Infections in early life and development of celiac disease

Brief Original Contribution

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Abbreviations:

CD, celiac disease

CI, confidence interval

HR, hazard ratio

ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems

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Abstract

Early infections have been suggested to be associated with increased risk for later celiac disease (CD). We analysed prospective claims data of n=295,420 infants from Bavaria, Germany, born between 2005 and 2007 containing information on medically attended infectious diseases according to ICD-10 code on a quarterly basis to calculate hazard ratios and 95% confidence intervals of time to CD diagnosis by infection exposure, adjusting for sex, calendar month of birth and number of previous healthcare visits. CD risk was increased in children who had a gastrointestinal infection during the first year of life (hazard ratio 1.32, 95% confidence interval 1.12, 1.55) and to a lesser extent also in children with a respiratory infection during the first year (hazard ratio 1.22, 95% confidence interval 1.04, 1.43). Repeated gastrointestinal infections during the first year of life were associated with particularly increased CD risk in later life. These findings indicate that early gastrointestinal infections may be relevant for CD development.

Key words: Gastrointestinal infections, Respiratory infections, Celiac disease

Recent studies showed that infections in the first year of life are associated with increased risk for later celiac disease (CD), but were not consistent in whether respiratory or gastrointestinal infections are more relevant (1, 2). We investigated associations between types of medically attended infectious diseases and CD in a large population-based cohort. The main focus of our analyses lay on infections during the first year of life, but we additionally explored associations of CD and infections up to age 2 years.

METHODS

We used claims data provided by the Kassenärztliche Vereinigung Bayern of all n=295,420 statutorily insured infants born alive between 2005 and 2007 in Bavaria, Germany (92.6 % of all live-born children during this period in Bavaria), and followed up from birth to a median age of 8.5 years. These data covered diagnoses from both primary care and specialized physicians (e. g. general practitioners, paediatricians, gastroenterologists and doctors of internal medicine). Diagnoses of medically attended infectious diseases and CD were obtained using ICD-10 codes recorded in quarterly calendar intervals (3). Development of CD was defined by first occurrence of the ICD-10 code K90.0. The selection and classification of relevant infection diagnoses was done as previously described for the The Environmental Determinants of Diabetes in the Young (TEDDY) study (4). We distinguished infections by symptoms (mainly respiratory, gastrointestinal) and causes (mainly viral, bacterial) according to their ICD-10 code (see web table 1 for details). Infections with unknown causes were classified according to their symptoms only. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals of time to CD diagnosis by infection exposure, adjusting for sex, calendar month of birth and the number of previous healthcare visits (as a proxy for comorbidities). Infections were treated as separate individual binary covariates with non-exposure to a specific infection as reference category a) during the whole first year of life and b) in quarterly intervals during the first two years of life, i. e. we

calculated a separate Cox model for each infection type (including “any” infections, i.e. irrespective of symptoms or causes) and exposure interval. In sensitivity analyses, we a) adjusted all Cox models for the number of previous quarterly intervals with infections of the same type, b) excluded children with CD diagnoses recorded in only one quarterly interval in order to reduce the number of potential false-positive cases, and c) excluded infections occurring within 12 months prior to CD diagnosis to exclude potential bias by symptoms of undiagnosed CD. Cumulative risks of CD after age 12 months were compared by number of quarterly intervals with respiratory or gastrointestinal infections during the first year of life using Kaplan-Meier analysis and log-rank tests.

To avoid reverse causation bias, time at risk for CD was measured after the respective infection exposure period in each analysis. Interaction terms of the respective predictor variables with time were calculated to check the proportional hazards assumption. Statistical analyses were conducted using SAS 9.4 and R 3.1.1. Statistical significance was determined at the 5% level (2-sided). Data release was approved by the data protection officer in accordance with the German Guidelines for Secondary Data Analysis (5).

RESULTS

In total, 853 children (0.29 %; 415 (48.7%) males) were diagnosed with CD at a median age of 5.0 years, of which 820 (95.5%) developed CD after the first year of life (see web table 2 for detailed characteristics of study subjects by infection exposure). In 488 cases (57.2%), CD diagnosis was recorded in more than one quarterly interval. CD risk was increased in children who had a medically attended gastrointestinal infection during the first year of life (hazard ratio 1.32, 95% confidence interval 1.12, 1.55), accounting for an incidence rate of 46/100,000 person years compared to a rate of 34/100,000 person years in children without a gastrointestinal infection. The association was slightly weaker in children with a medically attended respiratory infection during the first year (hazard ratio 1.22, 95% confidence interval

1.04, 1.43), with incidence rates of 38/100,000 and 32/100,000 person years in children with and without respiratory infections, respectively. The proportional hazards assumption was not rejected for any of the two models. These associations were relatively constant across all quarterly age intervals during the first two years of life and also thereafter, but could not be attributed to either viral or bacterial infections only (figure 1), and were very similar when we adjusted the models for previous infections of the same type (web figure 1), or restricted the analysis to CD diagnoses recorded in more than one quarterly interval (web figure 2), or to infections occurring more than 12 months prior to CD diagnosis (data not shown). Repeated respiratory and particularly gastrointestinal infections during the first year of life were associated with increased cumulative risk of CD in later life (figure 2).

DISCUSSION

Medically attended gastrointestinal and also respiratory infections were associated with CD development by age 8 in a large, population-based sample. Particularly strong associations were observed for repeated gastrointestinal infections in the first year of life. Early gastrointestinal infections may therefore be relevant for CD development rather than for type 1 diabetes development, for which early respiratory infections have been found to be more relevant in the same data (3).

Our data are consistent with a similar prospective study that interrogated infection records, which showed strong associations of CD with gastrointestinal infections during the first 12 months of life (2), and partly also with another one in which a positive association with respiratory infections was observed (1). It should be mentioned, however, that in these studies infections were defined based on parental reports (1) or hospitalization records (2), respectively, indicating different levels of infection severity compared with our data. Further, our CD diagnoses could not be validated with data from other sources, such as questionnaires (1) or pathology reports (2), but we assume their validity as relatively high, as the diagnoses

were coded by physicians for the purpose of remuneration, for example to support fees claimed for diagnostic testing. Neither study has data on onset of CD-associated autoantibodies, so that it remains unclear from these findings whether early infections may be a trigger for the disease, or rather contribute to susceptibility. A number of mechanisms have been suggested for early infections to potentially cause CD, including alterations of the microbiome or induction of specific immune responses such as type I interferons (6). Our data do not allow to investigate these potential pathways further, but given that we observed the strongest associations for repeated gastrointestinal infections, but no major role for either viral or bacterial infections, our results may suggest that it is rather a persistent state of inflammation in the gastrointestinal tract in early life than a specific infectious agent which leads to increased CD risk.

Unfortunately, our data do not contain information about whether CD diagnosis was based on clinical, serological and/or histopathologic findings, or about socioeconomic status, infant feeding or antibiotic use which might be potential confounders in this context. Further, we investigated several infection types with different exposure ages, potentially introducing multiple testing errors.

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Contributions: AB performed the analyses and wrote the first draft of the manuscript together with AGZ. ED contributed to conception and design of this study and to the final version of the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest: None.

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FIGURE LEGENDS

Figure 1. Hazard ratios (dots) and 95% confidence intervals (bars) for celiac disease development by types of medically attended infectious diseases, adjusted for sex, month of birth and number of previous healthcare visits, based on data of n=295,420 infants from Bavaria, Germany, born between 2005 and 2007. Time at risk for celiac disease was measured after the respective infection exposure period for each model.

Figure 2. Cumulative risk of celiac disease development after age 12 months by number of quarterly intervals with a medically attended respiratory infection (panel A, log-rank p=0.006) or gastrointestinal infection (panel B, log-rank p<0.001) during the first year of life, based on data of n=295,420 infants from Bavaria, Germany, born between 2005 and 2007.

Web Figure 1. Hazard ratios (dots) and 95% confidence intervals (bars) for celiac disease development by types of medically attended infectious diseases, adjusted for sex, month of birth, number of previous healthcare visits, and number of previous quarterly intervals with infections of the same type, based on data of n=295,420 infants from Bavaria, Germany, born between 2005 and 2007. Time at risk for celiac disease was measured after the respective infection exposure period for each model.

Web Figure 2. Hazard ratios (dots) and 95% confidence intervals (bars) for celiac disease development as recorded in at least two quarterly intervals by types of medically attended infectious diseases, adjusted for sex, month of birth and number of previous healthcare visits, based on data of n=295,420 infants from Bavaria, Germany, born between 2005 and 2007. Time at risk for celiac disease was measured after the respective infection exposure period for each model.