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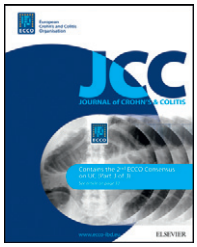

The risk of contracting pediatric inflammatory bowel disease in children with celiac disease, epilepsy, juvenile arthritis and type 1 diabetes—a nationwide study

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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.

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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.

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.[1,2] 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.[3,4] 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.[5] It is, however, agreed that intestinal microbiota plays a central role in triggering inflammation in IBD.[6]

Similar to IBD, the incidence of celiac disease (gluten-sensitive enteropathy) appears to be on the increase throughout developed countries.[7] There are some data indicating that IBD might associate with celiac disease[8] 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.[9] 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,[8] 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.[10] The association of celiac disease with UC may be stronger than with Crohn's disease, as suggested by adult data.[9,10] 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.[11] 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).