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Alimentary Tract

Nationwide population-based cohort study of celiac disease and risk of Ehlers-Danlos syndrome and joint hypermobility syndrome

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ABSTRACT

Background: Patients with celiac disease (CD) often have articular complaints, and small prior studies suggest an association with Ehlers-Danlos syndrome (EDS)/joint hypermobility syndrome (JHS).
Aims: This study examines the risks of EDS/JHS in patients with CD.
Methods: This cohort study compared all individuals in Sweden diagnosed with CD based on small intestinal biopsy between 1969–2008 (n = 28,631) to 139,832 matched reference individuals, and to a second reference group undergoing biopsy without having CD (n = 16,104). Rates of EDS/JHS were determined based on diagnostic codes in the Swedish Patient Register. Hazard ratios (HRs) for EDS/JHS were estimated through Cox regression.
Results: There are 45 and 148 cases of EDS/JHS in patients with CD and reference individuals, respectively. This corresponds to a 49% increased risk of EDS/JHS in CD (95%CI = 1.07–2.07). The HR for EDS was 2.43 (95%CI = 1.20–4.91) and for JHS 1.34 (95%CI = 0.93–1.95). Compared to reference individuals undergoing intestinal biopsy, CD was not a risk factor for EDS/JHS. A stronger association was seen in patients initially diagnosed with EDS/JHS and subsequently diagnosed with CD (odds ratio = 2.29; 95%CI = 1.21–4.34).
Conclusions: Individuals with CD have higher risk of EDS/JHS than the general population, which may be due to surveillance bias or factors intrinsic to celiac development.

1. Introduction

Celiac disease (CD) is an immune-mediated disease [1] triggered by exposure to gluten in genetically predisposed individuals [2]. It occurs in both children and adults, and until now the only available treatment consists of a gluten-free diet.

CD has been linked to a number of disorders including lymphoproliferative disorders [3], endocrine disease [4], and fatty liver disease [5]. Of particular interest is the link between CD, connective tissue disorders [6] and rheumatoid arthritis [7], with the latter two disorders sharing background genetics [8]. In addition, both peripheral and central arthritis as well as various musculoskeletal symptoms occur in those with CD [9–11].

Ehlers-Danlos syndrome (EDS) is a genetic disorder caused by defective collagen, the main component of connective tissue [12]. EDS is an important variant of joint hypermobility syndrome (JHS) [13,14]. The most obvious symptoms in these disorders are hypermobile joints and hyperextensive skin, but they may involve any organ systems relying on well-functioning collagen [12]. The involvement of connective tissue may have implications for both structural and functional gastrointestinal disease [15]. Past research has shown that symptoms such as abdominal pain, bloating, nausea, reflux, dysphasia, vomiting, and constipation are common in EDS/JHS patients [15,16]. In addition, EDS/JHS has been associated with a number of distinct gastrointestinal disorders, including dyspepsia and gastroesophageal reflux, irritable bowel syndrome, functional constipation, slow transit constipation [17], faecal incontinence [18], delayed gastric emptying [16] and Crohn's disease [19].

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Research on CD and disorders with dysfunctional collagen is, however, sparse. In fact, we are only aware of two publications attempting to systematically evaluate the association between CD and EDS/JHS [20,21]. The authors suggest that EDS/JHS may be 10–20 times more common in CD than in the general population [21]. Despite these findings, screening for CD is not generally recommended in EDS/JHS but is restricted to patients with either concomitant irritable bowel syndrome or significant pain or fatigue [22].

In this nationwide population-based study, we examined the future risk of EDS and JHS in more than 29,000 individuals with CD. Given the high prevalence of JHS among patients with diagnosed gastrointestinal disease, we also determined the odds ratio of having EDS/JHS prior to the CD diagnosis.

2. Methods

We linked data on biopsy-verified CD to data on EDS/JHS retrieved from the Swedish Patient Register [23].

2.1. Celiac disease (CD)

Through Sweden's 28 pathology departments we collected all data on small intestinal biopsies carried out from 1969 to 2008. We retrieved data on topography (duodenum and jejunum), date of biopsy, morphology codes, and personal identity number to allow for linkage with other registries [24]. The data collection has been described in detail before [25], and in the current study we used the same dataset as in our earlier paper on mortality in CD ($n = 29{,}096$ patients) [26].

2.2. Controls

For each patient with CD, the government agency Statistics Sweden matched up to five reference individuals with the same birth year, age, sex and county of residence ($n = 144{,}522$). In a sensitivity analysis we compared individuals with CD to patients undergoing a biopsy but not having villous atrophy (secondary controls: $n = 16{,}104$). These individuals have been described before [25–27] and while some had intestinal pathology corresponding to a Marsh score of 0, most had pathology corresponding to Marsh score I–II. Due to our study design, we restricted our study to individuals with a follow-up until at least the year 1997 (see below).

2.3. EDS and JHS

We defined EDS as having a relevant international classification of disease (ICD-10) code in the Swedish Patient Register: Q79.6. We also examined JHS (ICD-10: M35.7). The Patient Register in Sweden began in 1964 and became nationwide in 1987. However, specific codes for EDS and JHS were only introduced in Swedish healthcare in 1997 with the introduction of ICD-10 (as opposed to ICD-9 which was used in Sweden between 1987 and 1996).

2.4. Other co-variates

Through Statistics Sweden we retrieved data on a number of potential confounders: country of birth (Nordic vs. not Nordic), level of education, and socioeconomic status. We divided education into four pre-specified groups (≤9 years of primary school, 2 years of high school, 3–4 years of high school, college/university), while socioeconomic status was divided into six categories (according to the European Socioeconomic Classification, ESeC: levels 1, 2, 3 + 6, 7, 8, and 9) (for additional details see Olén et al. [28]). Data on education and socioeconomic status were missing in 750 (2.6%) and 8207 (28.9%) individuals with CD, respectively, with similar proportions in reference individuals. Individuals with missing data were fitted into separate categories when performing the statistical analyses.

We chose not to adjust our analyses for type 1 diabetes and autoimmune thyroid disease. Although these disorders have been linked to CD, they have not been convincingly linked to EDS/JHS and are therefore unlikely confounders.

2.5. Statistical analyses

To estimate relative risks of EDS/JHS we carried out internally stratified Cox regressions estimating hazard ratios (HRs). Internally stratified Cox regression resembles conditional logistic regression in that it compares each stratum of patients (one celiac patient and his/her reference individuals) before calculating a summary estimate (the HR we present in our paper). The proportional hazards assumption was tested through inspection of log minus log curves. We also calculated the attributable risk proportion (the percentage of all EDS/JHS in CD patients that can be explained by underlying CD) using the formula (1-1/HR).

Follow-up in our Cox regressions started with the first biopsy showing CD in patients, and on the corresponding date in matched controls. It ended on the date of the first EDS/JHS diagnosis, date of emigration, date of death or the date December 31, 2009, whichever came first. We a priori agreed on the following sub-analyses: risk of EDS/JHS overall, and risk according to sex, age at CD diagnosis, and calendar period. Furthermore, we examined the risk of EDS/JHS after adjusting for level of education and socioeconomic status. We also calculated the risk of EDS and JHS separately.

To examine the potential influence of the severity of mucosal lesions in CD and of surveillance bias, we carried out an additional analysis using biopsied individuals whose reports showed minor or no abnormalities (Marsh 0-II), but no villous atrophy, as reference. As these secondary controls were not matched to the CD patients, we adjusted this Cox regression for age, sex, and calendar period.

Finally, to investigate the temporal pattern in CD and EDS/JHS we also calculated odds ratios for EDS/JHS prior to CD diagnosis using conditional logistic regression. This analysis was based on the 29,096 individuals with CD and their 144,522 reference individuals.

We used SPSS 22 to calculate statistics. p-Values <0.05 were considered statistically significant.

2.6. Ethics

This study was approved by the Regional Ethical Review Board in Stockholm (2006/633-31/4). Because this was a register-based study, no participant was contacted and all data were anonymized prior to data analyses.

3. Results

3.1. Background demographics

We identified 28,631 individuals with CD, 139,832 matched controls and 16,104 secondary controls. Almost two thirds of study participants were female (Table 1). Slightly more than 40% were children at CD diagnosis, and 87% were diagnosed since 1990. The median follow-up was ten years in both individuals with CD and in reference individuals. The age at end of follow-up was 41 and 40 years, respectively. Table 1 shows additional characteristics. The percentage of matching characteristics differed somewhat because we required that study participants had to be alive on Jan 1, 1997 to be included in the study, and this was not an initial condition when the study database was constructed.