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***Helicobacter pylori* as a protective factor against food allergy**

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Summary

Background:

There is some evidence that *Helicobacter pylori* (Hp) infection may protect against asthma and allergy. The aim of the present study was to analyse the prevalence of Hp infection in adults with proven food allergy and to compare it with that in appropriate healthy controls. In addition, the effects of infection with Hp on urinary excretion of N-tele-methylhistamine and production of IgE and allergy mediators such as eosinophilic cationic protein (ECP) and mast cell tryptase, were assessed.

Material/Methods:

Hp infection, the production of IgE and several allergy mediators and mucosal expression of interleukin-4 were measured in 42 patients with food allergy and compared with those in 20 healthy subjects.

Results:

The prevalence of Hp infection among adult food allergy patients was 33.3% and it was significantly lower than that in the control group (40%). The excretion of urinary N-tele-methylhistamine was higher in food allergy patients than in healthy controls. In food allergy patients with Hp infection, the serum ECP was significantly lower than in food allergy patients without Hp infection. The serum IgE level was significantly higher in food allergy patients infected with Hp than in food allergy patients without Hp infection.

Conclusions:

We conclude that: 1) Hp infection is associated with a decreased risk for food allergy; 2) presence of Hp in food allergy patients has ameliorating effect on the production of allergy mediators such as ECP and mast cell tryptase and 3) Hp infection appears to be a protective factor against food allergy.

key words:

***Helicobacter pylori* • food allergy • immune regulation**

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BACKGROUND

Helicobacter pylori (Hp) is recognized as the main cause of chronic gastritis and intimately associated with the development of peptic ulcer disease and in some cases with a gastric carcinogenesis [1]. There is also evidence that Hp is associated with a number of extragastric diseases including cardio- and cerebrovascular diseases, autoimmune disorders, hematologic diseases, atopy and skin diseases, chronic liver diseases and others. Despite epidemiological evidence the precise implication of Hp in extragastric diseases has still not been proven [2].

Recently, several studies have reported a possible association between Hp infection and food allergy. In the study by Corrado et al [3], which was performed in children with food allergy, it was found that the titers of anti-Hp antibodies were significantly higher among children with food allergy as compared to the control group. In another study by Figura et al. [4] the prevalence of Hp was similar among adult patients with symptomatic food allergy and non-allergic controls (42.1%, and 48.3%, respectively). However, anti-CagA-antibodies were detected in 62.5% of patients with food allergy versus 28% of controls. This last observation indicates that patients with food allergy are more frequently infected with bacterial Hp strains inducing stronger inflammatory reaction in the gastric mucosa.

A number of arguments supports the role of Hp in food allergy. First of all, Hp triggers in the gastric mucosa chronic inflammatory processes which could increase the permeability of gastric barrier and enhance the crossing of food antigen [1]. Secondly, water extracts of Hp cause degranulation of rat mast cells [5]. In addition, Nakajima et al [6] observed an increased density of mast cells in chronic Hp-induced gastritis. Thirdly, Hp leads to increased IgE production, what may contribute to allergic conditions [6]. Finally, in some patients with Hp infection a significant decrease in gastric acid secretion occurs [1], which can potentially lead to the reduced protein degradation and increased antigen transfer from the gastrointestinal tract to the blood with consecutive immune cell response [7].

Approximately up to 20% of the people in western countries suffer from adverse reactions to food [8]. Around a third of these have gastro-intestinal symptoms ranging from localized mouth itching and swelling to cramping abdominal pain, bloating and diarrhea. Non-specificity of the symptoms and lack of objective diagnostic methods are the main reason for the limited understanding of the pathophysiology of intestinal food hypersensitivity [9].

According to the revised nomenclature for allergy, food hypersensitivity embraces both food allergy and non-allergic food hypersensitivity [10]. Food allergy might be or might not be mediated by IgE. Mast cells, eosinophils and intra-epithelial T-cells are involved in the pathogenesis of food allergy. Mast cells release potent inflammatory and immune system modulating mediators that play a key role in allergic reactions to food. Tryptase represents an important marker of the degranulation of these cells. In 1981, Schwartz et al. [11] described the purification of tryptase, a proteolytic enzyme from mast cell secretory granules. This granule-bound tryptase in serum is highly related to mast cell activity of patients with food allergy.

Eosinophils accompany both the immediate and the late phases of allergic reactions and induce cell and tissue damage when activated. Eosinophilic cationic protein (ECP) is considered as an important mediator of these cells [12].

Another important indicator of food allergy is the excretion of a stable metabolite of histamine in urine such as N-tele-methylhistamine which is a more specific and sensitive marker of food allergy than histamine itself [13].

The aim of the present study was (1) to analyse the prevalence of Hp infection in adults with proven food allergy and to compare it with an appropriate healthy controls; (2) to assess the frequency of infection with cytotoxic CagA-positive Hp strains among patients with food allergy and appropriate healthy controls, (3) to analyse the effect of infection with Hp on the production of allergy mediators such as ECP and mast cell tryptase and (4) to analyse the gastric mucosal gene expression of interleukin-4, a key cytokine playing a regulatory role in the pathogenesis of allergic reaction.

MATERIAL AND METHODS

42 patients with food allergy (mean age 46.5 years; age range: 25–65 years) and 20 controls (mean age 49.1 years; age range: 18–65 years) were included in this study. The study was approved by the Regional Ethical Research Committee of the University Erlangen-Nuremberg and all patients and controls gave written informed consent. Persons were excluded from the study when conditions such as liver or renal diseases, pregnancy, coagulation disorders were present.

Food allergy was clinically confirmed by typical clinical history, skin prick tests, serum IgE radioallergosorbant test (RAST), double-blind, placebo-controlled food challenge, and determination of cell specific markers of allergy such as plasma histamine, urinary N-tele-methylhistamine, plasma tryptase and serum eosinophilic cationic proteins (ECP).

Determination of excretion of urinary N-tele-methylhistamine

Urinary excretion of N-tele-methylhistamine (UMH) was measured under a normal non-restricted diet and hypoallergic potato-rice diet. Urine samples were collected after overnight fast because intraindividual variation of histamine production and excretion caused by diet, hormonal influence, physical activities, smoking are lower during the night. Because excretion of UMH may be influenced by renal function, weight and body size, UMH values were related to creatinine excretion and concentration of UMH and were expressed as $\mu\text{g}/\text{mmol}$ creatinine per m^2 body surface area. Serum creatinine in all patients was below 1.4 mg/dl. Because microbial contamination may lead to bacterial production of histamine, bacterial overgrowth in urine was prevented by addition of 10 ml of 1 M HCl at the beginning of the urine collection period. Only urine samples whose pH values were between 1 and 3 were analysed to avoid false positive results. Concentration of UMH were measured by double antibody radioimmunoassay (Pharmacia, Upjohn Company, Freiburg, Germany). The RIA was performed according to the manufacturer's instruction as described before [13]. Coefficients of intra- and interassay variation were 12.5% and 14.2%, respectively.

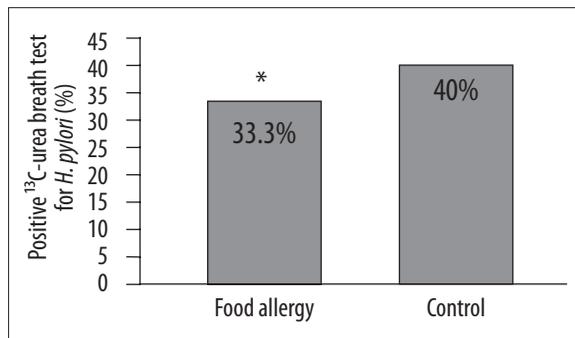


Figure 1. Prevalence of Hp infection among food allergy (FA) patients and healthy controls detected by ^{13}C urea breath test (UBT).

Measurements of ECP and tryptase, total IgE and food specific IgE

ECP and tryptase were measured in serum by means of radioimmunoabsorbent assay (Pharmacia, Uppsala, Sweden) according to the manufacturers guidelines as described previously [14]. Intraassay variation was 5.5% and interassay variation was 5.7%, respectively.

Total serum IgE and food specific IgE were determined using the CAP fluorescence-enzyme linked immunoassay technique (Pharmacia, CAP system, Freiburg, Germany).

Double-blind, placebo-controlled food challenge

Further clinical workup in patients with food allergy included double blind, placebo-controlled food challenge. This investigation was performed in a standardized fashion while the patients were hospitalised. Food was administered using a nasogastric tube. Three different doses of the same food were provided within one day. Initially, about half of the minimum quantity that is thought to produce symptoms was given, followed by a full dose, and eventually by a triple dose (at least 0.6 g of wet food per kg body weight). Placebo consisted of an oligopeptide diet (protein source: hydrolysed soja bean, survived OPD, Fresenius, Germany) which was also used in conjunction with a potato-rice diet for base line nutrition (minimum 1800 kcal per day) to prevent a catabolic state. Only one food challenge was performed per day, and blinding was carried out by the nutritionists who were responsible for the preparation of the food. The food to be tested was selected by the physician on the basis of the patient's history, skin prick test and radioallergosorbent test. During the provocation procedure, the patient was provided with a peripheral venous line and nurses and physicians were trained for medical intervention in case of an anaphylactic reaction. This procedure has been established by our group previously [14,15].

Helicobacter pylori detection

Detection of Hp infection was performed using ^{13}C -urea breath tests (Wagner Analysis Technik, Bremen, Germany). The assessment of CagA antibody prevalence was performed according to the manufacturer's instruction (Virotech, Rüsselsheim Germany) as described before [16].

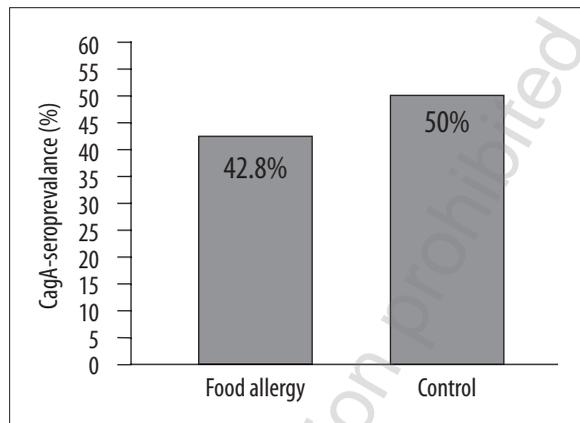


Figure 2. Seroprevalence for CagA among food allergy patients and healthy controls.

Determination of mRNA for IL-4

Analysis of mRNA expression of IL-4 was performed by RT-PCR. For RT-PCR analysis, gastric biopsy samples from gastric mucosa were homogenised in 200 μl of Trizol (Gibco BRL, Germany) and RNA was recovered according to manufacturers instruction before resuspension in 20 μl of diethyl pyrocarbonate-treated water and quantification as described before [17].

Human complementary DNA (cDNA) was generated by reverse transcription of total RNA extracted from mucosal biopsy specimens, using Moloney murine leukaemia virus reverse transcriptase (MMLV-RT) and oligo-dt primers (Stratagene, Heidelberg, Germany). The cDNA (2 μl) was amplified in a 50 μl reaction volume containing 2 U Taq polymerase, dNTP (200 μmol each), 1.5 mM MgCl_2 , 5 μmol 10x polymerase chain reaction buffer and primers used at final concentration of 1 mM (all reagents from Takara, Shiga, Japan). The polymerase chain reaction mixture was amplified in a DNA thermocycler. The sequence of primers for IL-4 and GAPDH were based on the sequences of published cDNA. All primers were synthesised by Gibco Life Technologies (Eggenstein, Germany). Polymerase chain reaction products were detected by electrophoresis on a 1.5% agarose gel containing ethidium bromide. The location of predicted products was confirmed using a 100-bp ladder (Takara) as the standard size marker. The intensity of bands was quantified using a densitometry unit from Kodak Digital Science.

Statistical analysis

The results are expressed as means \pm standard errors (SE). Differences between groups were evaluated by using the Mann-Whitney test. $P < 0.05$ was considered statistically significant.

RESULTS

Prevalence of Hp infection

The prevalence of Hp infection among adult food allergy patients was 33.3% and was significantly lower than in the healthy control group (40%) ($p < 0.05$) (Figure 1).

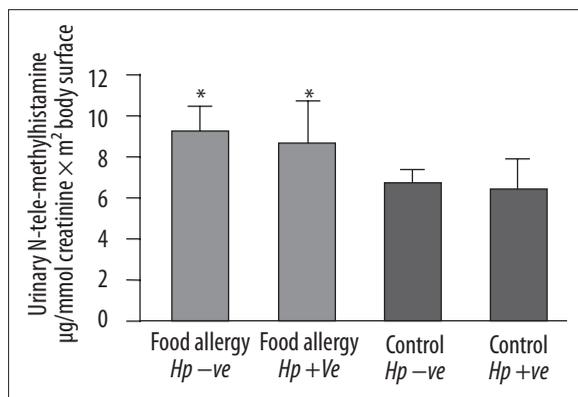


Figure 3. Excretion of N-tele-methylhistamine in urine over 24 hours in Hp-positive and Hp-negative patients with food allergy or control subjects. The excretion of UMH was significantly higher in patients with food allergy than in control subjects ($p < 0.05$).

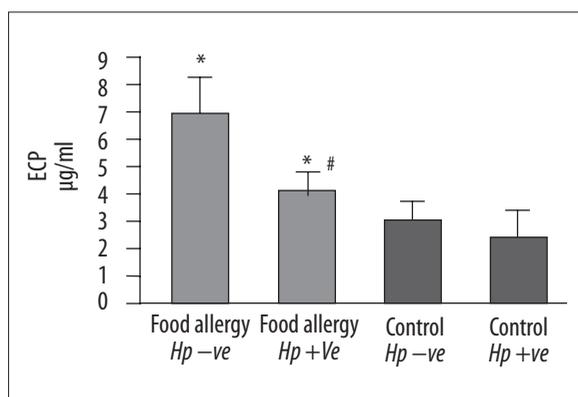


Figure 4. Serum levels of eosinophilic cationic protein (ECP) in Hp-positive and Hp-negative patients with food allergy or healthy controls. * means a significant increase over the value observed in control subjects. # means significant decrease in Hp+ve patients with food allergy as compared to value in Hp-ve with food allergy.

CagA seroprevalence

The seroprevalence of CagA among food allergy patients was 42.8% and among healthy control 50%. There was no significant difference in the Hp CagA prevalence among these investigated groups ($p > 0.05$) (Figure 2).

Urinary N-tele-methylhistamine

Urinary methylhistamine (UMH) was found to be elevated in food allergy patients compared with controls ($p < 0.05$). Among Hp negative food allergy patients there was a tendency for higher UMH excretion as compared to Hp positive food allergy patients. However, there was no significant difference between these groups. UMH was significantly lower in the control group and there was no significant difference between patients infected or not infected with Hp (Figure 3).

Serum eosinophilic cationic protein (ECP)

As illustrated in the Figure 4, the serum ECP level in food allergy patients (both Hp-positive and Hp-negative) was sig-

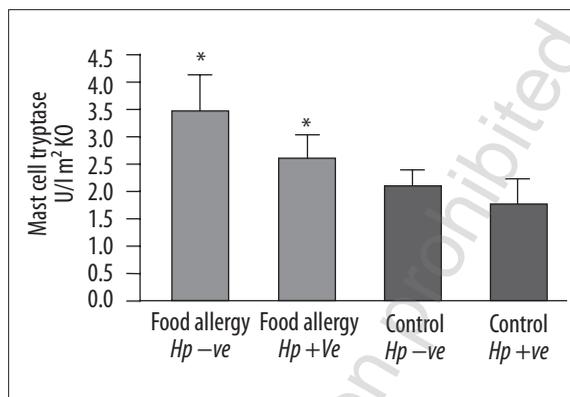


Figure 5. Serum mast cell tryptase in Hp-positive and Hp-negative patients with food allergy or control subjects. * means a significant increase over the value observed in control subjects.

nificantly higher than in appropriate healthy controls. In food allergy patients with Hp infection, the serum ECP was significantly lower than in food allergy patients without Hp infection. In the control group we observed a lower level of serum ECP and there was no significant difference between Hp-positive and Hp-negative group (Figure 4).

Mast cell tryptase

Similarly to other allergy mediators, the mean serum concentration of mast cell tryptase was significantly elevated in food allergy patients as compared to healthy controls. In Hp negative food allergy patients the concentration of serum mast cell tryptase tended to be higher than in food allergy patients with Hp infection. However, this difference was not significant. In control group, lower levels of mast cell tryptase were observed and there was no significant difference between Hp-positive and Hp-negative groups (Figure 5).

IgE concentration

Patients with food allergy showed significantly elevated total IgE levels as compared to the control group. The serum IgE level was significantly higher in food allergy patients infected with Hp than in food allergy patients without Hp infection. Compared to this group, the total IgE concentration in serum of healthy controls was significantly lower (Figure 6).

Expression of IL-4 mRNA

Using RT-PCR, mRNA expression for interleukin-4 was negligible in biopsies taken from antrum and corpus from healthy controls. In contrast, in patients with food allergy an increased expression of IL-4 was observed. The expression of IL-4 was higher in corpus than in antrum.

DISCUSSION

This study demonstrates for the first time that adult European patients with food allergy have significantly lower Hp prevalence than appropriate healthy controls. This may indicate that patients with Hp infection have a substantially reduced risk of food allergy. This is keeping with previous

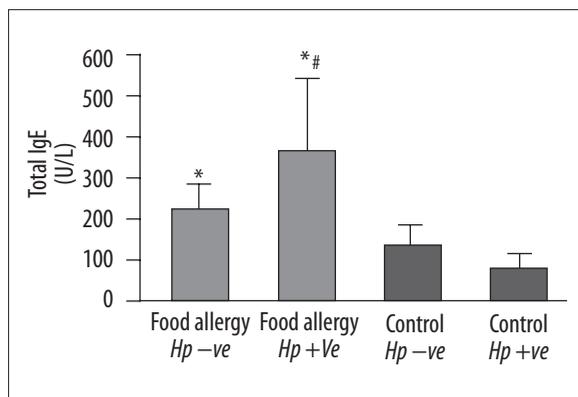


Figure 6. Serum IgE levels in Hp-positive and Hp-negative patients with food allergy or healthy control persons. * means a significant increase over the value observed in control subjects. # means significant increase in Hp+ve patients with food allergy as compared to value in Hp-ve with food allergy.

studies showing a reduced prevalence of allergic disorders in patients with Hp infection. Our observation is also consistent with so-called “hygiene hypothesis” postulating that early childhood infections can suppress allergic disorders [18,19]. A further evidence for the inverse relationship between the prevalence of atopy and seropositivity to Hp was demonstrated in a recent study performed in Finnish and Russian Karelia. In Finland the prevalence of atopy was found to be significantly higher than in Russia. This difference was explained, at least in part, by significantly higher Hp seropositivity in Russia than in Finland. The authors concluded that the exposure to Hp is associated with protection against atopy [20]. There is also an evidence that the acquisition of Hp, especially cagA-positive strain, is associated with the reduced risk for asthma and allergy [21]. This and our observation indicate that the elimination of Hp in childhood may result in increased risk in the development of atopic disorders including food allergy.

The possible explanation for the decreased prevalence of Hp infection among patients with food allergy could be also the increased Th2-type immune response expressed in the gastric mucosa of food allergy patients. There is an evidence indicating that the increased Th2-type immune response may ameliorate Th1-response observed during Hp infection. This aspect has been recently investigated in an experimental mouse model, in which a concurrent enteric helminth infection caused a significant inhibition in the progression of Hp-associated gastric atrophy [22,23]. Supporting for this hypothesis is our detection of increased expression for interleukin-4 mRNA in gastric mucosa of food allergy patients. According to the recent reports, IL-4 strongly enhances mast cell proliferation and shifts IgE-dependent cytokine production in mature mast cells toward an increased release of Th2 cytokines such as IL-3, IL-5, IL-13 [24].

Our results are in contrast to studies showing a permissive role of Hp in the induction of food allergy. Recently, it has been demonstrated that gastric infection with Hp can inhibit the development of oral tolerance to dietary antigens [25]. In addition, the same group showed that Hp increases the epithelial permeability to a food antigen in human

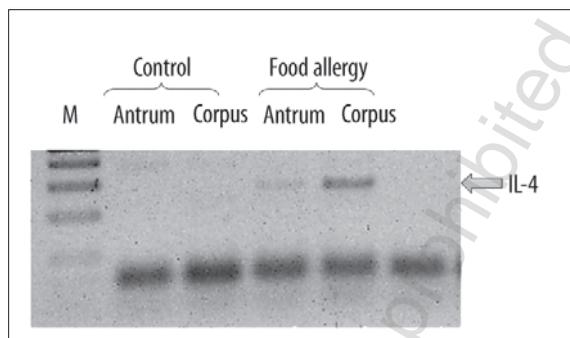


Figure 7. Representative expression of IL-4 mRNA in gastric mucosal biopsies analyzed by RT-PCR in Hp-positive healthy control and Hp-positive-patient with food allergy.

gastric biopsies [26]. Based on these results authors postulated that this phenomenon could play a crucial role in the development of allergic sensitisation to dietary antigens in susceptible individuals.

Although the serologic data in our study indicate a decreased risk of food allergy in Hp-infected patients, unclear is whether the presence of Hp modulates the metabolism of histamine. In the present study we measured urine excretion of N-tele-methylhistamine (UMH) as indirect parameter for histamine generation. UMH is a stable metabolite of the histamine catabolism and is produced by the enzymatic reaction of histamine N-methyltransferase which is predominantly present in intestinal, hepatic, central nervous and renal tissue. Although histamine can be inactivated by either oxidative degradation (diamine oxidase) or transmethylation (histamine N-methyltransferase), endogenously produced histamine in humans has been found to be largely inactivated by specific reaction of histamine N-methyltransferase [27]. In the present study we found an increased excretion of UMH in food allergy patients and this is keeping with our previous results [13]. However, there was no significant difference in the excretion of UMH in patients infected or non-infected with Hp, possibly due to the small patient number. Based on this observation we can assume that the presence of Hp in patients with food allergy does not significantly alter the metabolism of histamine. The other explanation could be that Hp produces by itself N-tele-methylhistamine [28] and this leads to an increased excretion of UMH or interferes with the RIA measurement, though Hp infected patients had lower urinary UMH levels.

Interestingly, there were significant differences in the serum levels of eosinophilic cationic protein (ECP) and mast cell tryptase indicating an ameliorating effect of Hp on the allergic reactions in the gastrointestinal mucosa. This observation is important since both mediators play a key role in the inflammatory and allergic reactions [11,12,29]. This observation suggests that the eradication of Hp could potentially aggravate the food allergy symptoms. This aspect has not been investigated in the present study but further investigations to clarify this hypothesis are of clinical importance.

Concerning the level of IgE, we found a significantly higher level of IgE in Hp positive as compared to Hp negative patients. This is keeping with previous studies showing a

marked increase in IgE production in Hp infected patients [30]. Although the significance of this IgE response is unclear, it is possible that the serum IgE increase could be the result of food specific-sensitization and increased gastric mucosal permeability.

CONCLUSIONS

In summary, we conclude that 1) the Hp infection is associated with a decreased risk for food allergy; 2) the presence of Hp in food allergy patients has ameliorating effect on the production of allergy mediators such as ECP and mast cell tryptase and 3) Hp infection appears to be a protective factor against food allergy.

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