also with appendectomy (1.42; 1.34-1.50), biliary tract surgery (1.26; 1.18-1.34) and uterine surgery (1.13; 1.06-1.21) and later CD. Results of stratified analyses for the above conditions are presented in Table 3. Final diagnosis after undergoing surgery was assessed in a post-hoc analysis using relevant ICD codes, where the proportion of appendicitis, cholecystitis and uterine myoma was explored in those having inpatient appendectomy, biliary surgery and uterine surgery respectively. Restrictions were made to only inpatient diagnoses, as the Patient Register did not include both outpatient procedure codes and diagnostic codes before 2001. For all these surgical procedures, patients with CD were less likely to have appendicitis ($p=0.001$), cholecystitis ($p<0.001$) and uterine myoma ($p<0.001$) at surgery than controls.

Prospective analysis

In order to examine the temporal relationship between abdominal surgery and CD we also carried out a Cox regression on CD and future risk of abdominal surgery. In this analysis we compared 25,030 CD patients and 120,610 matched controls without a record of abdominal surgery prior to CD diagnosis (and corresponding date in matched controls). 3536 (14.1%) of CD patients vs. 13,279 (11.0%) controls had later abdominal surgery corresponding to a Hazard ratio of 1.34 (95%CI=1.29-1.39).

DISCUSSION

In this large nationwide case-control study we demonstrate that patients with CD have an increased risk of abdominal surgery both before and after diagnosis of CD, compared to sex and age-matched controls. The highest ORs for developing CD were seen just after abdominal surgery. The most plausible explanation is that abdominal surgery occurs as a complication to both undiagnosed and diagnosed CD. This notion is supported by some recent work evaluating 512 CD patients where 36% of CD patients had operative interventions, of which 12% were directly for CD related problems (e.g. dysmotility, pain, malignancy).[43]

An alternative explanation for the increased surgical rates before CD diagnosis may be misdiagnosis. Misdiagnosis is recognized and frequent in celiac patients.[44] Although biliary disorders have been described in the context of CD, possibly needing surgical intervention, it is possible that the misdiagnosis of abdominal pain and iron-deficiency anaemia culminated in inappropriate abdominal surgical interventions such as appendectomy and laparotomy.[45] The lack of histological outcomes from the surgically removed specimens in our cohort does limit our ability to establish definitively whether misdiagnosis occurred, however the frequency of normal pathological specimens following surgical removal has previously been described, with 25.7% (64/249) of patients in a recent study having a normal appendix following appendectomy for suspected appendicitis.[46] Our assessment of final diagnoses in inpatients after surgery would also support our assumptions of misdiagnosis. Review of this data permitted calculations of absolute risk differences between CD patients and controls, suggesting that 1 in 24 appendectomies, 1 in 11 biliary surgeries and 1 in 16 uterine surgeries may be occurring due to unawareness of CD and its symptoms. These findings collectively support the potential of diagnostic inertia occurring in CD, contributing to identified diagnostic delays.

This study has several strengths, including its population-based design and the independent ascertainment of cases from national health registers. The Swedish National Patient Register has been validated repeatedly, and the majority of diagnoses have a high positive predictive value (85–95%).[29] Furthermore, CD was identified through biopsy records showing villous atrophy. During the study period, biopsy remained the gold standard for diagnosis in both children and adults, and ≥96% of all pediatricians and gastroenterologists in Sweden reported performing a small intestinal biopsy before diagnosis.[36] A patient chart review found that 95% of all samples with villous atrophy represented CD, a higher positive predictive value than physician-assigned diagnosis for CD in the Swedish National Patient register.[47] In addition, villous atrophy in Sweden is rarely explained by diagnoses other than CD (0.3% of individuals with villous atrophy had inflammatory bowel disease).[36] Although positive CD serology was not included within the definition of CD, it has been demonstrated that 88% of those with available CD serology data have positive antibodies at the time of first biopsy.[36]

Limitations to this work are that the Swedish Patients Registry does not include individual-based data on symptoms. This means that we are unable to accurately decipher symptoms of undiagnosed CD patients at the time of a surgery, which could enhance our assertion of diagnostic inertia. A previous subset analysis of CD patients within our biopsy database suggests diarrhea (36%) and anemia (35%) are the most common clinical characteristics seen at the time of diagnosis. Given that risk of CD is highest within 1 year of abdominal surgery, it is highly likely that undiagnosed CD patients are presenting to surgical teams with ‘classical CD’ symptoms.

This study compares favourably to a previous study demonstrating increased surgical risk in undiagnosed CD patients (n=476).[48] Our current study is significantly larger than that previous work, helping to establish high statistical precision and calculation of important subanalyses,

including stratified analyses according to sex, age and calendar period of CD diagnosis. Our work also draws comparisons to work in inflammatory bowel disease, with a recent study from China highlighting increased rates of abdominal surgery before the diagnosis of Crohn's disease.[49]

As undiagnosed CD is common and misdiagnosis frequent, our findings should provide the impetus for enhanced CD testing in patients with abdominal symptoms. Previous work has suggested that undiagnosed CD patients presenting with surgical abdominal pain are being missed.[50] Furthermore, this association is recognized in patients labelled with Irritable Bowel Syndrome.[51] We suggest that if a patient is considered not to have acute abdominal pain warranting surgical intervention, this should alert clinicians to consider the diagnosis of CD. The use of a celiac serology is cheap and minimally invasive compared to the potential costs of surgery, which are both psychological and financial (e.g. median cholecystectomy cost = $15,651 (13,787 EUR).[52] Through recognizing or questioning for celiac associated symptoms in this group of patients the detection of CD could be improved.

In conclusion this is the largest study to date showing that patients with CD have increased rates of abdominal surgery both before and after CD diagnosis. Although CD is likely to be associated with surgical complications, our work emphasizes the need for clinicians to be mindful of the protean manifestations of CD. This could help improve detection, reduce unnecessary medical interventions and ease psychological burden to CD patients.

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411 **Table 1** Characteristics of study participants

412 **Table 2.** Abdominal surgery and risk of later Celiac disease

413 **Table 3.** Subanalyses: Abdominal surgery and risk of later Celiac disease.

414 APPENDIX – online only supplement

415