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Associations between Three Types of Maternal Bacterial Infection and Risk of Leukemia in the Offspring

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A case-control study was nested within two maternity cohorts with a total of 7 million years of follow-up for assessment of the role of bacterial infections in childhood leukemia. Offspring of 550,000 mothers in Finland and Iceland were combined to form a joint cohort that was followed for cancer up to age 15 years during 1975–1997 through national cancer registries. For each index mother-case pair, three or four matched control mother-control pairs were identified from population registers. First-trimester serum samples were retrieved from mothers of 341 acute lymphoblastic leukemia cases and 61 other leukemia cases and from 1,212 control mothers. Sera were tested for antibodies to the genus *Chlamydia*, *Helicobacter pylori*, and *Mycoplasma pneumoniae*. Odds ratios and 95% confidence intervals, adjusted for sibship size, were calculated as estimates of relative risk. *M. pneumoniae* immunoglobulin M appeared to be associated with increased risk (odds ratio (OR) = 1.6), but the association lost statistical significance when the specificity of the immunoglobulin M was considered (OR = 1.5, 95% confidence interval: 0.9, 2.4). In Iceland, *H. pylori* immunoglobulin G was associated with increased risk of childhood leukemia in offspring (OR = 2.8, 95% confidence interval: 1.1, 6.9). Since *H. pylori* immunoglobulin G indicates chronic carriage of the microorganism, early colonization of the offspring probably differs between Iceland and Finland, two affluent countries.

antibodies; case-control studies; child; *Chlamydia*; *Helicobacter pylori*; leukemia, lymphocytic, acute; *Mycoplasma pneumoniae*

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; OR, odds ratio.

Leukemia accounts for 25 percent of childhood cancers worldwide (1). Acute lymphoblastic leukemia (ALL) comprises approximately 80 percent of all childhood leukemias (1, 2). Clustering of ALL cases, the association of increased ALL incidence with population mixing, and the association of increased ALL risk with birth order and sibship size suggest a link between infection and ALL (3–5), especially for cases diagnosed at less than 6 years of age. Recent studies support congenital infection or postnatal infection and microbial antigen stimulation as possible causes of ALL (5–8). However, most studies do not attempt to identify the causal agent.

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Infection with *Mycoplasma pneumoniae* has been suggested to be associated with childhood ALL (8, 9). Two other ubiquitous human bacterial pathogens, *Helicobacter pylori* and the genus *Chlamydia*, have been associated with lymphoproliferative disorders in adults (10–13). *H. pylori* is especially well recognized as an etiologic agent in mucosa-associated lymphoid tissue lymphoma (11). The evidence for associations of *H. pylori* and *Chlamydia* with leukemia is lacking.

To study the role of these three bacterial infections in childhood leukemia, we conducted a case-control study nested within a joint cohort of 550,000 mothers and their offspring. Acute maternal infection was defined by the presence of specific immunoglobulin M (IgM) antibodies to the genus *Chlamydia*, *H. pylori*, and *M. pneumoniae*. The presence of immunoglobulin G (IgG) antibodies to *H. pylori* was interpreted as evidence of persistent infection (14), with an increased predisposition of the offspring.

MATERIALS AND METHODS

Serum banks and cancer registries

The Finnish Maternity Cohort comprises 1,200,000 serum samples that have been collected from 650,000 pregnant women by the Finnish National Public Health Institute (Helsinki, Finland) since 1983 (6, 15). The samples are taken from practically all (>98 percent) pregnant Finnish women in municipal maternity care units at 12–14 weeks' gestation to screen for intrauterine infection. The samples are stored at −25°C. In addition, data on reproductive history (numbers of previous pregnancies and deliveries) and place of residence at the time of serum sampling are available in the Finnish Maternity Cohort data files.

The Rubella Screening Serum Bank at the Department of Virology, University of Iceland (Reykjavik, Iceland), comprises 75,000 serum samples collected during 1975–1997 from practically all (>95 percent; i.e., 50,000) pregnant women in Iceland at 12–14 weeks' gestation. The samples are stored at −20°C. Pertinent data on reproductive history were retrieved from the Icelandic Maternity Registry (6).

The Finnish and Icelandic cancer registries, which are population-based and country-wide, were established in 1952 and 1954, respectively. Various checks have shown that they receive notifications of virtually all histologically confirmed new cases of cancer (16, 17).

Identification of cases and controls

For the present study, cases of childhood leukemia among young persons registered in the Finnish and Icelandic cancer registries were classified into two categories: ALL and other leukemia (non-ALL). Stratification into four categories by age at diagnosis (<1, 1, 2–6, and >6 years) was applied to distinguish between infant leukemia cases, cases occurring in the ALL peak period, and other childhood leukemia cases.

Mothers of all children who developed leukemia before 15 years of age were identified through the Finnish and Icelandic national population registries. Final index mothers were those who had serum samples in the Finnish and Icelandic maternity cohorts (402 women altogether). For matching, we applied incidence density sampling; that is, three control mothers in Finland and four control mothers in Iceland with totally cancer-free offspring at the time of childhood leukemia diagnosis were matched with the index mother according to age at serum sampling (±2 years), date of specimen collection (±2 months), and offspring characteristics: date of birth (±2 months) and sex of the child. The matching was performed by country to ensure that differences between the national cohorts did not affect the validity of the study. If three or four control mothers were not found, the matching criteria for age and storage time were expanded stepwise by 1 month until control mothers were found.

The control group comprised 1,212 women altogether. The median and maximum differences in age between the index mothers and the control mothers were 0.3 years and 6.6 years, respectively.

Permissions for linkage between the population, cancer, and maternity cohort data files for identification of index and control pairs and use of the joint cohort data file were obtained from the national data protection authorities, the Finnish Ministry of Health, population registry centers, and the national ethical review boards.

Laboratory methods

To identify maternal infection or offspring susceptibility to perinatal infection, the presence of IgM and IgG antibodies to three human bacterial pathogens—*Chlamydia trachomatis*, *H. pylori*, and *M. pneumoniae*—was determined according to manufacturers' instructions by means of standard enzyme-linked immunosorbent assays (ELISAs) that used the same batches of purified elementary body (*C. trachomatis*), bacterial lysate (*H. pylori*), and P1-adhesin-enriched (*M. pneumoniae*) antigens. For *C. trachomatis*, we used IgG and IgM ELISAs (Thermo Labsystems, Helsinki, Finland) with reported sensitivity and specificity of 100 percent. For *M. pneumoniae*, we used IgG and IgM ELISAs (Thermo Labsystems) with reported sensitivity of 75.7 percent and reported specificity of 98.9 percent. For *H. pylori*, we used an IgG ELISA (Orion Diagnostica, Espoo, Finland) with reported 100 percent sensitivity and 94.3 percent specificity, as well as an IgM ELISA (Immunobiological Laboratories GmbH, Hamburg, Germany).

The cutoff levels were preassigned following the manufacturers' recommendations relative to internal positive and negative reference sera used on all plates. We further controlled for the specificity of the IgM antibody response by separately considering only IgM-positive mothers who were negative for IgM antibodies to the other two bacteria.

The laboratory analyses were carried out with masked samples, whereafter the data were submitted to the Finnish Cancer Registry for decoding and statistical analysis.

Statistical analyses

Relative risks, expressed as matched odds ratios and their 95 percent confidence intervals, were estimated by

conditional logistic regression at the National Public Health Institute. Associations with birth order (firstborn vs. others; dichotomous variable) and sibship size (number of siblings; quantitative variable) by the index pregnancy were considered by both adjustment and interaction analyses as planned a priori. The interactions were studied using observed solitary odds ratios and expected conditional odds ratio (OR) estimates from a multiplicative model, including the interaction between variable A (exposure) and variable B (birth order): $OR_{expected} = OR_{(A,\ nonB)} \times OR_{(nonA,\ B)}$ (18). Synergistic interaction was defined as an observed joint odds ratio greater than the expected joint odds ratio, tested by means of likelihood ratio statistics and considered to exist in a situation where most of the risk associated with A existed in the presence of B and vice versa.

The analyses were performed using SPSS for Windows (version 9.1; SPSS, Inc., Chicago, Illinois) and Stata (version 5.0; Stata Corporation, College Station, Texas) statistical software. All p values were two-sided; $p < 0.05$ was considered statistically significant.

RESULTS

We found 378 Finnish cases (203 girls and 175 boys) and 24 Icelandic cases (13 girls and 11 boys) for whom an archival serum sample taken from the index mother during the pregnancy was available. The 402 cases comprised almost all cases of leukemia in children born to Finnish and Icelandic mothers in 1983–1997 and 1975–1997, respectively, and their median ages were 3.1 years and 3.2 years. The median ages of the index mothers at the time of serum sampling were 28.4 years and 27.0 years, respectively. A total of 187 girls and 154 boys had ALL, and 29 girls and 32 boys had other forms of leukemia (non-ALL) (table 1). For both the Finnish ALL cases and the Icelandic ALL cases, the median age was 3.2 years; for the Finnish and Icelandic non-ALL cases, the median ages were 2.0 years and 3.2 years.

Chlamydia seroprevalence, as defined by the presence of IgG antibodies among the controls, was two times higher in Iceland (31 percent) than in Finland (16 percent) (table 1). *H. pylori* IgG antibodies were equally as common in Finland (32 percent) and Iceland (33 percent), but there was a clear predominance of both IgG and IgM antibodies in Icelandic index mothers (58 percent and 8 percent) compared with Finnish index mothers (30 percent and 2 percent). The frequencies of *M. pneumoniae* IgG and IgM antibodies were high in both countries: 81 percent and 5 percent, respectively, in Finland and 90 percent and 7 percent, respectively, in Iceland (table 1).

In the matched analyses, acute maternal *M. pneumoniae* infection, as defined by specific IgM positivity, appeared to be associated with an increased risk of childhood leukemia (OR = 1.6, 95 percent confidence interval (CI): 1.0, 2.5; table 2). However, the statistical significance was lost when specific *M. pneumoniae* IgM positivity, in the absence of *C. trachomatis* and *H. pylori* IgM antibodies, was used for the definition of acute infection (OR = 1.5, 95 percent CI: 0.9, 2.4). Adjusting for sibship size also dropped the lower

TABLE 1. Seropositivity of index mothers of acute lymphoblastic leukemia and other leukemia cases and matched* control mothers for *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, and *Helicobacter pylori* immunoglobulin G and immunoglobulin M antibodies in a joint cohort study of 550,000 Finnish and Icelandic women and their offspring, 1975–1997

Category	Acute lymphoblastic leukemia ($n = 341$)						Other (non-acute lymphoblastic) leukemia ($n = 61$)						Total (all leukemia) ($n = 402$)					
	No. of mothers		% positive for IgG*		% positive for IgM*		No. of mothers		% positive for IgG		% positive for IgM		No. of mothers		% positive for IgG		% positive for IgM	
	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control
Mycoplasma pneumoniae																		
Iceland	17	68	100	90	0	6	7	28	71	89	0	11	24	96	92	90	0	7
Finland	322	957	83	81	8	5	54	156	81	76	7	3	376	1,113	83	81	8	5
Both countries	339	1,025	84	82	8	5	61	184	80	78	7	4	400	1,209	84	81	8	5
Chlamydia trachomatis																		
Iceland	17	68	47	29	6	0	7	28	29	36	0	4	24	96	42	31	4	1
Finland	324	959	16	17	1	1	54	157	22	13	2	2	378	1,116	17	16	1	2
Both countries	341	1,027	18	18	1	1	61	185	23	17	2	2	402	1,212	19	18	1	1
Helicobacter pylori																		
Iceland	17	68	47	28	0	3	7	28	86	46	29	0	24	96	58	33	8	2
Finland	322	956	31	32	2	2	54	156	22	31	2	1	376	1,112	30	32	2	2
Both countries	339	1,024	32	32	2	2	61	184	30	34	5	1	400	1,208	32	32	2	2

* 1:3 for Finland; 1:4 for Iceland.
† IgG, immunoglobulin G; IgM, immunoglobulin M.

TABLE 2. Odds ratios for acute lymphoblastic leukemia and other leukemia according to maternal seropositivity for immunoglobulin G and immunoglobulin M antibodies to *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, and *Helicobacter pylori* in a joint cohort study of 550,000 Finnish and Icelandic women and their offspring, 1975–1997

Category	Acute lymphoblastic leukemia ($n = 341$)				Other (non-acute lymphoblastic) leukemia ($n = 61$)				Total (all leukemia) ($n = 402$)			
	IgG*		IgM*		IgG		IgM		IgG		IgM	
	OR*	95% CI*	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Mycoplasma pneumoniae												
Iceland	8	0.0, ∞	NA*		0.3	0.0, 2.3	NA		1.3	0.3, 6.2	NA	
Finland	1.2	0.8, 1.6	1.7	1.0, 2.8	1.3	0.6, 2.8	2.2	0.6, 8.2	1.2	0.9, 1.6	1.8	1.1, 2.8
Both countries	1.2	0.9, 1.7	1.6	1.0, 2.6	1.1	0.6, 2.3	1.5	0.4, 5.0	1.2	0.9, 1.6	1.6	1.0, 2.5
Chlamydia trachomatis												
Iceland	2.2	0.7, 6.8	8	0.0, ∞	0.7	0.1, 4.8	NA		1.6	0.6, 4.3	4.0	0.3, 64
Finland	1.0	0.7, 1.4	0.4	0.1, 1.9	1.8	0.8, 3.8	1.0	0.1, 9.6	1.1	0.8, 1.4	0.5	0.2, 1.8
Both countries	1.0	0.8, 1.4	0.7	0.2, 2.3	1.6	0.8, 3.2	0.8	0.1, 7.1	1.1	0.8, 1.5	0.7	0.2, 2.0
Helicobacter pylori												
Iceland	2.2	0.8, 6.1	NA		7.6	0.8, 74	8	0.0, ∞	2.8	1.1, 6.9	4.0	0.6, 28
Finland	0.9	0.7, 1.3	0.8	0.3, 2.1	0.6	0.2, 1.2	1.5	0.1, 17	0.9	0.7, 1.2	0.9	0.4, 2.1
Both countries	1.0	0.8, 1.3	0.8	0.3, 1.9	0.8	0.4, 1.6	5.1	0.8, 30	1.0	0.8, 1.2	1.1	0.5, 2.4

* IgG, immunoglobulin G; IgM, immunoglobulin M; OR, odds ratio; CI, confidence interval; NA, not available (no positive index mothers).

bound of the 95 percent confidence interval below 1 (OR = 1.6, 95 percent CI: 0.9, 2.6). Moreover, there was no significant interaction between *M. pneumoniae* and birth order per se, and the observed joint odds ratio ($OR_{obs} = 1.1$) for *M. pneumoniae* IgM positivity (solitary OR = 1.6) and birth order (solitary OR = 1.3) did not differ from that expected on the basis of a multiplicative model ($OR_{exp} = 2.0$; $p = 0.8$, likelihood ratio statistic).

In Iceland, maternal IgG antibody positivity to *H. pylori* was associated with a significantly increased total risk of childhood leukemia (both ALL and non-ALL) in the offspring (OR = 2.8, 95 percent CI: 1.1, 6.9; table 2). Moreover, a considerably increased point estimate was observed when the analysis was restricted to those Icelandic cases who were under 6 years of age at diagnosis (OR = 3.7, 95 percent CI: 1.4, 9.9). In Finland, *H. pylori* IgG antibodies were not associated with an increased risk of childhood leukemia (table 2), even if the case-index mother pairs were stratified by the cases' age at diagnosis or calendar time of serum sampling (data not shown).

DISCUSSION

In this study, the presence of maternal *H. pylori* IgG antibodies was associated with increased risk of childhood leukemia in the offspring in Iceland but not in Finland. Previously, *H. pylori* has been associated only with adult hematologic malignancies, such as mucosa-associated lymphoid tissue lymphoma (10, 11, 19, 20). In our study, the association was restricted to leukemia diagnosed in offspring under 6 years of age.

Adult leukemia patients have been reported to have low *H. pylori* seroprevalence (21), but in general, *H. pylori* seroprevalence varies greatly by time, location, and ethnic group (22). The Icelandic mothers of the leukemic children had significantly higher *H. pylori* seroprevalence than would be expected for their age group. In general, reproductive-age Finnish and Icelandic women appear to have similar background exposures to *H. pylori* over time (23, 24; the present study). However, the described phenomenon could not be found in Finland in any calendar-time strata of the Finnish index child-mother pairs. However, the possibility that a certain subset of ALL cases (for example) could be associated with *H. pylori* remains open.

H. pylori produces chronic and persistent infection in the gastric mucosa, and IgG antibodies disappear only after a period of several months after eradication of the microorganism (14). Thus, the presence of maternal *H. pylori* IgG antibodies implies the presence of the bacterium and the opportunity for mother-to-child transmission in very early infancy, which is recognized as an important route of infection for *H. pylori* (25). We are not aware of any differences in social class or lactation practices between Icelandic and Finnish women that would affect *H. pylori* exposure in their offspring, but pertinent questionnaire data are lacking. The sex ratio of the leukemia cases fits the Icelandic and Finnish cancer statistics (6). If *H. pylori* exposure really differs between Icelandic and Finnish infants and small children, the resulting early exposure to the microbial antigen is probably important in increasing the risk of childhood leukemia (4, 5).

The nested case-control design, which was based on quality-controlled cancer registers (15, 16), cross-generation linkage, and a long follow-up time from the index pregnancy to the leukemia diagnosis, rules out the possibility that the disease process could have activated *H. pylori* infection in

the pregnant women (26). It is also noteworthy that no other associations with bacterial IgG antibodies were observed.

Our approach was restricted to serologic analyses of first-trimester maternal serum samples and thus suffered from the common problem of misclassification bias (18). Indirect inferences about the offspring's susceptibility to or protection from infection are especially prone to this bias. On the other hand, the risk associated with *H. pylori* IgG antibodies was specific for the Icelandic women and their offspring, who were diagnosed with childhood leukemia at less than 6 years of age (i.e., with the bulk of ALL cases). Such a finding is unlikely to have resulted from misclassification, but this possibility cannot be ruled out.

M. pneumoniae has been associated with childhood leukemia in case reports, cross-sectional seroepidemiologic studies, and animal studies (8, 9, 27, 28). However, *M. pneumoniae* IgM antibody positivity, an indicator of acute maternal infection, lost statistical significance when results were controlled for sibship size and birth order, which are common risk factors for childhood leukemia and lymphoma (3, 29). This was also the case when the generally poor specificity of the IgM antibody determination was considered further using a robust method of excluding cases and controls with multiple positive IgM antibody findings.

To our knowledge, we have documented for the first time the possibility of an association between maternal *H. pylori* infection and risk of childhood leukemia in the offspring. Independent confirmatory studies are needed.

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