

Cow's Milk Allergy, Asthma, and Pediatric IBD

*Lauri J. Virta, [†]Merja Ashorn, and [‡]Kaija-Leena Kolho

ABSTRACT

We identified a total of 595 Finnish children born in 1994–2008 and diagnosed as having inflammatory bowel disease (IBD) by October 2010 from the National Reimbursement Register (based on certificates including the diagnostic criteria) to determine whether the presence of cow's milk allergy (CMA) or asthma is associated with the risk of contracting IBD (altogether 2380 matched controls). A diagnosis of CMA in infancy was associated with Crohn disease (odds ratio [OR] 1.92, confidence interval [CI] 1.09–3.36, $P < 0.05$) and ulcerative colitis (OR 1.71, CI 1.04–2.83, $P < 0.05$), but childhood asthma only with Crohn disease (OR 2.33, CI 1.41–3.86, $P = 0.001$). Thus, CMA in infants is a risk factor for contracting pediatric IBD and accordingly, asthma for Crohn disease.

Key Words: children, Crohn disease, ulcerative colitis

(JPGN 2013;56: 649–651)

Inflammatory bowel disease (IBD), comprising Crohn disease, ulcerative colitis (UC), and unclassified colitis, has rapidly increased in pediatric populations in Western countries during recent years (1). Environmental factors such as breast-feeding, the number of siblings, household characteristics, and dietary patterns, in addition to having a family history of IBD, have provided no definite clues for the rapid increase. Day care attendance and owning a pet may bring an increased risk of Crohn disease, whereas living in homes that are less crowded may be protective (2); however, there are no such data for pediatric UC. Comparably, the increase in allergic diseases together with the process of westernization is considered to reflect changes in the socioeconomic environment; however, it is not clear whether childhood allergic diseases and IBD cluster. Thus, we conducted a population-based, case-control study based on nationwide registers to assess the risk of contracting pediatric-onset Crohn disease and UC in Finnish children up to 16 years of age with a diagnosis of cow's milk allergy (CMA), the most common food allergy in early childhood (3), and/or asthma. Asthma and CMA were proxy indicators for allergic diseases because atopy as such is not entitled to special reimbursements and nationwide data are not available.

Received October 28, 2012; accepted January 3, 2013.

From the *Department of Research, Social Insurance Institution, Turku, the [†]Pediatric Research Center, University of Tampere, Tampere, and the [‡]Children's Hospital, Helsinki University Central Hospital and Helsinki University, Helsinki, Finland.

Address correspondence and reprint requests to Dr Kaija-Leena Kolho, Children's Hospital, University of Helsinki, Box 281, FIN-00029 Helsinki, Finland (e-mail: kaija-leena.kolho@helsinki.fi).

The present study received funding from the Finnish Pediatric Research Foundation, and the Helsinki University Central Hospital Research Fund. The authors report no conflicts of interest.

Copyright © 2013 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
DOI: 10.1097/MPG.0b013e318285e9d8

METHODS

All Finnish residents are assigned shortly after birth a unique personal social security identifier number revealing the date of birth and sex. Data from the national registers, including the Special Reimbursement Register and the Population Register, both of which are maintained by the Social Insurance Institution (SII) of Finland, were linked with this identifier code. The Finnish population (5.3 million) is stable and ethnically homogenous.

In Finland, patients with certain chronic diseases, such as IBD and asthma (*International Classification of Diseases-10* code J45), are entitled to special refunds for the drug costs, and patients with CMA (K52.2, L27.2) are entitled to refunds for the formula costs. The socioeconomic status of the family has no effect on these reimbursements. Drug reimbursement is done according to a written certificate, which includes the diagnostic criteria and which has been signed by a specialist in pediatrics and/or a respective field (eg, gastroenterology, allergology, pulmonology). For IBD, the criteria include endoscopy and usually histologic verification, and for CMA, the criteria include elimination and milk challenge evaluated by a specialist, but double-blind testing is not required. All special reimbursement applications are checked by the SII, and this administrative process takes only a couple of weeks. During 2000–2009, 98% of the special reimbursement applications for IBD were accepted by SII; rejections are exceptional, particularly in children. Besides the subtypes of IBD diagnoses (*International Classification of Diseases-10* codes K50 or K51), register information includes the date of the special refund decision. This particular date was used as a proxy indicator for the date of IBD diagnosis and defined here as the index date for both the cases and their respective controls.

Study Population

The same study population of patients with IBD was included in our recent study on the risk of contracting pediatric IBD in children with celiac disease, epilepsy, juvenile idiopathic arthritis, and type 1 diabetes mellitus (4). Briefly, children born between January 1, 1994 and December 31, 2008 who had received a special reimbursement for IBD by the end of September 2010 ($n = 595$; $n = 233$ with Crohn disease and $n = 362$ with UC) were identified from the Special Reimbursement Register. For each incident case, 4 eligible control children ($n = 2380$) were randomly selected from the Population Register and individually matched to the cases based on their date of birth, sex, and place of residence at birth.

Both for the IBD cases and for their controls, the date on which the reimbursement for CMA and/or asthma became effective before the index date (see above) was extracted from the Special Reimbursement Register.

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

Statistical Analyses

The data consisted of individually matched sets with 1 case and 4 controls, and the associations between comorbid disease and the risk of development of IBD, Crohn disease, and UC, were analyzed using conditional logistic regression analysis. The strengths of the associations were quantified using odds ratios (OR) with 95% confidence intervals (95% CI). For CMA, subgroup analyses were made in major symptom presentations (the skin or the gastrointestinal tract) and for asthma in dichotomised age groups (<3 years and >3 years because younger children often have wheezing associated with respiratory infections and may not have true asthma).

RESULTS

The risk of contracting pediatric-onset IBD, both Crohn disease and UC, was increased in children with CMA in infancy and the risk of Crohn disease in children with asthma, with the diagnoses having been made before the IBD diagnosis (Tables 1 and 2). Among children with Crohn disease, the frequency of a previous diagnosis of CMA was 8.2%, whereas it was 6.4% in UC; these percentages are significantly higher when compared with the frequency of 4.0% among the controls ($P = 0.020$ and $P = 0.032$, respectively; χ^2 test). Of patients with CMA, 30% had intestinal symptoms as the major presenting symptom, approximately 60% had skin manifestations, and in 10%, the classification was not available (data from the 1990s). Interestingly, the risk of contracting Crohn disease was highest (OR 2.95) in children with abdominal symptoms as a major presentation of CMA (Table 2).

Among children with Crohn disease, a previous diagnosis of asthma was more frequent (11.6%) than in pediatric UC (6.4%, $P = 0.025$) or in matched controls (5.5%, $P < 0.01$). Asthma diagnosed beyond 3 years of age showed stronger association with Crohn disease than asthma in younger patients (Table 2). The risk of pediatric-onset Crohn disease was higher in children with asthma alone (OR 2.18) compared with children with CMA alone (OR 1.69), but the risk of contracting Crohn disease was highest (OR 3.84) in children with both asthma and CMA ($P < 0.003$ for subgroup difference).

DISCUSSION

In total, 18% of the pediatric patients with Crohn disease and 12% of the respective patients with UC had been diagnosed as having either asthma and/or CMA before the IBD diagnosis, which was significantly more often than among the matched controls (9%) in this nationwide study. In both Crohn disease and UC, CMA was diagnosed in infancy significantly more frequently than among the controls. Here, all of the diagnoses (IBD, CMA, and asthma) were based on written certificates, including the diagnostic criteria by specialists, and checked by the SII. Thus, the possibility

of misdiagnoses is low. Furthermore, the patient data were contrasted with individually matched, population-based controls.

To the best of our knowledge, an association of CMA with IBD has previously been reported only in a small study comparing a history of CMA between 78 patients with IBD and 36 controls (5). Because of the register-based study design here, all patients with CMA were infants with reimbursement for formula. These reimbursements were included in the routine care of the patients and not affected by the socioeconomic status of the family. Although the diagnostic criteria of CMA include elimination and milk challenge to entitle formula reimbursements, it is possible that there was some regional variation in the diagnostics of CMA because the national guidelines for performing elimination challenge tests were only published in 2009. Thus, it may be that some of the CMA diagnoses were not correct; however, because reimbursement for formula was used as a proxy indicator for CMA, it is possible that some infants of approximately 1 year of age diagnosed as having CMA may not have been introduced to formula and thus remained undetected. These weaknesses, however, would not cause information bias between cases and their matched controls and seem to be of minor importance to the results because the frequency of CMA in controls was comparable with the approximate incidence of 2% to 5% in developed countries (3).

Unexpectedly, the strongest association to contracting Crohn disease was with CMA presenting with predominantly abdominal symptoms and not with skin symptoms related to atopy. It is known that an adverse reaction to food may trigger intestinal inflammation and provoke intestinal bleeding, particularly in babies (6), but it is unclear whether this may later induce chronic inflammation in the gut. Interestingly, a subset of T-helper cells, Th17, has been implicated as an important functional player, not only in chronic intestinal inflammation in IBD but also in allergy (7). These T cells are considered to bridge innate and adaptive immunity, transforming growth factor- β being one of the main regulators balancing the reciprocal differentiation of regulatory T cells and Th17, the latter fostering allergic and autoimmune diseases (7). Furthermore, disturbances in innate immunity and pattern recognition receptors (such as Toll-like receptors or NOD-like receptors) may be linked to the composition of the microbiota and adversely influence the inflammatory response and risk of disease (8). Because microbiota provide protective effects for most individuals, it may depend on genetic–microbial–environmental interaction and timing of these exchanges in early life why some contract IBD (9,10). Thus, it is an intriguing possibility that the intestinal symptoms related to CMA have indeed been preliminary symptoms of IBD provoked by milk consumption because it has been reported that pediatric patients tend to have prolonged phase of symptoms until the diagnosis of IBD is made, with one-fifth having symptoms for >1 year, but delays may range up to several years (11).

In line with adult studies (12–15), asthma was associated with Crohn disease in children. Here, a preceding diagnosis of

TABLE 1. Characteristics of children diagnosed with pediatric IBD (total: 595 patients) and their matched controls in Finland, 1994–2010

	Crohn disease	Ulcerative colitis	Controls
No. children	233	362	2380
Age at IBD diagnosis, median (IQR), y	10.9 (7.7–13.0)	9.5 (5.4–12.2)	10.2 (6.1–12.6)
Sex (% males)	63	52	57
No. children with CMA	19	23	96
Age at diagnosis of CMA, median (IQR), y	0.6 (0.5–0.9)	0.5 (0.4–0.9)	0.6 (0.4–0.8)
Sex (% males)	79	65	58
No. children with asthma	27	23	135
Age at diagnosis of asthma, median (IQR), y	3.1 (1.9–4.9)	4.1 (1.9–7.5)	3.0 (1.4–5.9)
Sex (% males)	81	56	69

CMA = cow's milk allergy; IBD = inflammatory bowel disease; IQR = interquartile range.

TABLE 2. Diagnosis of CMA and/or asthma and the risk of pediatric inflammatory bowel diseases in Finland 1994–2010

Comorbid disease	Crohn disease				Ulcerative colitis			
	Cases, n = 233	Controls, n = 932	OR	95% CI P	Cases, n = 362	Controls, n = 1448	OR	95% CI P
No CMA	214	891	1.00		339	1393	1.00	
CMA	19	41	1.92	1.09–3.36 0.023	23	55	1.71	1.04–2.83 0.035
Main symptoms of CMA								
In the skin	11	29	1.56	0.77–3.18	13	29	1.86	0.95–3.65
In the gastrointestinal tract	7	10	2.95	1.09–7.98	8	16	2.03	0.87–4.75
Data not available	1	2	2.00	0.18–22.06 0.098*	2	10	0.79	0.17–3.72 0.116*
No asthma	206	881	1.00		339	1364	1.00	
Asthma	27	51	2.33	1.41–3.86 0.001	23	84	1.11	0.68–1.80 0.684
Age of asthma diagnosis, y								
<3	11	22	2.15	1.04–4.45				
≥3	16	29	2.50	1.30–4.78 0.004*				
Neither CMA nor asthma	192	846	1.00		319	1323	1.00	
CMA alone	14	35	1.69	0.89–3.20	20	41	2.03	1.17–3.51
Asthma alone	22	45	2.18	1.26–3.76	20	70	1.20	0.71–2.03
Both CMA and asthma	5	6	3.84	1.09–13.48 0.003*	3	14	0.87	0.25–3.09 0.082*

CI = confidence intervals; CMA = cow's milk protein; OR = odds ratio.

* For subgroup difference.

asthma was present in 12% of the pediatric patients with Crohn disease compared with a 6% frequency among the controls, with the latter corresponding to published figures from Finland. Asthma diagnosed beyond 3 years of age showed stronger association to the development of Crohn disease than infant asthma. It was not possible, however, to more specifically assess the characteristics of asthma. Interestingly, in pediatric UC, there was no increase in the frequency of asthma compared with the controls matched for age, sex, and place of residence. Because both subtypes of IBD (Crohn disease and UC) were associated with an increased frequency of CMA but only Crohn disease with asthma, it is unlikely that these observations were proxy for a shared gene or a single confounding factor.

In contrast to the adult studies, we assessed the comorbidities diagnosed before IBD diagnosis that were not cross-sectional at any given time point. The main strength of the present study is the use of nationwide, comprehensive register-based data with high coverage, for IBD 94% when 98% of the cases met modern diagnostic criteria (16). In Finland the eligibility for the special reimbursements for chronic diseases assessed here is not dependent on a family's socioeconomic status or the place of residence.

Taken together, CMA in infancy is associated with an increased risk of contracting Crohn disease and UC during childhood, and childhood asthma with the development of pediatric-onset Crohn disease. The mechanisms underlying these associations are yet to be explored.

Acknowledgments: Ms Kristiina Tyrkkö is thanked for management of the register sample in the Social Insurance Institution.

REFERENCES

- Benchimol EI, Fortinsky KJ, Gozfyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;17:423–39.
- Amre DK, Labmrette P, Law L, et al. Investigating the hygiene hypothesis as a risk factor in pediatric Crohn's disease: a case-control study. *Am J Gastroenterol* 2006;101:1005–11.
- Host A. Frequency of cow's milk allergy in childhood. *Ann Allergy Asthma Immunol* 2002;89 (6 suppl 1):33–7.
- Virta L, Kolho KL. The risk of contracting pediatric inflammatory bowel disease in children with celiac disease, epilepsy, juvenile arthritis and type 1 diabetes. *J Crohns Colitis* 2013;7:53–7.
- Glassman MS, Newman LJ, Berezin S, et al. Cow's milk protein sensitivity during infancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 1990;85:838–40.
- Arvola T, Ruuska T, Keränen J, et al. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. *Pediatrics* 2006;117:e760–8.
- Hemdan NYA, Birkenmeier G, Wichmann G, et al. Interleukin-17-producing T helper cells in autoimmunity. *Autoimmun Rev* 2010;9:785–92.
- Shanahan F. The microbiota in inflammatory bowel disease: friend, bystander, and sometime-villain. *Nutr Rev* 2012;70 (suppl 1):S31–7.
- Vercelli D. Gene-environment interactions in asthma and allergy: the end of the beginning? *Curr Opin Allergy Clin Immunol* 2010;10:145–8.
- Wlasiuk G, Vercelli D. The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. *Curr Opin Allergy Clin Immunol* 2012;12:461–6.
- Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;88:995–1000.
- Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastroenterology* 2005;129:827–36.
- Gearry RB, Richardson AK, Frampton CM, et al. Population-based cases control study of inflammatory bowel disease risk factors. *J Gastroenterol Hepatol* 2010;25:325–33.
- Hemminki K, Li X, Sundquist J, et al. Subsequent autoimmune or related disease in asthma patients: clustering of diseases or medical care? *Ann Epidemiol* 2010;20:217–22.
- Haapamäki J, Roine RP, Sintonen H, et al. Increased risk for coronary heart disease, asthma, and connective tissue disease in inflammatory bowel disease. *J Crohns Colitis* 2011;5:41–7.
- Lehtinen P, Ashorn M, Iltanen S, et al. Incidence trends of pediatric inflammatory bowel disease in Finland, 1987–2003, a nationwide study. *Inflamm Bowel Dis* 2011;17:1778–83.