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Original Article

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Helicobacter pylori Infection and Risk Factors in Relation to Allergy in Children

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Purpose: To analyze presence of *Helicobacter pylori* infection and environmental risk factors among children with and without allergy.

Methods: Parents of children at primary health care centres/kindergartens and allergologist consultation were asked to answer a questionnaire and to bring a faecal sample. *H. pylori* infection was detected by monoclonal stool antigen test. Prevalence of *H. pylori* infection and risk factors were compared between individuals with and without allergy using χ^2 test, ANOVA test and parameters and logistic regression.

Results: Among 220 children (mean age, 4.7 years; ±standard deviation 2.3 years) *H. pylori* positivity was non-significantly lower among patients with allergy (n=122) compared to individuals without allergy (n=98): 13.9% (17/122) vs. 22.4% (22/98); p=0.106. In logistic regression analysis presence of allergy was significantly associated with family history of allergy (odds ratio [OR], 8.038; 95% confidence interval [CI], 4.067-15.886; $p<0.0001$), delivery by Caesarean section (OR, 2.980; 95% CI, 1.300-6.831; p=0.009), exclusive breast feeding for five months (OR, 2.601; 95% CI, 1.316-5.142; p=0.006), antibacterial treatment during the previous year (OR, 2.381; 95% CI, 1.186-4.782; p=0.015).

Conclusion: Prevalence of *H. pylori* infection did not differ significantly between children with and without allergy. Significant association of allergy with delivery by Caesarean section and antibacterial therapy possibly suggests the role of gastrointestinal flora in the development of allergy, while association with family history of allergy indicates the importance of genetic factors in the arise of allergy.

Key Words: Allergy, *Helicobacter pylori*, Risk factors

INTRODUCTION

Opposite prevalence trends of *Helicobacter pylori* infection and allergy in different populations have given rise to speculations about the possible role of *H. pylori* in the development of allergy [1,2]. Although

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evidence from observational studies indeed shows a weak inverse association between prevalence of *H. pylori* infection and allergy [3], lower prevalence of infection observed in allergic children could also be influenced by several confounders like socioeconomic factors, antibiotic use and others. Therefore analyzing the possible association between *H. pylori* infection and allergy, controlling for several confounding factors is important, in order to see if *H. pylori* is independently inversely linked to the presence of allergic diseases. Since developement of allergy is influenced by many factors during childhood, the possible association between the bacterium and allergy could be better observed in children, since effect of several factors could disappeared later in life, as suggested also by Chen and Blaser [2].

Despite *H. pylori* prevalence decrease in Eastern European countries, previous studies show rather high *H. pylori* prevalence in Latvia, both in children [4] and adults [5]. However, the prevalence of allergic diseases is also increasing in the area during the previous decades. Therefore the association between *H. pylori* and allergy could be easily evaluated in Latvian population.

Aim of the study was to compare the prevalence of active *H. pylori* infection among children with and without allergy and further, to analyse the association between different environmental risk factors and presence of allergy.

MATERIALS AND METHODS

Study design

The study was performed in two primary health care centres, in three kindergartens and in an out-patient allergologist consultation at Children Clinical University Hospital Gailezers, Riga, Latvia from 2009 to 2011. The parents of the children were asked to fill-out a questionnaire and to bring a faecal sample of the child.

Different risk factors as well as presence of *H. pylori* were compared between children with and without allergy.

Patients

The study included consecutive children (1-7 years of age) attending allergologist consultation and diagnosed with allergy. The control group included consecutive children (aged 1-7 years) coming for general check-up or due to minor health problems at primary care out-patient clinics and children of the same age at kindergartens.

Children diagnosed with allergy at allergologist consultation were considered as individuals with "physician diagnosed allergy." Children, whose parents had marked the presence of physician diagnosed allergy in a questionnaire, were excluded from the final sample.

Methods

1. Questionnaire

A structured questionnaire asked data about the presence of allergic disease in first stage relatives, the type of the delivery of the child (vaginal vs. Caeserain section), perinatal period (normal vs. with complications), duration (in months) of exclusive and total breast feeding, number of siblings and number of household members, as well as parental education (12 years vs. more than 12 years) and possession of different household facilities and equipment (washing machine, dish-washer, computer, mobile phone). Further, questionnaire asked about usage of different vegetables and fruit (banana, oranges, tomatoes, grapes, apples, local fruit, imported fruit) and soft carbonated drinks, indicating frequency of consumption of the product (every day, 2-3 times per week, once per week or once per months). Parents/family doctor were asked to specify, if child had been treated with antibiotics during the first year of life, during the previous year or more than a year before.

2. Monoclonal enzyme-linked immune assay stool antigen test

Presence of *H. pylori* infection was detected by monoclonal enzyme-linked immune assay stool antigen test (Meridian Diagnostics Inc., OH, USA). In Caucasian population the monoclonal stool anitgen test has shown a sensitivity of 88.9% (95% con-

fidence interval [CI], 77.3-96.3) and a specificity of 94.0% (95% CI, 88.1-97.7) [6]. The faecal samples were stored at −20°C until analysis. The analysis was performed according to manufacturer's instructions in a certified laboratory and read by one person. The samples with values >0.18 were considered positive.

Statistics

The Pearson χ^2 test and Fisher exact were used to assess the univariate associations between presence of allergy and *H. pylori* positivity and possible risk factors. Mean values were compared with ANOVA test. Variables with a *p*-value<0.08 were entered into a multivariate logistic regression analysis model and the odds ratios (OR) with the 95% CI were calculated. Statistical analysis was performed using statistical programme MedCalc Statistical Software ver. 13.2.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

The study was approved by the Ethics Committee of University of Latvia, Institute for Experimental and Clinical Medicine. Parents of the children signed patient written consent form.

RESULTS

The patient sample involved 242 children (122, at allergologist consultation; 120, healthy children). Among 120 healthy children, parents of 22 individuals had marked the presence of allergy in the questionnaire; therefore the final patient sample for analysis contained 220 children (mean age, 4.7 years; standard deviation [SD], ±2.3 years; median of age, 5 years; range, 1-7 years; boys, 54% [119/220]): 98 children without allergy and 122, with physician diagnosed allergy (food allergy, allergic rhinitis, atopic dermatitis, asthma).

In the total patient sample *H. pylori* positivity was 17.7% (39/220). *H. pylori* positivity was non-significantly lower among patients with allergy compared to individuals without allergy: 13.9% (17/122) vs. 22.4% (22/98); OR, 0.565; 95% CI, 0.281-1.136; $p=0.106$. However, *H. pylori* positivity was 31.8% (7/22) among individuals with a parent-reported allergy, 22.4% (22/98) among individuals without allergy and 13.9% (17/122) among patients with physician diagnosed allergy (*p* for trend=0.031).

In the univariate analysis presence of allergy was significantly associated with the following variables: "allergy in family history," "delivery by Caesarean section," "exclusive breast feeding for five months," "education of the mother >11 years," "treatment with antibiotics during the previous year," "antibacterial treatment during the first year of life" (Table 1).

Duration of exclusive and total breast feeding was longer among children with allergy compared to children without allergy: 4.7±2.1 vs. 4.2±2.8; $p=0.129$ and 10.07±7.57 vs. 8.31±5.42; $p=0.051$, respectively.

Presence of allergy was not associated with the fol-

Table 1. Factors Associated with the Presence of Allergy in the Univariate Analysis

Risk factor	Allergy status	n/total of the group (%)	*p*-value
Allergy in family	Physician diagnosed allergy	82/117 (70.1)	<0.0001
	No allergy	21/98 (21.4)	
Delivery by Caesarean section	Physician diagnosed allergy	38/118 (32.2)	0.002
	No allergy	14/98 (14.3)	
Maternal education >11 years	Physician diagnosed allergy	70/121 (57.9)	0.108
	No allergy	46/98 (46.9)	
Exclusive breast feeding at least five months	Physician diagnosed allergy	61/119 (51.3)	0.011
	No allergy	31/92 (33.7)	
Antibacterial treatment during the first year of life	Physician diagnosed allergy	61/116 (52.6)	0.106
	No allergy	38/92 (41.3)	
Antibacterial treatment during the previous year	Physician diagnosed allergy	81/117 (69.2)	0.0003
	No allergy	41/92 (44.6)	

lowing factors: number of siblings, consumption of different kinds of fruit, carbonated drinks and variables, indicating socioeconomic status.

In the logistic regression model the following variables showed a significant association with allergy: "family history of allergy" (OR, 8.038; 95% CI, 4.067-15.886; $p<0.0001$), "delivery by Caesarean section" (OR, 2.980; 95% CI; 1.300-6.831; $p=0.009$), "exclusive breast feeding for five months" (OR, 2.601; 95% CI, 1.316-5.142; $p=0.006$), "antibacterial treatment during the previous year" (OR, 2.381; 95% CI, 1.186-4.782; $p=0.015$).

DISCUSSION

The present study showed that the prevalence of *H. pylori* infection did not differ significantly between children with and without allergy and identified the role of interaction of genetic (family history of allergy) and environmental (type of delivery, breast feeding, previous antibacterial therapy) factors in the development of allergy, thus suggesting the importance of gastrointestinal microbiota in the formation process of allergy.

An inverse association between *H. pylori* infection and allergy has been demonstrated in several meta-analyses [7-9]. However, as mentioned previously, the main criticism in respect to the association between infection and allergy is related to the confounding factors that could influence lower prevalence of infection in allergic children.

In our patient sample prevalence of *H. pylori* infection was only non-significantly lower among patients with allergy compared to healthy children. We have to mention that socioeconomic status was evaluated by different variables regarding socioeconomic class (possession of household utilities, parental education and other factors) and the studied patient sample appeared to be rather homogeneous in respect to socioeconomical factors. Further, we observed a significant association between presence of allergy and previous antibacterial treatment. Therefore we could speculate that allergic children are frequently treated with antibiotics due to respiratory diseases that could further lead to disappearance of *H. pylori* infection or false negative *H. pylori* faecal tests. Transient *H. pylori* infection in children and negative association between *H. pylori* and antibacterial treatment has been reported by O'Ryan et al. [10].

On the other hand, studies show, that antibacterial therapy *per se* (especially during infancy) could be independently linked to the development of an allergic disease. For example, Xie et al. [11] in a meta-analysis demonstrate that use of antibacterial agents in the first years of life increases the risk of childhood asthma. Morover, Timm et al. [12] has demonstrated that even prenatal exposure to antibiotics could be associated with an increased risk of atopic dermatitis among children born by atopic mothers. However, in our patient sample antibacterial therapy during the first year of life was not independently significantly associated with the presence of allergy, suggesting that therapy could be a marker of compromised health status during infancy.

Nevertheless, possible changes of microbiota due to frequent antibacterial therapy go together with the idea about the role of microbiota in the development of allergy, supported also by a study that demonstrate association between type of delivery and allergy [13]. For example, an association between Caesarean section and childhood asthma is shown by meta-analysis of studies in 2008, suggesting that delivery by Caesarean section influences the formation of gastric microbiota and further leads to development of allergy [14]. A subsequent meta-analysis by Huang et al. [15] demonstrates even a a 20% increase in risk of asthma in children delivered by Caesarean section, that made the authors speculate that the rise in asthma could be explained by increasing rate of Caesarean section during the same time period. A significant independent association between type of delivery and presence of allergy was identified also in our studied patient sample, thus supporting the hypothesis about the association between the delivery by Caesarean section and development of allergy.

Further, the formation of gastrointestinal microbiota is also largely influenced by the type of infant

feeding (breast feeding vs. formula feeding), that is also related to the development of allergy. However, recently results of a systematic review of studies concluded that the association between breast feeding and allergy is still controversial [16]. It could be explained by co-existence of several pathogenetic mechanisms. Firstly, it has been proposed that different immunological components in human milk could influence the development of immune system and protect against the development of allergy (also by promoting formation of normal microbiota) [17]. On the other hand, in allergic mothers food antigens could be transfered to the infant [18] and a recent study even showed, that transforming growth factor-beta levels in human milk were associated with increased risk of eczema in infant [19].

Therefore the association between allergy and exclusive breast feeding for at least five months observed in our patient sample, could be explained by possible transfer of allergens in human milk, promoting development of allergy in infants with genetic predisposition. On the other hand, breast feeding could be an indicator of higher parental education together with higher living standards, that could be associated with increased risk of allergy. Therefore we could speculate that the possible protective effect of breastfeeding probably depends on the right ballance of the amount of antigens in breast milk, presence of immunomodulatory factors as well as interaction of all other factors (like family history), suggested also by Verhasselt [20]. Interestingly, Munblit and Verhasselt [21] have proposed an idea that the composition of breast milk could be modified to induce tolerogenic potential.

Nevertheless, family history of allergy showed the highest risk for development of allergy in a child, thus confirming the role of genetic factors in the development of allergy. Family history of atopy as a risk factor for allergy in children has been identified by several authors [22,23], also supported by twin studies [24] and many genes that have been identified in the pathogenesis of asthma [25]. However, Wu et al. [26] argue that family might also share common environmental risk factors, indicating the need to study environmental risk factors further.

Prevalence of *H. pylori* infection did not differ significantly between children with and without allergy suggesting that bacteria *per se* may not be linked to the protection against allergy and previously observed associations could be biased by more frequent antibacterial therapy among children with allergy.

The observed significant association between presence of allergy and delivery by Caesarean section, previous antibacterial therapy and family history of allergy indicates the role of interaction of environmental and genetic factors in the development of allergy. The finding indirectly emphasizes also the importance of gastrointestinal tract microflora in the formation of immune system; therefore, *H. pylori* could be regarded as one of the components of microbiota indicating complex changes in gut microbiome.

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