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Inflammatory changes of the gastric mucosa and serum concentration of chosen growth factors in children

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ABSTRACT

Purpose: To assess whether there is a correlation between the severity of gastritis and concentration of chosen growth factors in the serum of children infected with *H. pylori*.

Material and Methods: The study included 64 children of whom 50% (Group I) were infected with *H. pylori* and had gastritis; 18.7% (Group II) of the examined children had a positive titre of IgG against *H. pylori* and normal gastric mucosa. Controls (Group III) comprised 31.3%. The gastric mucosa was evaluated histopathologically according to the Sydney System. The serum concentrations of growth factors: EGF, TGF-α, VEGF, were determined using ELISA.

Results: Mean concentrations of the growth factors were also the highest in Group I compared to Group II and Group III (EGF - 137.3±10.4 pg/mL, TGF-α - 0.4±1.2 pg/mL, VEGF - 146.8 pg/mL). Analysis of correlations between growth factors and the severity of gastritis as well as the activity of antral gastric mucosa inflammation proved that mean EGF concentration in H. pylori infected children was the highest (149.5±84.8 pg/mL) in severe gastritis, whereas mean concentrations of TGF-α (2.0±4.3 pg/mL) and of VEGF (148.1±92.6 pg/mL) were the highest in moderate gastritis. Mean concentrations of EGF (155.1±116.4 pg/mL) and of VEGF (156.0±118.9 pg/mL) were the highest in high activity antral gastritis, whereas the mean concentration of TGF-α was the highest (2.0±4.2 pg/ml) in moderate activity gastritis.

Conclusions: In the children with H. pylori infection, serum concentrations of EGF, TGF-a, VEGF were the highest in moderate and severe antral gastritis.

Key words: Helicobacter pylori, epidermal growth factor, transforming growth factor-alpha, vascular endothelial growth factor

INTRODUCTION

Growth factors as peptides or glycoproteins, are released by given cells, e.g. neutrophils, macrophages, fibroblasts, lymphocytes, trombocytes, some tissues (epithelial, smooth muscles), or some organs, e.g. the kidneys, the liver. They bind with the receptors on the surface of the cells and trigger their growth and division, thus forming the system of chemical signaling, organizing and coordinating cell proliferation in the organism. They are released in the physiological state and in the damaged tissue in response to a pathogenic stimulus with local release and to the circulation, acting as an activator or inhibitor, *via* the endo-, para-, or autocrine way [1]. Taking into consideration their functions, these cytokines are believed to condition the normal tissue growth in the embryo's development and to regulate cell proliferation in the tissues of a grown - up organism and in the pathological processes, such as wound healing and inflammation [2].

Helicobacter pylori (H. pylori) infection is one of the most common infections in the world, in which growth factors play an important role in healing inflammatory lesions in the gastric mucosa. Two main groups of growth factors of the cytokines discussed in the study take part in healing of the damaged gastric mucosa. One of them includes the factors regenerating the epithelial component: epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α) and platelet-derived

growth factor (PDGF). The other group consists of the factors regenerating the vascular component: vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF). The damaged mucosa regeneration partly depends on cooperation of many growth factors [3]. These factors activate mitotic divisions in the regeneration of the damaged mucosa and stimulate migration and proliferation of vascular endothelium cells. According to Coffey *et al.* [4] and Cartlidge and Elder [5], they also take part in the inhibition of gastric juice secretion and stimulation of mucus production. Hovever, EGF, TGF-α and bFGF increase indirectly the blood flow *via* the stimulation of VEGF secretion [6].

H. pylori infection induces chronic gastritis. The studies to date present an increase in concentrations of growth factors, mainly in the site of damage to the gastric mucosa: in bioptates [7-12] and gastric juice [13]. It would be interesting to find the answer to the question whether the local increase in the secreted growth factors is significant enough to expect the analogous increase in the serum. The population of developmental age, representing a slightly different clinical picture of *H. pylori* infection, should be taken into consideration in the study group.

The aim of the study was to assess what is a concentration of chosen growth factors: EGF, TGF-α, VEGF, in the serum of children infected with *H. pylori,* and whether there is a correlation between severity of gastritis and their concentrations.

MATERIAL AND METHODS

Subjects

The study included 64 children, aged from 1 to 18 years old, hospitalized in the III Department of Children's Diseases of the Teaching Children's Hospital in Bialystok, Poland.

The inclusion criteria were: dyspeptic symptoms of an unknown cause, troubling enough to qualify patients for the Giemza examination of and the assessment of the titre of IgG against *H. pylori*. Due to dyspeptic symptoms all children had gastroscopy performed and the level of antibodies against *H. pylori* determined. After examination children were divided into three groups.

Group I with actual *H. pylori* infection confirmed by two tests: Giemza stain, rapid urease test and gastritis confirmed by the histopathological examination; with a positive titre of IgG antibodies. This group included 32 children (50.0%), aged from 3 to 18 years; mean age 11.6±4.4 years. There were 12 girls (18.8%) and 20 boys (31.2%).

Group II without actual *H. pylori* infection (negative Giemza stain, rapid urease test and without gastritis confirmed by histopathology); with a positive titre of IgG antibodies. The group included 12 children (18.7%), aged from 2 to 18 years; mean age: 9.7±4.4 years. There were 7 girls (10.9%) and 5 boys (7.8%).

Group III without *H. pylori* infection (negative Giemza stain, rapid urease test and without gastritis confirmed by histopathology); with a negative titre of IgG antibodies. Group III was regarded as controls and consisted of 20 children (31.3%) aged from 1 to 14 years; mean age: 9.1±3.6 years. There were 12 girls (18.7%) and 8 boys (12.6%).

Upper gastrointestinal endoscopy

After getting consent from patients and /or their guardians, all patients had endoscopy of the upper section of the gastrointestinal tract. General anesthesia was applied during endoscopy in children below the age of 6 and older children, not cooperating. Pediatric size gastroscopes (Olympus Q 145) were used. Due to dyspeptic complaints all patients had 4 biopsy specimens taken to examine histopathologically from the stomach (2 from *antrum*, 2 from body – each to a separate vial). Additional biopsy specimen was taken from *antrum* for rapid urease test.

Rapid urease test

During gastroscopy a rapid urease test was performed (CLO-test = *Helicobacter pylori*), using kits produced by the Institute of Food and Nutrition in Warsaw, Poland. A mucosa specimen from the antral region of the stomach was placed on the blotting paper saturated with 0.9 % NaCl and the change in color of the blotting paper after 30 min was observed. The blotting paper changed from yellow to amaranth due to the hydrolysis of urea to ammonia by *H. pylori* urease.

Histopathology

Four biopsy specimens were taken (2 from the gastric *antrum* and 2 from the body for histological examination. Gastric mucosa specimens taken in gastroscopy were fixed in 10% formalin, next embedded in paraffin and cut off on the microtome. Hematoxyline and eosine were used for staining specimens and staining by means of the Giemza method was also applied for *H. pylori* infection. According to the updated Sydney System [14], each histological parameter of an activity (polymorphonuclear cell infiltration), grade of chronic inflammation (severity) (mononuclear cell infiltration), intensifity of infection was graded on a four-point scale: 0 - absent, 1 – mild, 2 – moderate, 3- severe. All preparations were evaluated by the same histopathologist not knowing the results of examinations to date, in the Department of General Pathomorphology of the Medical University of Bialystok, Poland.

Serum assays

In the morning, each fasting patient had about 2 cm of blood taken to the tube, left for coagulation and rotated at 1000 rpm. The sera collected in such a way were frozen at a temperature of – 80˚C until determination.

Immunoenzymatic method of ELISA was applied to evaluate specific antibodies of IgG against *H. pylori*, using a kit Recom Well Helicobacter IgG (Mikrogen GmbH). Specimens