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Coeliac disease and invasive pneumococcal disease: a population-based cohort study

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SUMMARY

Severe infections are recognized complications of coeliac disease (CD). In the present study we aimed to examine whether individuals with CD are at increased risk of invasive pneumococcal disease (IPD). To do so, we performed a population-based cohort study including 29 012 individuals with biopsy-proven CD identified through biopsy reports from all pathology departments in Sweden. Each individual with CD was matched with up to five controls ($n = 144$ 257). IPD events were identified through regional and national microbiological databases, including the National Surveillance System for Infectious Diseases. We used Cox regression analyses to estimate hazard ratios (HRs) for diagnosed IPD. A total of 207 individuals had a record of IPD whereas 45/29 012 had CD (0·15%) and 162/144 257 were controls (0·11%). This corresponded to a 46% increased risk for IPD [HR 1·46, 95% confidence interval (CI) 1·05–2·03]. The risk estimate was similar after adjustment for socioeconomic status, educational level and comorbidities, but then failed to attain statistical significance (adjusted HR 1·40, 95% CI 0·99–1·97). Nonetheless, our study shows a trend towards an increased risk for IPD in CD patients. The findings support results seen in earlier research and taking that into consideration individuals with CD may be considered for pneumococcal vaccination.

Key words: Coeliac disease, pneumococcal infection, pneumococci, septicaemia.

INTRODUCTION

Patients with coeliac disease (CD) have been suggested to be more susceptible to infectious diseases [1]. Hence individuals with CD are considered to be at increased

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risk for influenza requiring hospital care [2] and tuberculosis [3]. In addition, CD has been linked to sepsis [4], with a particularly high risk for sepsis caused by pneumococci [hazard ratio (HR) 3·9, 95% (CI) confidence interval 2·2–7·0] [5].

Several factors may contribute to this susceptibility including an increased intestinal permeability [6] and hyposplenism (hypofunction of the spleen with or without atrophy) in CD [7].

Streptococcus pneumoniae (pneumococcus) is a Gram-positive encapsulated bacterium. This widespread pathogen is one of the most common causes of bacterial respiratory tract infections [8] including otitis media, especially in children [9], but pneumococci are also a common cause of life-threatening disorders such as sepsis and meningitis [8, 10].

Considering that several studies have demonstrated an increased risk of sepsis in CD [4, 5] and the fact that CD has been linked to hyposplenism, it is surprising that so far only one study has specifically examined the risk for invasive pneumococcal disease (IPD) in CD [11]. In the current Swedish study we examined the risk of IPD in more than 29 000 individuals with biopsy-verified CD compared to the general population. We hypothesized that individuals with CD would be at increased risk of IPD.

METHODS

Nationwide data from biopsy reports were used to identify individuals with CD. In a population-based cohort study these were matched to subjects without CD (controls) from the general population and thereafter linked with healthcare databases containing information on IPD. Linkage of all the databases was performed by the National Board for Health and Welfare to keep the data anonymous.

Study participants (coeliac individuals and controls)

Data on small intestinal biopsies were collected from all Swedish pathology departments ($n = 28$) during 2006–2008. The biopsies had been performed in 1969–2008, with a majority of patients undergoing biopsy in 1990 or later (Table 1). CD was defined as having villous atrophy (VA), which is equivalent to Marsh histopathology stage III. Local IT personnel at each pathology department collected the biopsy reports and delivered data on personal identity number, date of biopsy, topography and morphology according to the Swedish SnoMed classification (see Supplementary Table S1) to the research group. A positive CD serology was not required for a CD diagnosis; however, a previous validation of a random subset of individuals with biopsy-proven CD (VA) found that 88% of patients were serologically positive at the time of biopsy [12]. After data irregularities and duplicates were removed we identified 29 096 individuals with VA of whom 29 012 had a follow-up extending to 1987 or beyond and hence were included in the study.

Table 1. *Characteristics of study participants*

Characteristics	Controls, *n* (%)	Coeliac disease, *n* (%)
Total	1 44 257 (100)	29 012 (100)
Sex		
Male	54 835 (38)	11 040 (38·1)
Female	89 422 (62)	17 972 (61·9)
Age, years*		
0–19	58 818 (40·8)	11 796 (40·7)
20–39	26 368 (18·3)	5306 (18·3)
40–59	32 205 (22·3)	6457 (22·3)
⩾60	26 866 (18·6)	5453 (18·8)
Calendar year*		
1969–1989	20 142 (14)	4029 (13·9)
1990–1999	59 864 (41·5)	12 055 (41·6)
2000–2009	64 251 (44·5)	12 928 (44·6)
Country of birth		
Nordic	1 36 017 (94·3)	28 056 (96·7)
Not Nordic	8240 (5·7)	956 (3·3)
Comorbidity		
Diabetes†	595 (0·4)	954 (3·3)
Liver disease	4880 (3·4)	1524 (5·3)
End-stage renal disease	235 (0·2)	135 (0·5)
Asthma	6363 (4·4)	1935 (6·7)
Ischaemic heart disease	8322 (5·8)	2141 (7·4)

* At time of coeliac disease diagnosis.
† Diagnosed at age ⩽30 years.

The Swedish government agency, Statistics Sweden, thereafter matched each individual with up to five randomly selected controls from the Swedish Total Population Register (1 44 257 of these had a follow-up to 1987 or beyond). Matching criteria included age, sex, calendar year, county and the controls were not to have any prior record of small intestinal biopsy. Details on this data collection have been published elsewhere [12].

Demographic data

We obtained data on socioeconomic status (occupational data), educational level (a detailed description

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has been published elsewhere [13]) and country of birth from Statistics Sweden (the Swedish government agency responsible for producing official statistics). Information from the different databases were linked using the Swedish personal identity number [14]. We did not have access to data on smoking or alcohol consumption.

Data on pneumococcal infections

We defined IPD as growth of *Streptococcus pneumoniae* in a culture from a normally sterile site [i.e. blood, cerebrospinal fluid (CSF), pleural effusion, pericardial fluid, or synovial fluid]. Outcome data were obtained from two sources (see below), and linked to our biopsy data through the personal identity number [14] a unique number assigned to all Swedish residents.

(i) Nationwide data from the Public Health Agency of Sweden. In Sweden, IPD has been a notifiable disease since 1 July 2004 and data on IPD are consecutively registered at the Public Health Agency of Sweden (formerly Swedish Institute for Infectious Disease Control). The reporting system includes both active reporting from clinicians as well as automatic reporting from all Sweden's microbiological laboratories resulting in an almost 100% coverage (from 2005 and onwards).
(ii) Data from Southern Sweden were obtained from computerized databases from the seven microbiological laboratories covering the area: Växjö (representing Kronoberg region) 1987–2004, Kalmar 1990–2004, Malmö (Skane region) 1990–2004, Kristianstad (Skane) 1991–2004, Lund (Skane) 1991–2004, Karlskrona (Blekinge region) 1994–2004 and Halmstad (Halland region) 1995–2004.

Statistics

Cox regression was used to estimate HRs for IPD in coeliac patients compared to controls. Proportional hazards assumption was verified using log-minus-log curves. Follow-up started with date of first biopsy (and equal date in matched controls). Follow-up ended at IPD (positive culture), death, emigration or end of study (31 December 2009), whichever occurred first. HRs were adjusted for level of education, socioeconomic status, country of birth and in a separate analysis also for several possible confounding comorbidities. Diabetes has a strong association with CD [15] and is also linked to IPD [16], while we considered diabetes to be a potential major confounder. We also adjusted for liver disease, end-stage renal disease, asthma and ischaemic heart disease (defined according to relevant ICD codes), conditions which are all linked with CD [17–20] as well as with IPD [16, 21, 22]. Since each individual with CD was compared to his/her matched controls, matching variables were automatically considered (in this regard our analysis resembled a conditional logistic regression). Follow-up specific HRs for IPD (<1 year, 1–4·99 years and ⩾5 years) were calculated. In addition we performed *a priori*-defined sub-analyses stratifying for age, sex and calendar period (1969–1989, 1990–1999, 2000–2009) at CD diagnosis. The statistical significance of difference in risk estimates between strata was tested with formal interaction tests. In a final analysis we also restricted our study population to include only individuals diagnosed with CD (and IPD) 1994 or later (the year when the IPD database from southern Sweden became complete) and also to individuals diagnosed 2004 and beyond (the year when IPD became a notifiable disease).

We used SPSS v. 22 (IBM Corp., USA) for all analyses. HRs with a 95% CI not including 1 and $P < 0{\cdot}05$ were considered statistically significant.

Ethical approval

This study was approved by the Stockholm Ethics Review Board (2006/633–31/4). Since data were strictly register-based no individual consent was required.

RESULTS

The median age at IPD diagnosis was 62·3 years in the CD group and 68·7 years in the control group. The mean follow-up time (i.e. duration from CD diagnosis to IPD) was 10·5 years in individuals with CD and 11·6 years in the control group. Nearly all the IPD cases had bacterial growth in blood and only a few in CSF and other sites. Additional details of the study participants are presented in Table 1.

Out of 1 73 269 study participants, 207 had a record of IPD. The proportion of patients with IPD was higher in the CD group (45/29 012, 0·15%) than in controls (162/1 44 257, 0·11%). Hence the HR for encountering IPD was 1·46 in the CD group compared to the general population (95% CI 1·05–2·03).

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Table 2. *Risk of IPD based on follow-up time in individuals with coeliac disease*

Follow-up	Observed events	Expected events	HR (95% CI)	*P* value	Attributable percentage*
All	45	31	1·46 (1·05–2·03)	0·025	32
Year <1	1	2	0·58 (0·08–4·52)	0·61	−72
Year 1–4·99	10	4	2·25 (1·08–4·70)	0·03	56
Year ⩾5	34	25	1·38 (0·94–2·01)	0·10	27

IPD, Invasive pneumococcal disease; HR, hazard ratio; CI, confidence interval.
Reference is general population comparator cohort.
* Calculated as [1 – (1/HR)] × 100.

Table 3. *Risk of IPD in relation to characteristics of patients with coeliac disease*

Subgroup	Observed events	Expected events	HR (95% CI)	*P* value	Attributable percentage*
Sex					
Males	8	11	0·70 (0·33–1·47)	0·35	−43
Females	37	20	1·90 (1·30–2·76)	0·001	47
Age, years†					
<20	5	2	2·24 (0·79–6·37)	0·13	55
20–39	6	5	1·18 (0·49–2·85)	0·71	15
40–59	21	12	1·81 (1·11–2·96)	0·018	45
⩾60	13	12	1·08 (0·59–1·98)	0·81	7
Calendar period†					
1969–1989	8	6	1·31 (0·60–2·89)	0·50	24
1990–1999	22	14	1·55 (0·96–2·50)	0·07	36
2000–2008	15	11	1·42 (0·81–2·51)	0·22	30

IPD, Invasive pneumococcal disease; HR, hazard ratio; CI, confidence interval.
Reference is general comparator cohort.
* Calculated as [1 – (1/HR)] × 100.
† At coeliac disease diagnosis and corresponding age in controls.

Adjusting for education, economy and country of birth did not influence the risk estimate [adjusted hazard ratio (aHR) 1·48, 95% CI 1·06–2·07]. In a separate analysis where we also added type 1 diabetes, chronic liver disease, end-stage renal disease, asthma and ischaemic heart disease as covariates in our statistical model, the HR was 1·40 (95% CI 0·99–1·97)

To minimize the risk of missing IPD cases, in a separate analysis we also restricted the study population to individuals diagnosed with CD in 1994 or later (the year when the regional microbiological database became complete). Restricting study participants to the last two decades did, however, not influence our risk estimate for IPD more than marginally (aHR 1·58, 95% CI 1·05–2·37). We had also intended to examine the risk of IPD in coeliac patients diagnosed during 2004–2008 but due to lack of positive IPD cases we were unable to calculate any HRs.

The highest risk for IPD was seen 1–4·99 years after CD diagnosis (HR 2·25, 95% CI 1·08–4·70), with lower HRs both at 1 year and ⩾5 years follow-up (Table 2). The risks according to follow-up were not substantially influenced by comorbidities. The increased risk for IPD was mainly seen in women (HR 1·90, 95% CI 1·30–2·76) and a formal test for interaction revealed a statistically significant difference between sexes ($P = 0·017$). We found similar risk estimates in the different age groups (*P* for interaction = 0·2). Further data on risk of IPD in relation to characteristics (sex, age, calendar period) at CD diagnosis are summarized in Table 3.

DISCUSSION

In this large population-based cohort study we found a 46% increased risk of IPD in patients with CD (HR 1·46, 95% CI 1·05–2·03). The excess risk of IPD seen in our study is consistent with earlier reports of a positive association between CD and pneumococcal disease (in a British study, Thomas *et al.* found a

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twofold risk increase for IPD in CD [11] and in 2008 our group reported an almost fourfold increased risk for pneumococcal sepsis [5]). The slightly lower risk estimates in the current study might be due to our access to outpatient data while the British study as well as the earlier Swedish study were mainly limited to inpatients, patients potentially suffering from a more severe CD than the average patient. In addition, biopsy was mandatory for the diagnosis of CD in our study. Therefore, misclassification is minimized, since the diagnoses are based on biopsy report data. Likewise, our IPD diagnoses were based on positive cultures and not ICD codes, probably reducing the number of false positives. Furthermore, in the present study we have been able to adjust for diabetes as well as several other potentially confounding comorbidities, which was not done in the British study [11].

During the last 10 years the incidence of IPD in Sweden has varied between 12 and 19/100 000 person-years and most cases are aged >60 years [23]. IPD is a severe and potentially life-threatening condition. Taking that into account, we consider the almost 50% increased risk of IPD in individuals with CD in our study important. The attributable fraction of CD was as high as 32% (Table 2). Our results indicate that patients with CD are a risk group for pneumococcal disease and therefore CD patients may be considered for pneumococcal vaccination also in countries, which unlike the UK [24], do not yet recommend such vaccinations. However, due to herd immunity and serotype replacement, caused by pneumococcal vaccination in the childhood immunization programme introduced in Sweden in 2009, the potential serotype coverage of these vaccines in CD patients need to be addressed in future studies [25].

One of the most frequently suggested mechanisms explaining the elevated risk for infectious diseases in CD is CD-associated hyposplenism. Many researchers consider CD to be a major cause of splenic hypofunction or atrophy. However, the clinical significance of CD-associated hyposplenism is still not fully understood, but there is evidence suggesting that splenic atrophy can cause a deficiency of IgM memory B cells, which are crucial for the immunity against encapsulated bacteria [26, 27]. The prevalence of hyposplenism in CD varies between 19% and 80% and is highest in individuals with complicated CD or additional autoimmune diseases [28] and it is mainly seen in adults [29]. Studies are contradictory regarding whether this dysfunction is reversible or not [30, 31]. It is, however, believed by some authors that the hypofunction is reversible after introduction of a gluten-free diet but an atrophy of the spleen might remain [26]. Considering this possibility of improvement of spleen function we also calculated risks for IPD based on follow-up time (Table 2). However this sub-analysis reduced the study power and the confidence intervals for the IPD risk in our three *a priori*-defined follow-up periods overlapped and therefore we cannot state that the IPD excess risk really decreases over time.

The major strength of this study is its high validity. Both the CD and the IPD diagnoses are highly reliable. The CD diagnoses were based on biopsy reports showing VA, and small-intestinal biopsy was the gold standard for diagnosing CD during the whole study period. The histopathology examinations were carried out by a large number of pathologists. It was not possible to carry out an agreement rate for CD diagnosis between all these pathologists, but when representatives from the different pathology departments carried out a blinded test, 90% (95% CI 87–94) of the biopsies with VA (according to the national steering group of small intestinal pathology) were correctly classified [12]. Likewise, the IPD diagnoses are based on positive cultures and active as well as automatic reporting, minimizing the risk for misclassification. However, we cannot rule out that IPD cases have been missed (false negatives), especially since we only had access to regional data from the first part of the study period. Despite this, our study was large and had a long follow-up time during which we identified more than 200 IPD cases. This was sufficient to demonstrate a positive association with CD, but generally insufficient to confirm an IPD excess risk in sub-analyses. Another limitation is that we lacked information on actual hyposplenism. Splenic size and function are not routinely examined in patients with CD and therefore hyposplenism is not recorded in Swedish national registers. In addition, we did not have data on vaccination status. However, pneumococcal immunization was introduced in the Swedish national vaccine programme as late as 2009 [32] and has been recommended for elderly people (>65 years), since 1994 [33] but not routinely to individuals with CD so vaccinations are therefore unlikely to have affected our relative risks more than marginally. Smoking is considered to be a risk factor for IPD [34], but due to lack of smoking data we were unable to adjust for smoking. Given its neutral [35] or negative [36] association with CD smoking should not explain the positive association between CD and IPD. Likewise, we

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lack data on alcohol abuse; however, we have been able to adjust our risk estimate for socioeconomic status which might serve as a proxy for both these variables. Furthermore, other chronic illnesses than CD, such as diabetes, are known to influence the incidence of IPD [16, 22, 37]. Diabetes is common in individuals with CD [15] and since the risk for splenic hypofunction is increased in individuals with CD who also have additional autoimmune diseases [28] we chose to adjust for diabetes (as well as liver disease, end-stage renal disease, asthma and ischaemic heart disease, which are also linked to CD) in our analyses. This did not influence our risk estimates substantially; however, after adjustments the risk estimates just failed to reach statistical significance and diabetes is certainly an important risk factor for IPD.

In conclusion, this study found a moderately increased risk for IPD in individuals with CD. The positive association between CD and pneumococcal disease supports earlier findings in this field [11] and is consistent with current UK guidelines on CD [24]. Taken together this suggests that preventive pneumococcal vaccination may be considered in individuals with CD.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0950268816003204.

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DECLARATION OF INTEREST

None.

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