The risk of contracting pediatric inflammatory bowel disease in children with celiac disease, epilepsy, juvenile arthritis and type 1 diabetes—
a nationwide study

Lauri J. Virta a, Kaija-Leena Kolho b,*

a Research Department, the Social Insurance Institution of Finland (KELA), Turku, Finland
b Children's Hospital, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

Received 16 January 2012; received in revised form 28 February 2012; accepted 28 February 2012

Abstract

Background and aims: The association of celiac disease with inflammatory bowel disease (IBD) in children is unclear. This study assesses the risk of IBD in children diagnosed with celiac disease and three other chronic diseases, namely epilepsy, juvenile idiopathic arthritis (JIA) and type 1 diabetes using nationwide, comprehensive registers.

Methods: We identified Finnish children born between 1994 and 2008 and diagnosed with IBD (n=596) by October 2010 (aged up to 16 years) in a national register of medical reimbursements, which all these patients are entitled to. The presence of other chronic diseases, such as celiac disease, epilepsy, JIA and type 1 diabetes, diagnosed before the diagnosis of IBD was accordingly identified in patients and their population-based, individually matched controls (n=2380). The data on chronic diseases are based on certificates including the diagnostic criteria. The risk of contracting IBD in children with a diagnosis of a chronic disease was analyzed using conditional logistic regression analysis.

Results: Chronic diseases were more common in children contracting IBD than in their matched controls (frequency of chronic diseases 5.9% and 1.0%, respectively, p<0.001). Celiac disease associated with later development of ulcerative colitis (p<0.01) but the association with Crohn's disease was less clear (p<0.05). For the other chronic diseases, association was seen only between epilepsy and ulcerative colitis (p<0.01).

Abbreviations CI, confidence interval; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; OR, odds ratio; SII, Social Insurance Institution; UC, ulcerative colitis.

* Corresponding author at: Children's Hospital, University of Helsinki, Box 281, FIN-00029 HUS. Tel.: +358 40 7615172; fax: +358 9 47172599.
E-mail address: kaija-leena.kolho@helsinki.fi (K.-L. Kolho).

1873-9946/$ - see front matter © 2012 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.crohns.2012.02.021
1. Introduction

Inflammatory bowel disease, IBD, Crohn’s disease, ulcerative colitis (UC) and unclassified colitis, has rapidly increased in pediatric populations in Western countries during recent years. The causes for this increase are unknown. IBD may develop at any age but most often affects adolescents or young adults. It has been estimated that there are about 1–1.5 million patients with IBD in the United States. The prevalence of pediatric IBD being approximately 71 per 100,000 the treatment of this disease burdens significantly the health care. Childhood factors are considered important for the development of the disease, but household characteristics, dietary patterns or the role of family history of IBD have not been firmly established. It is, however, agreed that intestinal microbiota plays a central role in triggering inflammation in IBD.

Similar to IBD, the incidence of celiac disease (gluten-sensitive enteropathy) appears to be on the increase throughout developed countries. There are some data indicating that IBD might associate with celiac disease although the risk may not be high. A recent cross-sectional study in Italy, with more than 1000 patients with IBD enrolled in it, showed a prevalence of 0.5% of celiac disease based on screening and duodenal biopsies. Tursi and coauthors reported celiac disease in about 20% of adult patients with Crohn’s disease, but the number of patients studied, less than 30, was low, and most of the studies include small series or are case reports. A cohort study from UK estimated that the risk to develop IBD might be increased 10-fold in adults with celiac disease. The association of celiac disease with UC may be stronger than with Crohn’s disease, as suggested by adult data. To the best of our knowledge, there are no large studies on the association of celiac disease with IBD in children.

We used the opportunity to study the risk of contracting IBD in children with celiac disease in nationwide, comprehensive registers and matched controls individually, based on their age, gender and place of residence. For comparison, the presence of other chronic diseases available including epilepsy, juvenile idiopathic arthritis (JIA) and type 1 diabetes before the diagnosis of IBD was analyzed accordingly.

2. Subjects and methods

In Finland, all patients with chronic diseases, such as IBD, epilepsy, JIA and type 1 diabetes are, irrespective of the socioeconomic status, entitled to special refunds governed by the Social Insurance Institution (SII) to cover part of the medical costs (Special Reimbursement). Accordingly, all pediatric patients with celiac disease receive reimbursement, a so-called disability benefit, to cover some of the dietary costs and to provide compensation for the disease burden. This benefit is also administered by SII. To be eligible for these benefits, the diagnosis has to be verified and meet specific criteria, for IBD including endoscopy and usually histological verification. A written certificate including the diagnostic criteria and signed by a specialist in pediatrics and/or respective subspecialty is needed. The certificates are checked in SII. During 2001–2009, 98% of the special reimbursement applications for IBD were accepted by the SII. Rejections are exceptional, particularly in children. Besides the subtypes of diagnoses for IBD (ICD-10 codes K50 or K51), the register information includes the date of the special refund decision. The administrative process for decision-making by the SII takes only a couple of weeks. Thus, the date of entitlement decision was used as the index date for diagnosis of IBD.

We identified Finnish children born between January 1, 1994 and December 31, 2008 and diagnosed with IBD by October 2010 from Special Reimbursement Register for drug costs. Control children (four per each IBD patient) were randomly picked from the Population Register Centre and matched individually to the cases based on their age, gender and place of residence at birth. The presence of celiac disease (K90) before the diagnosis of IBD (the index date of the study) was picked from the Disability Benefit Register including written certificates and diagnostic criteria, a biopsy among the latter. The presence of other chronic diseases available, epilepsy (G40 or ICD-9 code 345), JIA (M08) and type 1 diabetes (E10) diagnosed before the index date of the study was identified accordingly from the drug Reimbursement register. Registry linkage was based on a unique personal identifier, including date of birth and gender. The diagnoses of the control children were identified accordingly.

2.1. Ethical consideration

The ethical committee of the Research Department of SII approved the study protocol. In accordance with Finnish regulations, no informed consent was required for registry-based studies.

2.2. Statistical analyses

The data consisted of individually matched sets, with one case and four controls. The associations between the presence of a chronic disease (see above) and the risk of development of IBD were analyzed using conditional logistic regression analysis. The strengths of associations were quantified using odds ratios (OR) with 95% confidence intervals (95% CI). Cross-tabulation with chi-square test or ordinary logistic regression analysis was used when associations were separately studied in cases and controls. Statistical significance was set at the 5% level (two-sided). Statistical analyses were performed using the SAS system for Windows (version 9.2 SAS Institute Inc., Cary, NC, USA).

Conclusion: Pediatric patients with celiac disease or epilepsy have an increased risk of developing IBD during their childhood but the risk is not high. This finding warrants a thorough investigation of intestinal symptoms in these children.
3. Results

The study group comprised 595 children with IBD (233 children with Crohn’s disease and 362 with UC), and 2,380 control children (Table 1). In total, chronic diseases were more common among patients with pediatric IBD (5.2%) than in controls (1.9%; \( p<0.001 \), Table 2). A diagnosis of celiac disease associated with the later development of pediatric IBD (Table 2). The total prevalence of celiac disease was 2.2% in the IBD group and 2.5% in those with UC. In IBD, the majority of celiac disease diagnoses were made by the age of 6 years, at a median of 3 years before the diagnosis of IBD.

The pediatric patients with UC had more often a diagnosis of epilepsy than their matched controls (Table 2). In Crohn’s disease the frequency of JIA was at the level of statistical significance when compared to controls (\( p=0.049 \); Table 2). The frequency of type 1 diabetes did not differ between the study groups (Table 2). The number of children with more than one diagnosis of chronic diseases (other than IBD), before the index date of the study, was low (none in the patient group, Table 2). Gender was not significantly associated with the presentation of co-morbid diseases and IBD, except in epilepsy, 75% of the patients being girls (\( p=0.027 \)).

4. Discussion

In this nationwide study, we assessed the risk of contracting IBD in children with a diagnosis of a chronic disease, such as celiac disease, epilepsy, JIA or type 1 diabetes, when compared to population-based controls. We identified Finnish children born between 1994 and 2008 and diagnosed with IBD up to the age of 16 years and found that the presence of a chronic disease increased the risk to develop pediatric IBD. More specifically, children with celiac disease had an increased risk of contracting IBD and children with epilepsy accordingly UC during their childhood when compared to population-based controls. Although the actual number of patients with chronic disease developing IBD was not high, the findings warrant thorough investigation of intestinal symptoms in these children.

Celiac disease associated with later development of IBD (\( p<0.01 \)), the frequency of celiac disease being approximately 2%. Among control children, the frequency of celiac disease was lower, 0.5–0.7%, corresponding well with the published figures of the prevalence of celiac disease in Finnish children.12 In screening studies, however, the prevalence may reach 2–3% reflecting the fact that only a minor proportion of celiac patients have been diagnosed.13 This is possibly due to mild, non-specific symptoms in the majority of the patients.14,15

Interestingly, the diagnosis of celiac disease had been made approximately 3 years (median) before the diagnosis of IBD. It is possible that these patients had been actively screened for celiac disease because of gastrointestinal symptoms, and the possibility of IBD had been overlooked. Indeed, the frequency of celiac disease in the IBD group was comparable to the prevalence of celiac disease reported in population screening studies (see above). Whether the recent increase in the incidence of pediatric IBD1,2 shares factors associated with the reported increase in celiac disease16 is not known. Recent data showed that region of the interleukin-23 receptor (IL23R), but not the described single nucleotide polymorphisms, associates with IBD and celiac disease in Finnish families.17 The relevance of this finding to current results, however, is questionable as the IL-23R region has not been associated with UC, which comprises the major subgroup of Finnish patients with IBD.2

Joint diseases are more common in pediatric onset IBD than in respective controls, and about 5% of the patients develop joint symptoms within the first decade after diagnosis of IBD.18 However, as these data were based-on self-reports, the true proportion of JIA patients could not be assessed.18 Here, before the diagnosis of the intestinal disease, a diagnosis of a chronic pediatric rheumatic disease had been made in 0.68% of the patients with UC and in 1.3% of the patients with Crohn’s disease, the latter being at the level of statistical significance when compared to controls. Patients with JIA may show signs of immunological activation in their gut18 but we could not find reports of register-based studies on the risk of IBD in JIA. The current finding of a borderline association of JIA and pediatric onset of Crohn’s disease warrants a thorough assessment of intestinal symptoms in JIA patients.

To our knowledge, epilepsy has been linked to pediatric Crohn’s disease only in a case report.20 In adults a higher incidence of seizures in Crohn’s disease when compared to general population have been found in a retrospective chart review and suggested to reflect underlying cerebrovascular disease.21 A recent retrospective study in adult IBD reported that the presentation of neurologic symptoms was coincidental or occurred after the appearance of intestinal symptoms.22 Thus, the observed association with UC and a prior diagnosis of epilepsy here was unexpected and has not been reported before but needs to be replicated. Notably, the frequency of epilepsy in the controls was not different from the published figures.23

In Finland, the incidence of type 1 diabetes is the highest in the world for yet unknown reasons. In the very young, the annual increase in incidence reached 4.7% at ages 0–4 years by early 2000,24 being close to the annual increase of 6% to 8% in the incidence of pediatric IBD in children up to the age of 18 years.2 Here, we observed no association with pediatric IBD and type 1 diabetes. Interestingly, a recent report from North America suggests that the strongest risk alleles for type 1 diabetes within the major histocompatibility complex confer protection against IBD.25

The main strength of this study is the use of nationwide register-based data with high coverage,2,26–28 e.g. for type 1 diabetes the coverage was 99%24 and for pediatric IBD 94% when 98% of the IBD cases met modern diagnostic criteria.2 For epilepsy and JIA, however, there is no such data

| Table 1 Characteristics of children diagnosed with pediatric inflammatory bowel disease (IBD) and their matched controls in Finland 1994–2010. |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | IBD             | Crohn’s disease | Ulcerative colitis |
| No. of children                 | 595             | 233             | 362             |
| Age (years)                     | 10.2            | 10.9            | 9.5             |
| IBD diagnosis, median (IQR)     | (6.1–12.6)      | (7.7–13.0)      | (5.4–12.2)      |
| Sex (% males)                   | 57              | 63              | 52              |

IQR, interquartile range.
Table 2

<table>
<thead>
<tr>
<th>Chronic disease</th>
<th>IBD</th>
<th>Chronic disease</th>
<th>IBD</th>
<th>Chronic disease</th>
<th>IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR (95%CI)</td>
<td>P Value</td>
<td>Cases</td>
</tr>
<tr>
<td>No celiac disease</td>
<td>582</td>
<td>2366</td>
<td>1.00</td>
<td>2.23</td>
<td>0.001</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>362</td>
<td>1448</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>No epilepsy</td>
<td>583</td>
<td>2365</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>584</td>
<td>2364</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>No JIA</td>
<td>591</td>
<td>2375</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>JIA</td>
<td>592</td>
<td>2365</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>No type 1 diabetes</td>
<td>593</td>
<td>2365</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>594</td>
<td>2365</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>No chronic disease</td>
<td>595</td>
<td>2365</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
<tr>
<td>Any chronic disease</td>
<td>596</td>
<td>2365</td>
<td>1.00</td>
<td>3.80</td>
<td>0.005</td>
</tr>
</tbody>
</table>

a Among 2 children with Crohn’s disease and 2 children with ulcerative colitis, IBD was diagnosed within 1 month after the diagnosis of celiac disease.

b Here chronic disease defines celiac disease, epilepsy, JIA or type 1 diabetes.

c One control had both celiac disease and diabetes before the index date of the study, no other children presented more than one of the abovementioned chronic disease.

d No chronic diseaseb 564 2336 Chisq 0.001 223 919 Chisq 0.005 341 1417 Chisq 0.001

e Any chronic disease 31 44 c 10 13 21 31 c

% chronic diseases: 5.2 1.9 4.3 1.4 5.8 2.1

In conclusion, the presence of a chronic disease, such as celiac disease or epilepsy is associated with an increased risk of contracting pediatric onset IBD, particularly UC, but the risk is not high. The increased risk of IBD in celiac disease may reflect more active screening in children with probrome of IBD.

Conflict of interest statement

There is no conflict of financial interest.

Acknowledgements

Ms Kristiina Tyrkkö is thanked for the management of the register sample in the Social Insurance Institution. Finnish Pediatric Research Foundation Helsinki (KLK), and University Central Hospital Research Fund (KLK). The Foundations providing grants had no role in the study design, the collection, analysis and interpretation of the data, writing the report or the decision to submit the paper. The authors had no writing assistance. LV participated in the design of the study, carried out the data analyses and critically revised the manuscript. K.LK participated in the design of the study, drafted the manuscript and critically revised it. Both authors read and approved the final manuscript.

References


