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Alimentary Tract

Risk of bacterial pneumonia and pneumococcal infection in youths with celiac disease — A population-based study

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ABSTRACT

Objective: Assess the risk of hospitalizations for bacterial pneumonia or pneumococcal infections, in a cohort of young individuals with celiac disease (CD) compared to matched references.
Study design: The cohort consists of 213,635 individuals, born in 1989–2012 and resident in Friuli-Venezia Giulia (Italy). Through pathology reports, hospital discharge records or co-payment exemptions, we identified 1294 CD patients and 6470 reference individuals matched by gender and birth year. We considered hospital admissions for first episodes of bacterial pneumonia and pneumococcal infections. Hazard ratios (HRs) for episodes after CD diagnosis were calculated with Cox regression and odds ratios (OR) for the ones before CD diagnosis with conditional logistic regression. Further analyses were performed on unvaccinated follow-up periods.
Results: 14 CD patients (in 9450 person-years) and 42 references (in 48,335 person-years) experienced a first episode of bacterial pneumonia, with an increased risk among CD patients (HR 1.82; 95%CI 0.98–3.35). Risks of bacterial pneumonia were significantly increased before CD diagnosis and especially the year before CD diagnosis (OR 6.00, 95%CI 1.83–19.66). Risks of pneumococcal infections showed a non-significant increase in CD patients.
Conclusions: CD children and youth showed an increased risk of bacterial pneumonia, especially in proximity to CD diagnosis. Anti-pneumococcal vaccination should be recommended to all young CD patients.

1. Introduction

Celiac disease (CD) is associated with hyposplenism and splenic atrophy, both possible risk factors for infection by *Streptococcus pneumoniae* [1]. *S. pneumoniae* is an encapsulated bacterium and can cause bacteremia, otitis media, meningitis and pneumonia. It is the main cause of severe pneumonia in children less than 5 years old [2].

Previous evidence suggests that almost one third of adult patients with CD have some evidence of splenic dysfunction which seems: (i) to improve on a gluten-free diet [3,4], (ii) to be more frequent in CD patients with associated autoimmune diseases and with CD complications (refractory CD, lymphoma, ulcerative jejunoileitis) [5], and (iii) not to affect *children* with CD [6].

We are not aware of any study focusing on the risk of pneumococcal infection, specifically in children with CD, while an increased risk of pneumococcal infection has been well described in adult CD patients, when compared to general population, especially if unvaccinated [7–10]. The British Society of Gastroenterology guidelines (2014) [11] recommend, in fact, vaccination against *S. pneumoniae* in CD patients.

The 7-valent pneumococcal conjugate vaccine (PCV7) has been available in Italy since 2001. Initially it was recommended exclusively for patients considered at high risk, including individuals with hyposplenism or asplenia. In 2003, this vaccination had been given to less than 3% of children aged 0–2 years and less than 10% of the groups at risk. In 2008, the vaccination coverage varied from 10% to 85% in different Italian regions. The 13-valent pneumococcal conjugate vaccine (PCV13) has only been available since 2010, but

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it is now recommended for all children (although vaccination is not compulsory) [12]. In the period 2010–2014, in Friuli-Venezia Giulia, the vaccination coverage, among children aged less than 2 years, has increased from 71.3% to 82.4% [13].

We aimed to study a large population-based birth cohort of CD children and young adults and matched reference individuals, using data from the linked and integrated epidemiological system of the Friuli-Venezia Giulia Region (Italy), in order to estimate risks of hospital admissions for any bacterial pneumonia, pneumococcal pneumonia and pneumococcal infection (including pneumococcal pneumonia as well as sepsis and meningitis) during childhood and adolescence in more than 1200 patients diagnosed with CD.

2. Methods

2.1. Study population

We examined 213,635 individuals (we first excluded abortions, stillbirths, and neonatal deaths≤30 days of age) born and residing in the region of Friuli-Venezia Giulia (FVG) (in northern Italy) between 1989 and 2012. Study participants were identified through the regional Medical Birth Register. This register contains information from all hospital and home deliveries in the region. The regional healthcare system in FVG was initiated in the 1980s and aims to collect and pool data on healthcare funded by the National Health Service (NHS). We have previously described this healthcare system [14].

In this study, we used the following health data (up to December 31, 2012): mortality records; pathology reports from all the pathology departments in the Region, coded in the Systematized Nomenclature of Medicine; hospital discharge records collected during episodes of inpatient care occurring within or outside the Region with up to 6 diagnostic codes in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); exemption from healthcare copayment coded in a national coding system; drug prescription records coded in the Anatomical Therapeutic Chemical (ATC) Classification System (available from 1995) and vaccination registry that has recorded vaccinations on an individual level since 1995.

2.2. Celiac disease identification

CD was defined as having at least one of the following [14]: a pathology report indicating villous atrophy (SnoMed codes D6218, M58, M58005, M58006, and M58007); a hospital discharge record (ICD9-CM code = 579.0); or CD-specific exemption from health-care copayment (code I0060) according to the national coding system in Italy. We used the earliest date identifiable for CD diagnosis as proxy for disease onset (information was retrieved from 3 sources: pathology, hospital admission and copayment exemption).

2.3. Pneumonia definition

"Bacterial pneumonia" was defined as having a hospital discharge record with a principal diagnosis (in order to exclude hospital-acquired pneumonia and because a principal diagnosis is likely to have a higher specificity than contributing diagnoses) (ICD9-CM code) of 481–483, 485–486 [15]. Pneumococcal pneumonia was defined in the same way, using ICD9-CM code (481) of pneumonia with the identification of *S. pneumoniae* as causal agent. A further analysis was conducted on pneumococcal infections, that included: pneumococcal pneumonia (ICD9-CM 481), pneumococcal sepsis (ICD9-CM 038.2) and pneumococcal meningitis (ICD9-CM 320.1), using a previously adopted definition [8].

In a sensitivity analyses we considered also secondary diagnoses of bacterial pneumonia in the hospital records.

For each individual, only the first infective event in life was considered.

2.4. Statistical analyses

For each patient with CD, we selected 5 reference individuals from the Medical Birth Register. Reference individuals had to be alive on the date when the matched index individual with CD had received his/her diagnosis and with same sex and birth year. Follow-up began on the date of CD diagnosis (and corresponding date in reference individuals, i.e. study entry) and lasted until the end of the study period (December 31, 2012), death, migration out of the area, or first hospital admission of any type of pneumococcal infection (and separately for each outcome). Only the first hospital admission for pneumonia in life was considered. In the prospective analysis, separately for each outcome analyses, we excluded individuals with previous hospital admission for pneumonia, pneumococcal pneumonia or pneumococcal infections prior to study entry (index date). Matched cox regression was used to estimate Hazard Ratios (HRs) and 95% confidence intervals (CI) for any bacterial pneumonia, pneumococcal pneumonia and pneumococcal infections subsequent to study entry. CD individuals were only compared to references within the same stratum and then a summary HR was calculated. The proportional hazards assumption was examined by studying graphs over the log cumulative hazards function and the Shoenfeld residuals and verified by a global test of rho. In a retrospective analysis, we carried out a conditional logistic regression to calculate odds ratios (ORs) for having a bacterial pneumonia, pneumococcal pneumonia or pneumococcal infections prior to index date. This means that we included incident cases of bacterial pneumonia before CD diagnosis (or index date in reference individuals) in this latter sensitivity analysis.

In sensitivity analyses we adjusted for maternal education (up to 8th grade; up to 13th grade; university). Further adjustments for the presence of autoimmune diseases (type I diabetes, autoimmune hypothyroidism, autoimmune hyperthyroidism) which have shown to have some correlation with CD [16] were conducted on individuals with index date dated 1995 or later, but the very small number of individuals with the abovementioned autoimmune conditions who had pneumonia precluded any statistical analysis.

Through the linkage of our cohort with the vaccination registry, all pneumococcal vaccinations were identified (keeping the date of the first vaccination). We restricted analysis to unvaccinated follow-up periods for CD individuals and their corresponding references: time preceding the date of pneumococcal vaccination, for vaccinated individuals and the entire follow-up time for unvaccinated individuals.

The analyses were also stratified by time periods between date of CD diagnosis (index date for matched reference individuals) and bacterial pneumonia for both retrospective and prospective analyses events occurred within 1 year before (≤1) and more than 1 year before diagnosis (>1); events occurred within 1 year after (≤1) and more than 1 year after diagnosis (>1).

Statistical analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

The study was approved by the Institutional Review Board of the University of Padua (Italy). Patient data were anonymized and de-identified prior to analysis. Therefore, no informed consent and no Ethics Committee approval were required.

3. Results

Table 1 shows the characteristics of the studied participants. Overall, 1294 CD individuals and 6470 matched references were included in the study. Biopsy confirmation was available for 920

Table 1
Characteristics of the study participants.

Characteristics	CD n (%)	References n (%)
Total	1294	6,470
Gender		
Male	504 (38.9)	2520 (38.9)
Female	790 (61.1)	3950 (61.1)
Age at CD diagnosis, years		
<6	660 (51.0)	3300 (51.0)
≥6	634 (49.0)	3170 (49.0)
Year of CD diagnosis		
1989–2004	548 (42.3)	2740 (42.3)
2005–2012	746 (57.7)	3730 (57.7)
Maternal education		
Up to 8th grade	471 (36.8)	2603 (40.8)
9th–13th grade	648 (50.6)	2968 (46.5)
University	160 (12.5)	812 (12.7)

CD, coeliac disease.

(71%) CD individuals. Median age at CD diagnosis was 6 years (range 0–23 years) and 61% of the study participants were female.

In the period following CD diagnosis, 14 cases had a first-time in life hospital admission with primary diagnosis of bacterial pneumonia, as opposed to 42 reference individuals, in respectively 9450 person-year (py) (1.8/1000 py) and 48,335 py (1.0/1000 py). This corresponded to an increased risk of bacterial pneumonia in CD patients (HR 1.82, 95% CI0.98–3.35), after having received a diagnosis of CD, although the result did not reach statistical significance (Table 2). Adjusting for maternal education did not influence the risk estimate (HR 1.87, 95%CI 1.00–3.51). Eighteen episodes of bacterial pneumonia occurred among cases and 50 among reference individuals with a significant increased risk (HR 1.94, 95%CI 1.13–3.35) when considering also secondary diagnoses in hospital records. This result was confirmed, even after adjusting for maternal education (HR 1.94, 95%CI 1.11–3.39). When follow-up periods of subjects that underwent pneumococcal vaccination were excluded from the analyses, the risks of first-time events, subsequent to diagnosis, did not show a significant risk (HR 1.73, 95%CI 0.89–3.37), not even after maternal education adjustment (HR 1.87, 95%CI 0.95–3.67). Similarly pneumococcal pneumonia (HR 2.50, 95%CI 0.62–10.0) and pneumococcal infection (HR 2.14, 95%CI 0.55–8.29) showed a non-significant increased risk (Table 2). Among the individuals with index date dated 1995 or later and with a first-time in life hospital admission with primary diagnosis of bacterial pneumonia *following* CD diagnosis, 1 out of 33 controls (3%) and 1 out of 11 cases (9%) had also an associated autoimmune disorder (at least one of the three conditions considered: type I diabetes, autoimmune hypothyroidism, autoimmune hyperthyroidism).

Prior to CD diagnosis, 32 (2.47%) cases had a hospital admission, for the first time in life, with a principal diagnosis of bacterial pneumonia, as opposed to 82 (1.48%) reference individuals. Individuals with CD were hence at increased risk of bacterial pneumonia *before* CD diagnosis (OR 1.97, 95%CI 1.30–2.97; adjusted OR 1.86, 95%CI 1.24–2.86) (Table 3). This risk slightly decreased when considering secondary diagnoses (OR 1.76, 95%CI 1.18–2.63; adjusted OR 1.68, 95%CI 1.12–2.53). By excluding follow-up periods, after the individual underwent pneumococcal vaccination, the risk of bacterial pneumonia (OR 1.89, 95%CI 1.24–2.88) remained relatively unaltered, even after adjusting for maternal education (OR 1.80, 95%CI 1.17–2.77). The risk of acquiring pneumococcal pneumonia (OR 2.00, 95%CI 0.39–10.31; adjusted OR 2.03, 95%CI 0.39–10.46) and pneumococcal infection (OR 1.67, 95%CI 0.34–8.26; adjusted OR 1.67, 95%CI 0.34–8.28) did not reach statistical significance, as shown in Table 3. Among the individuals with index date dated 1995 or later and with hospital admission with primary diagnosis of bacterial pneumonia *before* CD diagnosis, 1 out of 82 controls (1.2%) and 6 out of 31 cases (19%) had also a at least one of the considered autoimmune disorders.

Tables 4 and 5 show risk estimates, stratified by time periods between bacterial pneumonia and date of CD diagnosis. The risk of bacterial pneumonia in the first 12 months after diagnosis was similar to the one observed after the first year. On the other hand the

Table 3
Risk of *previous* bacterial pneumonia in individuals with CD compared to references (reference individuals) (conditional logistic regression), n = 7764 subjects at risk.

	CD # (%)	References # (%)	OR (95% CI)
Bacterial pneumonia	32 (2.47)	82 (1.48)	1.97 (1.30–2.97)
Bacterial pneumonia (all diagnoses)	33 (2.55)	95 (1.47)	1.76 (1.18–2.63)
Bacterial pneumonia[a]	30 (2.32)	80 (1.24)	1.89 (1.24–2.88)
Pneumococcal pneumonia	2 (0.15)	5 (0.08)	2.00 (0.39–10.31)
Pneumococcal infection	2 (0.15)	6 (0.09)	1.67 (0.34–8.26)

#Number of individuals with event; CD: coeliac disease.
[a] Excluding follow-up periods after pneumococcal vaccination.

Table 4
Risk of bacterial pneumonia subsequent to index date, in individuals with coeliac disease compared to references, in relation to the time of diagnosis (index date).

	#		Person-years		HR (95% CI)
	CD	References	CD	References	
≤1 year after index date (n = 7650)	5	15	1226	6144	1.92 (0.69–5.39)
>1 year after index date (n = 6884)	9	27	8494	42,808	1.77 (0.83–3.80)

#Number of individuals with event; CD: coeliac disease.

Table 5
Risk of previous bacterial pneumonia in individuals with CD compared to references (reference individuals) (conditional logistic regression), in relation to the time of diagnosis (index date), n = 7764 subjects at risk.

	# (%)		OR (95% CI)
	CD	References	
≤1 year before index date	6 (0.46)	5 (0.08)	6.00 (1.83–19.66)
>1 year before index date	26 (2.01)	77 (1.19)	1.71 (0.80–3.64)

#Number of individuals with event; CD: coeliac disease.

Table 2
Risk of bacterial pneumonia *subsequent* to index date, in individuals with coeliac disease compared to references.

	#		Person-years		HR (95% CI)
n = Subjects at risk	CD	References	CD	References	
Bacterial pneumonia (n = 7650)	14	42	9450	48,335	1.82 (0.98–3.35)
Bacterial pneumonia (all diagnoses) n = 7636	18	50	9491	48,321	1.94 (1.13–3.35)
Bacterial pneumonia[a] (n = 6904)	12	39	8888	46,167	1.73 (0.89–3.37)
Pneumococcal pneumonia (n = 7757)	3	6	9820	49,253	2.50 (0.62–10.0)
Pneumococcal infection (n = 7756)	3	7	9820	49,236	2.14 (0.55–8.29)

#Number of individuals with event; CD: coeliac disease; âdjusted for maternal education
[a] Excluding follow-up periods after pneumococcal vaccination.

risk of bacterial pneumonia prior to CD diagnosis was much higher in the 12 months before diagnosis (OR 6.00, 95%CI 1.83–19.66).

4. Discussion

4.1. Main results

In this study, conducted in North-Eastern Italy, we have observed an increased risk of having a first time in life event of bacterial pneumonia among subjects with CD, compared to reference individuals, during the entire post-diagnosis period. Laboratory-confirmed pneumococcal pneumonia and pneumococcal infection, also showed an increased post-diagnosis risk, even if a statistically significant difference was not reached. A greater risk of having bacterial pneumonia, pneumococcal pneumonia and pneumococcal infection was also present before CD diagnosis. The risk of acquiring a bacterial pneumonia was especially high during the 12 months preceding CD diagnosis.

Further analyses among subjects with bacterial pneumonia showed that the risk of a first event, slightly increased when considering all diagnoses (primary and secondary diagnoses) in hospital discharge records, as opposed to primary diagnosis only. On the other hand, when we excluded time after pneumococcal vaccination, the risk remained relatively unchanged in the period preceding CD diagnosis and only slightly diminished, when considering post-CD diagnosis. This is probably due to a small number of subjects undergoing pneumococcal vaccination, since a population-based vaccination process had started only towards the end of the study period and was initially indicated for more vulnerable subjects. In the population we examined, only about 11% had undergone pneumococcal vaccination. Only in future analyses, it will be possible to establish how vaccination modifies the risks of acquiring bacterial pneumonia and particularly pneumococcal pneumonia, among CD subjects.

4.2. Previous literature

We are not aware of any study on the risk of pneumococcal infection specifically in a pediatric population. However, Ludvigsson et al. [7] reported that CD children (age <15 years) were at risk for severe pneumococcal sepsis but less than older individuals with CD. Nevertheless, this latter study contained no data on the vaccination status of the study participants. In contrast, an English study (*covering a period of wide availability of pneumococcal vaccination*) found no increased risk of pneumococcal infection (including pneumonia, sepsis and meningitis) in CD individuals aged 15 years or less, but an excess risk in CD patients aged 16–64 years [8]. Zingone et al. [9] found that unvaccinated CD patients, with less than 65 years of age, had an excess risk of community-acquired pneumonia, especially due to *S. pneumoniae,* compared to unvaccinated reference individuals of the same age. The highest risk was seen in the period around CD diagnosis (twofold higher for any community acquired pneumonia and fourfold higher for pneumococcal pneumonia), but the risk persisted up to at least 5 years following diagnosis. Finally, Tjernberg et al. [10] found an increased risk of invasive pneumococcal infection limited to CD patients aged 40–69 years.

4.3. Interpretation

One of the possible reasons of an excess risk of diagnoses for bacterial pneumonia, nearby CD diagnosis, may be an increased number of visits at this time, that give opportunity to pediatricians, to recognize an infection (*ascertainment bias*). However, in Italy and especially in a pediatric population, it is unlikely that parents will not contact a pediatrician in case of infection-correlated symptoms.

Moreover, it is also possible that pneumonia itself, could lead to an increased attention toward comorbidities affecting the child and therefore increase the chances of receiving a diagnosis of celiac disease/CD. For this reason, in the prospective study, subjects with a precedent event have been excluded from analyses.

In our study we only found a statistically significant increased risk of bacterial pneumonia in CD patients. However, *S. pneumoniae* is one of the most common causes of bacterial pneumonia in children [17,18], especially during the observed period, when pneumococcal vaccination was not widely spread. Therefore, even when the diagnosis was not confirmed by laboratory tests, we believe that most pneumonias were pneumococcal pneumonias. Another possibility is that some ICD 9 coding was incorrect, when indicating pneumonia from *S. pneumoniae*.

In CD adults, one of the causes attributed to an increased risk of infections from *S. pneumoniae* is related to hyposplenism, that has been described in this population. However, hyposplenism has not been described in CD children [6]. Our results suggest that there is the need for new studies with a larger sample size and with a complete diagnostic work-up to assess splenic dysfunction. However, tests to assess splenic function are invasive or lack of a standardization. The presence of Howell Jolly bodies in circulating erythrocytes (RBC) and the percentages of pitted red cells are considered valid biomarkers [19] and they can be used as first line in the diagnostic work-up, followed by the liver–spleen scintigraphy scanning that provides a qualitative and/or semi-quantitative measurement of splenic function, by evaluating the splenic uptake of either heat-denatured RBC or nano-colloids, labelled with technetium-99 m [20]. Recently a simple non-invasive technique has been proposed based on flow cytometry to detect Howell Jolly bodies containing in RBC and precisely quantify their percentage in the circulation [21].

Due to a lack of data on nutritional intake, we were unable to explore if nutritional deficiencies around CD diagnosis could contribute explaining the excess risk of pneumonia at that time.

4.4. Strengths and limitations

We used a population-based cohort design, thereby minimizing selection bias. We used different sources to identify CD patients and believe that we were able to capture a large proportion of all individuals with a diagnosis of CD, in the geographic area of our study. However, we did not screen for CD and therefore our data does not apply to undiagnosed CD. Diagnostic standards for pediatric CD have seen important changes during the last year of follow-up, with the publication of the updated European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGAN) guidelines [22]. In our study, coeliac diagnosis was confirmed by biopsy in 71% of the CD individuals. However, our algorithm included also cases that had been admitted to the hospital or that had received a healthcare copayment exemption for the disease. The inclusion of these health data sources is due to the fact that biopsy-confirmed diagnoses might have been performed in other Italian Regions, and these cases would not have been included in the FVG Regional pathology reports. We are confident of the accuracy of our data, since in Italy, copayment exemption is given only after a gastroenterologist diagnosis of CD.

The major limitation of our study is the relatively low number of subjects hospitalised for pneumonia. Unfortunately, we had no data on primary care setting, therefore we cannot exclude that pneumonia events, not requiring hospital admission, have higher rates among individuals with CD.

Other limitations include lack of data on potential confounders, such as a comprehensive socioeconomic index (we could only adjust for maternal education), smoking, comorbidities or ongoing therapies. Due to a small number of cases, it was also not possible to perform all attempted adjustments. We tried to adjust for autoim-

mune diseases, but there were not enough cases to add them to our models.

Despite not being widely spread, an initial and progressively more frequent use of pneumococcal vaccination could have started changing the etiological spectrum of pediatric pneumonia, reducing the role of pneumococcal infections. Previous research conducted in the same area, showed that hospital admissions for pneumonia during the period 2004–2012 decreased significantly for infants (0–4 years old) as the PCV7 coverage rate improved, and even more after the introduction of the PCV13 vaccine [12]. This means we cannot determine what proportion of pneumonia is attributable to *Streptococcus pneumonia.*

5. Conclusion

In conclusion, data from our Italian cohort showed that children and adolescents with CD tend to have a higher risk of bacterial pneumonia compared with their matched reference individuals, especially in proximity to CD diagnosis. Furthermore, considering most of these infections are *S. pneumoniae* related, we suggest to firmly recommend pneumococcal vaccination to all CD children, regardless of risk stratification. Future studies are needed to evaluate the clinical impact of the recently initiated pneumococcal vaccination campaigns in Italy, on CD morbidity. An evaluation for splenic disfunction, including the search for Pitted cells or Howell-Jolly bodies, might also be recommended in CD children with occurrence of bacterial pneumonia.

Conflict of interest

None declared.

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