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SECRETORY IMMUNOGLOBULIN A AND ITS ROLE IN FORMATION OF CLINICAL COURSE OF SHIGELLOSIS IN CHILDREN INFECTED WITH HELICOBACTER PYLORI

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Secretory immunoglobulin A (sIgA) is a crucial factor in protection of the gastrointestinal (GI) tract mucosa directly providing the first line of defense of the intestine from the impact of foreign antigens. sIgA is considered to be a key cleaner of the intestine because it is a basic effector molecule of the mucosal immunity system and it comprises most immunoglobulins of the intestinal discharge. Maintenance of the homeostatic equilibrium between the intestinal microbiota and the plethora of luminal macromolecules and the human intestinal epithelial cell barrier requires the secretion of copious amounts of mucosal IgA into the gut lumen. In humans, 40–60 mg/kg/day of IgA are produced daily by plasma cells located in the lamina propria (LP) of intestinal villi, that is almost 1.5 times more than daily IgG production about (30 mg/kg/day). And production tends to peak in childhood and start to decline after about sixty years old. The IgA is transported across the epithelium and secreted into the gut lumen, where it is thought to provide protection against pathogens by multiple biological properties, which include blocking toxins and pathogens from adhering to the intestinal epithelium at the earliest steps of the infection process, and from directly recognizing receptor-binding domains to block bacterial attachment to intestinal epithelial cells [1, 2]. At the same time, sIgA is able to form immune complexes not only with infectious agents and their constituent elements, which are found in the mucous membrane, but also with those, which for some reasons overcome the epithelial barrier and directly penetrate lamina propria [3, 4]. Most B-cells secreting IgA are commonly known to be located in GI, bronchopulmonary, genitourinary tracts mucosa [5, 6]. The release of sIgA from plasma cells occurs influenced by IL-4, IL-5, IL-6, IL-10 cytokines [7, 8].

According to researchers, sIgA decrease can be indicative of insufficient function of the local immunity and its increased level shows that there is immune system imbalance [9, 10]. Formation of long-term infectious processes as well as chronic pathology associated with increased local immunity, sIgA in particular, is considered in a range of studies [11, 12, 13]. sIgA deficiency in GI tract results in damage of intestinal “biofilm”, increased activity of aggressive compounds, impaired colonization resistance of the mucosa; it provides conditions for long-term course of intestinal infection [14, 15, 16]. Not only clinical trial data, but also laboratory experiment findings prove a particular role of sIgA in protection against pathogenic enterobacteria including shigella as the most frequent causative agents of bacterial intestinal infections in children [17].

The local immunity factors are of great importance in combination with two or more pathogenic causative agents that can be present in the intestine for a long time. As it is commonly known, infection with Helicobacter pylori, observed at an early age, becomes more and more widespread over the last years [18, 19]. The global burden of Shigellosis is still quite significant. There are no good estimates of the country-specific geographic distribution of this disease. However, between 120 and 165 millions incident cases are believed to occur each year. Furthermore, approximately 1 millions deaths occur annually, with greater than 60% of these experienced by children under 5 years of age [20]. Taking into consideration that Shigellosis mortality rate among children is still high up to now, the issue focused on local immunity state in children with Shigellosis, infected with Helicobacter pylori is currently of concern. Unfortunately, we did not find data dealing with this issue in the information sources available.

Purpose of the study is to define the status of local immunity in children with Shigellosis, infected with Helicobacter pylori, by identifying one of its main components – the level of sIgA in coprofiltrate.

Materials and methods. The study involved 68 children aged from 1 to 3, who were hospitalized in Regional Children’s Infectious Diseases Hospital (Kharkiv) and diagnosed with Shigellosis due to Shigella Sonnei of moderate severity. The diagnosis was made based on clinical epidemiological data along with verification of an etiological causative agent via bacteriological and/or serologic methods. In addition to the commonly used research methods, children were tested for H. pylori presence by polymerase chain reaction (PCR) method and an immunochromatographic assay for detecting Hp antigens in fecal specimens CITO TEST H.PyloriAg (CerTest Biotec, S.L., Spain, «Pharmasco») and for the level of sIgA in coprofiltrate in the dynamics of the pathological process by immune-enzyme assay using the standard set applying "Immunoglobulin A secretory - IFA-BEST". The studies were conducted in acute period (1-2 days of illness) and in the period of early reconvalescence (5-7 days of illness), if necessary – more often. The treatment of children was carried out in accordance with approved clinical protocols (Order N 354 of 09.07.2004 "On the approval of protocols for the diagnosis and treatment of infectious diseases in children").

The patients were divided into two group: *Group 1* (31 children) was made up by children with Shigellosis with confirmed H. pylori infection and *Group 2* (37 children) – children with Shigellosis without laboratory markers of Helicobacter infection. The study groups were compared based on age (26.35±4.74 and 24.49±6.27 months, $p>0.05$), sex and comorbidity. The control group was represented by 20 apparently healthy children of the same age and sex who were not infected with H. Pylori and whose rates were taken as reference values. Statistical processing of the obtained data was carried out by means of Excel and Statistica 6.0 applications. The significance of difference between the groups was estimated via Student’s test (Student’s t-test), correlation between the parameters – via the Pearson correlation coefficient (r).

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Results and discussion. In order to achieve the purpose, we compared basic clinical laboratory values of the study groups. It was revealed, that in the children with background infection with H. pylori, the fever was present longer (4.61±0.15 days vs 3.42±0.14, p<0.05) as well as regurgitation and/or (3.43±0.38 vs 2.09±0.15 days, p<0.05), loss of appetite (5.2±0.62 and 2.08±0.25 days, p<0.05), asthenoneurotic syndrome manifestations (4.78±0.28 and 3.06±0.17 days, p<0.05); the comprocytogram changes were also more long-term (6.68±0.33 and 3.85±0.16 days respectively, p<0.05), which were mainly characterized by longer preservation of vegetable and muscle fibers in patients of the first group. The findings detected are indicative of substantial differences in the course of Shigellosis depending on present background infection in a child. The study outcomes concerned with sIgA in the patients of both groups in acute period and early convalescence of Shigellosis are presented in the *Table* below.

Table. Secretory IgA content values in coprofiltrates of patients at different Shigellosis stages, mg/l, (M±m)

Disease stage	Group 1 (n = 31)	Group 2 (n = 37)	Control (n =20)
Acute period	$1.06\pm0.03^{1,2}$	1.18 ± 0.04^{1}	
Convalescence period	0.86 ± 0.03^{1}	0.98±0.02	

Note: feature significance

1. $p^1<0.05$concerned with healthy children

2. $p^2<0.05$ between values of children in the groups

Significantly higher sIgA level, in comparison with the same values of the control group, (p<0.05), was revealed in coprofiltrates of all children in acute period. At the same time, in children of Group 2 sIgA content was significantly higher than the values of patients0 with background infection, (p<0.05).

The quantitative sIgA content restored and significantly did not differ from the values of the control group (p>0.05) in early convalescence period of Shigellosis in children without background infection. However, significant difference was observed with the acute period value (p<0.05). sIgA concentration in children infected with H. pylori in the period of clinical recovery was significantly decreased in comparison with acute period values (p<0.05). It was significantly different from the data of healthy children and the children of *Group 2*, (p<0.05). The findings obtained are indicative of imbalance of local immunity competence of the intestine in Shigellosis in children infected with H. pylori, especially impaired sIgA production. Insufficient sIgA secretion in coprofiltrates of patients with Shigellosis, that has been revealed, is not contrary to the hypothesis of some scientists concerning the capacity of pathogenic H. pylori strains to carry out their cytotoxic effect associated with decrease of local protective mechanisms of the GI tract mucosa as well as system immunity, the ability to spin out of control of specific immunity mechanisms up to development of immune-dependent inflammation forms [18, 19].

Taking the revealed differences of sIgA content in coprofiltrates in Shigellosis in patients with and without background infection with H. pylori into consideration, we have carried out the study of correlational connection concerned with assessment of Pearson coefficient of this value with basic clinical laboratory values in the acute period of Shigellosis in patients infected with H. pylori. The study of interrelation of the laboratory values of patients is crucial not only considering scientifically, but also in terms of applied medicine. The outcomes obtained show weak negative correlation between sIgA content and defecation intensity (frequency) (r=-0.18); negative direction correlation in relation to the duration of diarrheal syndrome (r=-0.18); medium intensity correlation in relation to duration and alterations degree in coprocytogram (r=-0.33). Present correlational interactions between sIgA values in coprofiltrates of children suffering from Shigellosis, infected with H. pylori, and frequency of development of specific symptoms along with their duration, are indicative of sIgA role in formation of pathogenic mechanisms of the disease course.

Therefore, Shigellosis in children infected with H. pylori is accompanied by substantial impairment of local immunity competence that influences the frequency of manifestations of some clinical symptoms and pathologic changes of laboratory values, their duration. The data obtained can become the theoretical basis for the improvement of treatment of children with Shigellosis, infected with H. pylori, with due regard to detected disturbance of local immunity competence.

Conclusions

1. Infection of children with H. pylori affects local immunity of the intestine, especially intestinal sIgA secretion
2. Shigellosis in children infected with H. pylori proceeds in the form of hyporeactive reaction with substantially lower sIgA concentration in coprofiltates in acute period in comparison with the values in the patients who are not infected.
3. Within the period of early convalescence in children suffering from Shigellosis, infected with H. pylori, significantly decreased sIgA content in coprofiltrates is observed.
4. The revealed violations of sIgA in coprofiltrates in children with Shigellosis and infected with H. pylori may be a promising direction in the study of pathogenetic mechanisms for the formation of the pathological process..

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acute period values. It was significantly different from the data of healthy children and the children of Group 2. The findings obtained are indicative of imbalance of local immunity competence of the intestine in Shigellosis in children infected with H. pylori, especially impaired sIgA production. Insufficient sIgA secretion in coprofiltrates of patients with Shigellosis, that has been revealed, is not contrary to the hypothesis of some scientists concerning the capacity of pathogenic H. pylori strains to carry out their cytotoxic effect associated with decrease of local protective mechanisms of the GI tract mucosa as well as system immunity, the ability to spin out of control of specific immunity mechanisms up to development of immune-dependent inflammation forms. Taking the revealed differences of sIgA content in coprofiltrates in Shigellosis in patients with and without background infection with H. pylori into consideration, we have carried out the study of correlational connection concerned with assessment of Pearson coefficient of this value with basic clinical laboratory values. Present correlational interactions between sIgA values in coprofiltrates of children suffering from Shigellosis, infected with H. pylori, and frequency of development of specific symptoms along with their duration, are indicative of sIgA role in formation of pathogenic mechanisms of the disease course. **Conclusion.** Therefore, Shigellosis in children infected with H. pylori is accompanied by substantial impairment of local immunity competence that influences the frequency of manifestations of some clinical symptoms and pathologic changes of laboratory values, their duration. The data obtained allow to assume as the perspective direction in perfection of therapy of such patients use of complex immunoglobulin medications should be aimed primarily at inflammatory processes stopping. **Keywords**. Shigellosis, immunoglobulins, children, Helicobacter pillory

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