Concentrations of gastric mucosal cytokines in children with food allergy and *Helicobacter pylori* infection

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**Abstract**

**AIM:** To measure the concentrations of chosen cytokines in the antrum mucosa depending on the kind of harmful pathogenic factors and to compare the concentrations with the values of controls without allergy and coexisting *Helicobacter pylori* (*H. pylori*) infection.

**METHODS:** The patients (97 children) were divided into three groups according to the data obtained from the case history, to the main cause of the disease and to the dominant clinical symptoms. Group I: children with food allergy (Fa); group II: children infected with *H. pylori*; group III (control group): children with functional disorders of the alimentary tract (without Fa and Hp infection). *H. pylori* infection was determined by the presence of anti-Hp antibodies in serum (ELISA method) and urease test performed during endoscopic examination. Cytokine concentration in homogenates of gastric mucosa was detected by ELISA method.

**RESULTS:** The IL-2 concentration in gastric mucosa bioplates was the highest in children with *H. pylori* infection (116.5±179.5 pg/mg of the protein) and Fa and *H. pylori* infection (98.1±101.0 pg/mg), while decreased in children with Fa (44.8±50.3 pg/mg) and controls (45.7±23.5 pg/mg). The lowest mean concentration of IFN-γ was observed in children with *H. pylori* infection (18.9±16.4 pg/mg), with Fa and *H. pylori* infection (25.5±27.7 pg/mg), with Fa (40.6±39.7 pg/mg) and controls (49.9±33.4 pg/mg). The highest IL-4 concentrations were observed in children with *H. pylori* infection (35.3±52.8 pg/mg) and in children with Fa and *H. pylori* infection (37.2±51.7 pg/mg), while lower IL-4 concentration (23.6±35.8 pg/mg) was found in children with Fa compared to the controls (22.7±13.8 pg/mg). The analysis of IL-4 concentrations in children with *H. pylori* infection regarding the intensity of gastritis showed the highest value (62.2±61.2 pg/mg) in mild and moderate gastritis. The concentrations of IL-5 in the gastric mucosa of children with or without Fa did not differ significantly and were comparable to the control group. The highest mean IL-8 value was observed in *H. pylori*-infected children with or without Fa. The highest concentration of mucosal IL-10 was detected in children with *H. pylori* infection (79.3±41.2 pg/mg) and decreased in children with Fa and *H. pylori* infection (50.1±18.8 pg/mg) and in children with Fa (39.9±35.5 pg/mg). The intensity and activity of the inflammation did not affect IL-10 concentrations in the gastric mucosa. In children with *H. pylori* infection, TNF-α concentration was the highest (45.9±49.3 pg/mg) and in children with Fa and *H. pylori* infection was low (45.3±32.6 pg/mg), whereas decreased in children with Fa (21.7±34.2 pg/mg) and in controls (31.6±14.5 pg/mg).

**CONCLUSION:** The morphological changes of the gastric mucosa in children with *H. pylori* infection are comparable to those in children with Fa and coexisting *H. pylori* infection. Cytokine concentration in children with Fa and *H. pylori* infection is significantly different in IFN-γ, IL-2, IL-8, and TNF-α.

**Key words:** Mucosal cytokines; Food allergy; *Helicobacter pylori* dehydrogenase complex.

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**INTRODUCTION**

Many medical research centers dealing with food allergy (Fa) have assessed the morphological changes of gastric mucosa in children with hypersensitivity. Endoscopic evaluation of the alimentary tract and allergical and immunological examinations of food hypersensitivity are valuable diagnostic examination and pathogenetic inquiry elements. Numerous mast cells releasing histamine and triptase as well as the phenomenon of the selective accumulation of eosinophils and neutrophils have been observed in various parts of the alimentary tract of patients sensitive to food. Erosive gastritis and ulceration may occur periodically in the gastric and/or...
Examinations were conducted in 97 patients with dyspeptic symptoms, including recurrent or chronic stomachache, disorexia, recurrent diarrhea, nausea, vomiting, and loss of body weight. The symptoms were indications for gastroscopy. The patients were divided into three groups according to the cause and clinical symptoms observed.

Group I consisted of 48 children (49.5%) with Fa including 22 girls (45.8%) and 26 boys (54.2%) aged 4.6-18.4 years (mean 10.6±3.6 years). The case history, clinical complaints and the results of the upper alimentary tract endoscopic and histopathological examinations were the qualifying criteria for the further morphologic and biochemical analysis of the patients. The children with Fa were chosen on the basis of the clinical picture, positive immunological and allergic examinations, and inflammatory changes of gastric mucosa after Hp and giardiasis exclusion.

Group II comprised 34 children (35%) with Hp infection including 17 girls (50%) and 17 boys (50%). Fa and simultaneous Hp infection (Fa+Hp) were revealed in 16 (47%) children aged 3.3-16.2 years (mean 11.0±3.8 years). The rest of the 18 patients (52.9%) suffered from Hp infection without Fa. The age of the patients ranged from 5.0 to 18 years (mean 12.8±4.1 years). Children with Fa or without Fa and Hp infection were chosen on the basis of the same criteria as in group I and the positive results urease test (CLO-test) performed during endoscopy. The presence of Hp in the gastric antrum and corpus mucosa specimens was confirmed by hematoxylin and eosin staining (H+E) and the Giemsa method. Moreover, anti-Hp antibodies were determined by ELISA method (RecomWell Helicobacter IgG, Mikrogen, Germany). The amount of the bacteria as well as gastric antrum and corpus inflammatory activities were the decisive factors defining the severity of infection.

Group III included 15 children (9 girls -60%, 6 boys-40%) aged 4.9-14.9 years (mean 10.1±3.2 years) with functional disorders of the alimentary tract. The patients did not complain of allergy and showed no Fa symptoms. Hp infection was also excluded and endoscopy was carried out due to clinical symptoms mentioned above. The group constituted the control group (C). During gastroscopy, three specimens were collected from the prepyloric part of the stomach. Biopsies were weighed on an analytical scale immediately after the collection and then put in 1 mL of phosphatic buffer (molality 0.05 and pH 7.4) and placed in a thermos with ice.

Biopsies were homogenized using a tissue homogenizer. The protein was determined by Lowry method (mg/100 mL). Homogenates were divided into portions of 200 mL each, then frozen and stored at -20°C for further examinations. Determination was conducted separately for each homogenate sample after gradual warming up to the room temperature. The concentrations of tumor necrosis factor (TNF-α), IL-2, IL-4, IL-5, IL-8, IL-10, and INF-γ in homogenates of the gastric mucosa were determined by ELISA method using ENDOGEN standard kits (Cambridge, USA) according to the manufacturer’s instructions. Absorbance reading was performed spectrophotometrically with the wavelength

**MATERIALS AND METHODS**

Examinations were conducted in 97 patients with dyspeptic symptoms, including recurrent or chronic stomachache, disorexia, recurrent diarrhea, nausea, vomiting, and loss of body weight. The symptoms were indications for gastroscopy. The patients were divided into three groups according to the cause and clinical symptoms observed.

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recommended by the manufacturer. The concentrations of cytokines examined (in pg/mL) were calculated on the basis of the standard curve. The results were expressed in milligram of protein in homogenate of the tissue examined.

**Statistical analysis**

Statistical analysis included the arithmetic mean±SD, the minimum result (min), and the maximum result (max). The levels of parameters examined were compared using Student’s t-test for independent or paired trials. The differences were significant at P<0.05. The interdependence between measurable features was evaluated with Pearson’s linear correlation coefficient, of which significance was assessed using Student’s t-test for each correlation. The interdependence between non-measurable features evaluated using an independence test χ² or Fisher’s exact test is presented in the correlation tables.

**RESULTS**

The histopathological evaluation of the gastric mucosa in patients could distinguish the following categories of changes: normal mucous membrane, mucosa at the borderline of the norm (a slightly decreased number of mononuclear cells in superficial layers of the mucous membrane) and chronic inflammation. In children with Fa, normal gastric mucosa was observed in 43.7%, mucosa at the edge of the norm in 35.4% and chronic inflammation in 20.8% of children. In children with Fa and Hp infection and in those without Fa, morphological changes of the antrum mucosa resembled chronic inflammation in 100%. According to the Sydney System, three stages of gastritis could be distinguished: mild, moderate, and severe. The severe stage of antrum mucosal inflammation was observed in 55% of children with Hp infection and in 31.2% of children with Fa and Hp infection (Table 1). Moderate antrum gastritis concerned children with Fa and Hp infection (50%) and children with Hp infection (44.4%). Mild gastritis was revealed in 18.7% (group I) of children with Fa and in 18.7% of children with Fa coexisting Hp infection. Morphometric analysis regarding the severity of inflammation showed statistically significant pathological changes in the antrum (P<0.001). The evaluation of antral gastritis activity according to the Sydney System also presented a statistical significance (P<0.001). Severe antral gastritis was observed in 72.2% of children with Hp infection and in 68.7% of children with Fa and Hp infection (Table 2). The moderate activity was found in children with Fa and Hp infection (31.2%), in children with Hp infection (27.7%) and in children with Fa (6.2%). Group I showed the moderate activity in 6.2% of children. Histopathological examinations of the corpus mucosa were evaluated in the same way, i.e. in three categories of changes: normal mucosa, mucosa at the edge of the norm and chronic inflammation.

Group I showed chronic corpus gastritis in 16.6% of children, whereas the second category of changes was observed in 37.7% and normal mucosa was reported in 45.8% of children in this group. Chronic corpus gastritis was diagnosed in 100% of children with Hp infection. In children with Fa and Hp infection, 93.7% of children had chronic inflammation and 6.2% had mucosa at the edge of the norm. Severe corpus gastritis was observed in 12.5% of children with Fa and Hp infection and in 5.5% of children without Fa but with Hp infection (Table 1). The moderate corpus gastritis occurred in 50% of children with Hp infection and in 50% of those with Fa and coexisting Hp infection. Only 2% of children with Fa had moderate corpus gastritis. Mild gastritis was observed in children with Hp infection (44.4%) and in 31.2% of children with Fa and Hp infection. Severe activity of the corpus mucosa was found in 38% of children infected with Hp and in 37.5% of allergic children infected with Hp. The moderate activity was observed in 61.1% of children with Hp infection, 56.2% of allergic children with Hp infection and 6.2% of children with Fa.

Gastric mucosal biopsies showed the highest IL-2 concentration in children infected with Hp (116.5±179.5 pg/mg of the protein) and slightly lower level in allergic children with Hp infection (98.1±101.0 pg/mg). The levels were statistically significantly different from those in the control group (P<0.01). The lowest IL-2 concentration was observed in children with Fa (44.82±50.3 pg/mg), which was comparable to that in the controls (45.7±23.5 pg/mg;
Table 3 Cytokine concentration in gastric mucosa of children examined, according to Sydney System\cite{25} (pg/mg)

| Group | IL-2 | IL-4 | IL-5 | IL-8 | IL-10 | IFN-γ | TNF-α |
|-------|------|------|------|------|-------|-------|-------|
| Fa    | 44.8 | 23.6 | 35.5 | 59.9 | 39.9  | 40.6  | 21.7  |
| Hp    | 116.3 | 35.3 | 34.1 | 88.0 | 79.3  | 18.9  | 45.9  |
| Fa+Hp | 98.1 | 37.2 | 29.9 | 101.2| 50.1  | 25.5  | 45.3  |
| C     | 45.2 | 22.7 | 30.8 | 93.8 | 40.4  | 49.9  | 31.6  |

\*P<0.01 vs Fa and Hp, \*P<0.01 vs Fa and Fa+Hp, \*P<0.01 vs Fa and C, \*P<0.01 vs Hp and C, \*P<0.01 vs Fa+Hp and C.

Table 3). The highest IL-2 concentration in the gastric mucosa with regard to the intensity of inflammation (mild+moderate) was observed in the antrum of children with Hp (184.4±227.8 pg/mg) and the allergic process with coexisting Hp infection (125.4±109.4 pg/mg). The highest IL-2 concentration in relation to gastric mucosal inflammation activity was found in children with severe Hp infection (187.6±232.6 pg/mg), being statistically significant when compared to the control group (P<0.01; Tables 4 and 5). IFN-γ concentrations in the gastric mucosa ranged from undetermined levels to 188.2 pg/mg of the protein. The lowest mean concentration of IFN-γ was observed in children infected with Hp (18.9±16.4 pg/mg of the protein) and differed significantly when compared to the controls (P<0.01). In allergic children with Hp infection, the mean concentration of IFN-γ in the gastric mucosa was slightly higher (25.5±27.7 pg/mg, P<0.01; Table 3).

The mean concentration of IFN-γ was 40.6±39.7 pg/mg of the protein in children with Fa and was close to that in the controls (49.9±33.4 pg/mg). In Hp infected children, IFN-γ concentration was the lowest (13.1±16.5 pg/mg), being significantly different from that in the controls (P<0.01; Tables 4 and 5).

The values of IL-4 ranged from undetectable to 208.4 pg/mg in biopsies of the gastric mucosa. The highest IL-4 concentration was observed in Hp infected children. IL-4 concentration was 37.2±51.7 pg/mg in allergic and Hp infected children and 35.3±52.8 pg/mg in those without Fa.

The mean concentration of IL-4 was 23.6±35.8 pg/mg in children with Fa, being comparable with the control group (22.7±13.8 pg/mg). The highest IL-4 concentration in children with Hp infection regarding the intensity of gastritis was 62.2±61.2 pg/mg in mild and moderate gastritis (P<0.01).

The IL-5 concentration ranged from 6.7 to 250.9 pg/mg in the biopsies and was 35.5±50.9 pg/mg in allergic children, being not significantly different from that in the controls. The mean concentration of IL-5 in the gastric mucosa of children with or without Fa did not differ significantly and was comparable to that in the control group.

IL-8 concentration ranged from 10.5 to 618.8 pg/mg in

Table 4 Concentrations of cytokines in gastric mucosa of children examined depending on inflammation stage according to Sydney System\cite{25}

| Cytokines | (pg/mg of the protein) | Antrum | Corpus |
|-----------|-------------------------|--------|--------|
|           | Mild+moderate | Mild+moderate | Mild+moderate | Severe | Mild+moderate | Moderate+severe | Mild+moderate | Severe | Mild+moderate | Moderate+severe | Mild+moderate | Severe | Mild+moderate | Moderate+severe | Mild+moderate | Severe | Mild+moderate | Moderate+severe |
| IL-2      | 17.7                    | 17.9                | 184.4\* | 38.8                | 77.7                | 150.4\* | 125.4\* | 38.3                | 106.7\* | 98.6                |
| IFN-γ     | 54.9                    | 46.6                | 13.1\* | 24.1                | 17.8\* | 19.7\* | 21.9                | 34.3                | 23.1                | 27.1                |
| IL-4      | 15.4                    | 6.7\* | 62.2\* | 3.9                | 37.6                | 32.7                | 44.3                | 1.7                | 32.1                | 46.4                |
| IL-5      | 24.5                    | 25.5                | –                | –                | –                | –                | 29.7                | –                | –                | 33.0                |
| IL-8      | 37.5                    | 37.5                | 101.2                | 72.9                | 93.6                | 83.1                | 98.0                | 108.2                | 71.1                | 118.3                |
| IL-10     | 30.4                    | 24.4                | –                | –                | –                | –                | 44.6                | –                | –                | 58.9                |
| TNF-α     | 20.6                    | 4.8                | 65.2                | 24.1                | 48.7                | 43.3                | 54.8\* | 24.3                | 49.0                | 44.8                |

\*P<0.01, cytokine concentrations statistically significantly different from controls. Fa, food allergy; Hp, H pylori; C, control group.

Table 5 Cytokine concentrations in gastric mucosa of children examined depending on the inflammation activity according to Sydney System\cite{25}

| Cytokines (pg/mg protein) | Fa | Corpus |
|---------------------------|----|--------|
|                           | Mild+moderate | Mild+moderate | Mild+moderate | Severe | Mild+moderate | Severe | Mild+moderate | Severe | Mild+moderate | Severe | Mild+moderate | Severe | Mild+moderate | Severe | Mild+moderate | Severe | Mild+moderate | Severe | Mild+moderate | Severe |
| IL-2                      | 17.7 | 17.9 | 204.3\* | 72.5 | 69.0 | 187.6\* | 50.1 | 110.9 | 119.3 | 74.3 |
| IFN-γ                     | 54.9 | 46.6 | 20.4 | 18.4 | 21.8\* | 14.6\* | 25.6 | 25.4 | 22.4 | 33.4 |
| IL-4                     | 15.4 | 6.7\* | 81.3\* | 6.7\* | 30.0 | 47.8 | 52.0 | 29.8 | 39.9 | 39.0 |
| IL-5                     | 24.5 | 25.0 | – | – | – | – | – | – | – | – |
| IL-8                     | 37.5 | 37.5 | 83.5 | 90.2 | 86.9 | 89.6 | 69.8 | 115.5 | 83.2 | 131.6 |
| IL-10                    | 30.4 | 24.0 | – | – | – | – | – | – | – | – |
| TNF-α                    | 20.6 | 4.8 | 76.0 | 33.3 | 37.4 | 57.9 | 24.6 | 54.6 | 60.4 | 24.9 |

\*P<0.01 vs cytokine concentrations statistically significantly different from controls. Fa, food allergy; Hp, H pylori; C, control group.
gastric mucosal biopsies before the treatment. The highest mean IL-8 value was observed in Hp-infected children (with or without Fa). The mean IL-8 concentration was 101.2 ± 68.3 pg/mg in allergic children with Hp infection. This value was statistically significant (P<0.005) in comparison to that in allergic children. In children with Hp infection, the mean gastric mucosa IL-8 concentration was 88.0 ± 40.4 pg/mg, being statistically significant (P<0.005) in comparison to that in children with Fa. The evaluation of mucosa IL-8 concentration with regard to the intensity and activity of inflammatory process in the gastric mucosa did not show any statistically significant dependence (Tables 4 and 5).

In gastric mucosal biopsies, IL-10 concentration ranged from undetectable to 141.8 pg/mg. The highest mean concentration of mucosa IL-10 was detected in children with Hp infection (79.3 ± 41.2 pg/mg) and in allergic children with Hp infection (50.1 ± 18.8 pg/mg).

The mean IL-10 concentration was 39.9 ± 35.5 pg/mg in children with Fa, being statistically significantly different from that in children with Hp infection (P<0.01, Table 3). The intensity and activity of inflammation did not affect IL-10 concentration in the gastric mucosa (Tables 4 and 5).

TNF-α concentration ranged from undetectable to 208.4 pg/mg in gastric mucosal biopsies. The mean TNF-α concentration was the highest in children with Hp infection and 45.9 ± 49.3 pg/mg, in children without Fa compared to that in the controls (P<0.06). Infection revealed the mean TNF-α concentration of 45.3 ± 32.6 pg/mg in allergic children with coexisting Hp infection, being statistically different from controls (P<0.01). The mean TNF-α concentration was 21.7 ± 34.2 pg/mg in allergic children and showed statistically significant difference (P<0.003) in comparison to children with Hp infection or with Fa and coexisting Hp infection (P<0.004).

The analysis of TNF-α concentration in the gastric mucosa with regard to the intensity and activity of the inflammation showed no statistically significant differences.

**DISCUSSION**

Our study proved that the pathogenic factors like harmful food could induce certain morphological changes of the gastric mucosa. They are smaller with regard to the percentage and “depth” than in the combined activity of allergy and Hp. It seems essential to check the intensity of the changes and their dynamics by assessing their characteristics and size as well as local properties of cytokines produced. The concentration of chosen cytokines in the antrum mucosa in children with Fa was comparable to that in the controls. However, IL-4 concentration was statistically significantly different from the control group. IL-4 is secreted by antigen- or mitogen-inactivated lymphocytes Th2 and by mast cells in the gastric mucosa infiltrates in children with Fa.

Another frequent etiological factor, Hp infection leading to gastritis, was observed besides the allergic one affecting the gastric mucosa. Histopathological changes induced by the activity of this factor were far greater than those observed in children with Fa. It should be assumed that the intensified local production of many inflammatory cytokines, including IL-2, takes place in Hp infection where gastric mucosa is infiltrated by such cells as neutrophils, lymphocytes, monocytes/macrophages and cytoplasmic cells. The IL-2 concentration was the highest in the gastric mucosa of children with Hp infection (116.5 pg/mg) and slightly lower in children with Fa and Hp infection (98.1 pg/mg). The values were statistically significant when compared to the control group.

IL-8 is another cytokine, whose chemotactic properties are directed selectively towards neutrophils. The activity of IL-8 on neutrophils is triggered by binding to a specific receptor, which can be found on the surface of the cells (5 ku).

A population of children with Fa and coexisting Hp infection was included additionally in our study. The mean concentration of IL-8 in the gastric mucosa of children with Hp infection was 88.0 pg/mg, being statistically significantly different (P<0.01) in comparison to 59.9 pg/mg in allergic children. The mean IL-8 concentration was even higher (101.2 pg/mg) in allergic children with Hp infection.

Another cytokine with a wide range of biological actions is IL-4 secreted by antigen-inactivated Th lymphocytes (Th2) and mast cells. We evaluated IL-4 concentration in particular groups of children and found IL-4 levels were increased in allergic patients, though the values were not statistically different from those in the controls.

TNF-α is one of the most potent cytokines activating numerous functions of neutrophils. It stimulates directly oxygenic metabolite release by neutrophils and the effectiveness of this phenomenon depends on the doses used. Isolauri et al. and Majamaa et al. showed that TNF-α is elevated in feces of allergic children, which is thought to be a delayed reaction type to food challenge. Children with immediate reaction have a significant increase in α1-antitripsin and eosinophil cationic protein (ECP) in their feces as compared to patients who do not respond to food challenge.

The relatively low TNF-α concentration in the antrum mucosa (21.7 pg/mg) of allergic children may be due to the fact that a marked percentage of the patients revealed IgE-dependent mediators engaged in allergic reactions. TNF-α assessed in biopsies of the alimentary tract mucosa or excrements feces seems to be a good factor for active immunological reactions to food allergens ingested by children who react to food without IgE participation. Isolauri et al. showed that TNF-α can be equally used as a factor of pathogenic process activation and food hypersensitivity as cationic protein (ECP) and α1-antitripsin in case of patients whose cytokines secreted by T lymphocytes are responsible for clinical symptoms.

In conclusion, the pathogenic process is individually different with regard to morphological examinations and proinflammatory and proallergic cytokine production. Concentrations of IFN-γ, IL-2, IL-8, and TNF-α in the gastric mucosa of children with Fa and those with Hp infection (without Fa) are different.
