ОСОБЕННОСТИ ЦИТОКИНОВОГО ПРОФИЛЯ КРОВИ ПРИ ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНИ У ШКОЛЬНИКОВ С ГАСТРИТОМ И СЕМЕЙНЫМ ОТЯГОЩЕНИЕМ ПО ЯЗВЕННОЙ БОЛЕЗНИ

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Резюме. Гастроэзофагеальная рефлюксная болезнь (ГЭРБ) представляет собой распространенное кислотозависимое заболевание среди населения, в том числе детского с мультифакториальным генезом. Она, как и многие другие кислотозависимые заболевания (язвенная болезнь и др.), ассоциирована с семейной предрасположенностью к заболеванию. Интерес представляет изучение роли цитокинов в регуляции патологии в детском возрасте в зависимости от отягощенности семейного анамнеза по язвенной болезни. Цель – оценить показатели цитокинов в сыворотке крови при семейном отягощении по язвенной болезни у школьников с гастритом, ассоциированным с ГЭРБ. В ходе научного исследования обследовано 142 ребенка с гастроэнтерологическими жалобами в возрасте 7-17 лет. Диагноз «ГЭРБ» выставлялся при наличии еженедельной изжоги в соответствии с глобальным консенсусом по патологии у детей. Всем обследуемым была проведена гастроскопия с взятием биопсийного материала из слизистой желудка и морфологическим подтверждением у них диагноза гастрит в соответствии с Сиднейской классификацией. Методом иммуноферментного анализа получена концентрация цитокинов в сыворотке крови (IL-2, IL-4, IL-6, IL-8, IL-10, IL-18, IL-1β, IFNα, TNFα). При статистической обработке использовались критерии χ^2 и Манна–Уитни. Исследования одобрены этическим комитетом и до начала исследования получены информированные согласия пациентов и их родителей. Результаты исследования не показали значимых различий концентрации цитокинов у школьников в зависимости от наличия ГЭРБ. У детей с семейным отягощением по язвенной болезни ГЭРБ определялась чаще ($p = 0,054$), что, вероятно, является следствием наличия у них повышенного кислотообразования. Отмечены изменения в цитокиновом профиле крови. В течение ГЭРБ при отягощении по язвенной болезни было усиление репликации IL-4 ($p = 0,027$) и IFNα

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(p = 0,001). Увеличение IFNα в крови у детей с ГЭРБ при семейном отягощении очевидно направлено на усиление иммунных реакций с участием всего организма на повреждение. Это обусловлено его функциональной ролью – участие в иммунном ответе. Усиление репликации IL-4, очевидно, обеспечивает усиление метаболических, иммунных процессов в организме, направленных на обеспечение оптимизации течения пролиферативных процессов в слизистой пищевода в условиях повышенной секреции соляной кислоты в желудке. Таким образом, при отягощении семейного анамнеза по язвенной болезни у школьников с гастритом, ассоциированным с ГЭРБ наблюдается переход ряда звеньев цитокиновой сети (IL-4, IFNα) на системный уровень регуляции.

Ключевые слова: цитокины, дети, гастроэзофагеальная рефлюксная болезнь, гастрит, язвенная болезнь, семейная предрасположенность

FEATURES OF THE BLOOD CYTOKINE PROFILE IN GASTROESOPHAGEAL REFLUX DISEASE IN SCHOOLCHILDREN WITH GASTRITIS AND FAMILY HISTORY OF PEPTIC ULCER

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Abstract. Gastroesophageal reflux disease (GERD) is a common acid-dependent disease among the population, including children, with multifactorial genesis. It, like many other acid-dependent diseases (peptic ulcer, etc.) is associated with a family predisposition to the disease. Of interest is the study of the role of cytokines in the regulation of pathology in childhood, depending on the severity of a family history of peptic ulcer disease. Aim: to evaluate the levels of cytokines in the blood serum in case of family history of ulcerative diseases in schoolchildren with gastritis associated with GERD. In the course of a scientific study, 142 children with gastroenterological complaints aged 7-17 years were examined. The diagnosis of GERD was made in the presence of weekly heartburn in accordance with the global consensus on pathology in children. All subjects underwent gastroscopy with taking biopsy material from the gastric mucosa and morphological confirmation of their diagnosis of gastritis in accordance with the Sydney classification. The concentration of cytokines in blood serum (IL-2, IL-4, IL-6, IL-8, IL-10, IL-18, IL-1β, IFNα, TNFα) was obtained by enzyme immunoassay. During statistical processing, the χ^2 and Mann–Whitney tests were used. The studies were approved by the ethics committee and informed consents of patients and their parents were obtained prior to the start of the study. The results of the study did not show significant differences in the concentration of cytokines in schoolchildren depending on the presence of GERD. In children with a family burden of peptic ulcer, GERD was detected more often (p = 0.054), which is probably a consequence of their increased acid formation. Changes in the cytokine profile of the blood were noted. During GERD, with aggravation of peptic ulcer, there was an increase in the replication of IL-4 (p = 0.027) and IFNα (p = 0.001). The increase in blood IFNα in children with GERD with family burden is obviously aimed at enhancing immune responses involving the whole body to damage. This is due to its functional role – participation in the immune response. Increased replication of IL-4, obviously, provides an increase in metabolic, immune processes in the body aimed at optimizing the course of proliferative processes in the esophageal mucosa under conditions of increased secretion of hydrochloric acid in the stomach. Thus, when a family history of peptic ulcer is aggravated in schoolchildren with gastritis associated with GERD, a number of links in the cytokine network (IL-4, IFNα) move to the systemic level of regulation.

Keywords: cytokines, children, gastroesophageal reflux disease, gastritis, peptic ulcer, family predisposition

Introduction

Gastroesophageal reflux disease (GERD) is a common pathology in all age groups, which has a multifactorial origin and is related to acid-mediated diseases [3, 4]. The latter explains the increase in the prevalence and severity of esophageal lesions in GERD in adults compared with children, which is largely predetermined by the functional state of acid formation in the population in age populations [6, 9]. In a number of studies, scientists emphasize the close relationship between acid-dependent diseases of the stomach, in particular, with peptic ulcer. Such a close relationship between diseases is due, according to researchers, to the presence of common pathogenetic mechanisms in their development: the presence of an imbalance of protective and aggressive factors of the stomach and motor disorders of the organ [5, 13]. Similarly, like any other diseases with high acid production in genesis, they have a genetic nature associated with a family predisposition to the disease, which manifests itself already in childhood and adolescence [2, 10].

In this context, of undoubted interest is the question of the role of regulatory mechanisms (cytokine link) in the course of GERD in childhood and whether there is an influence of family predisposition to peptic ulcer on the formation of the disease. This issue has not been studied in child populations.

The aim of this work was to evaluate the levels of cytokines in the blood serum (IL-2, IL-4, IL-6, IL-8, IL-10, IL-18, IL-1β, IFNα, TNFα) in case of family history of ulcerative diseases in schoolchildren with gastritis associated with GERD.

Materials and methods

The concentration levels of cytokines in the blood of 142 children with gastroenterological complaints were studied. All existing complaints and their characteristics were recorded in the questionnaires. In parallel, the questionnaire method collected data on the presence of diseases of the gastrointestinal tract in relatives (1-2 degrees of kinship) of the examined children.

All schoolchildren underwent endoscopic examination of the digestive system (esophagogastroduodenoscopy) with the taking of biopsy material from two sections of the stomach (antral, body). The biopsies were placed in separate vials containing 10% buffered formalin. Staining with hematoxylin-eosin and Giemsa was performed, followed by a morphological assessment of the state of the mucous membrane in accordance with the Sydney classification [1, 12]. In all cases, gastritis was morphologically confirmed.

The study does not include schoolchildren: less than 7 years old and over 17 years old; in the presence of acute inflammatory diseases during the last month; with recrudescence of chronic diseases of other organs; in the presence of functional insufficiency of organs and systems of the body; in the presence of allergic diseases; in the absence of morphological signs of inflammation in the gastric mucosa; in the presence of organic pathology of the stomach (peptic ulcer, erosive gastritis).

The presence of GERD was determined based on the global pediatric consensus definition of GERD [11]. This nosology was registered in schoolchildren with complaints of heartburn at least once a week. Heartburn was considered as a feeling of discomfort and/or burning behind the sternum.

The study of the cytokine profile of blood serum (IL-2, IL-4, IL-6, IL-8, IL-18, IL-1β, IFNα, TNFα, IL-10) was carried out using a set of reagents from the company "Vector-Best" (Russia) for the ELISA method. Direct preparation of biological material for enzyme immunoassay included taking blood from children with a volume of 5 ml. Next, the serum was separated from the blood sample by centrifugation and stored until the time of the study itself at a temperature of -20 °C.

The study protocol complies with the ethical principles of the Helsinki Declaration of the World Medical Association (1964) and Article 24 of the Russian Constitution. The Ethics Committee of the Research Institute of Medical Problems of the North (Krasnoyarsk) reviewed and approved the plan and protocol of the scientific study (No. 9 dated September 12, 2016). Written informed consents were obtained from all examined patients prior to the start of the study.

SPSS software, version 23.0 (IBM) was used for statistical processing of the received scientific data. The significance of differences was calculated for qualitative features using the χ^2 criterion; and to compare the severity of quantitative traits, the nonparametric Mann–Whitney U test was used for unrelated samples. The data obtained were calculated for samples that do not correspond to the normal distribution of feature values and are described by the median (Me) and interquartile interval ($Q_{0.25}$-$Q_{0.75}$). The significance level of differences in variables was taken equal to 0.05.

Results and discussion

The results of the study did not show significant differences in the cytokine profile in schoolchildren with GERD in comparison with children with other gastroenterological complaints (Table 1). It is important that both groups of children were dominated by those examined with functional diseases related to other nosologies (dyspepsia syndrome, irritable bowel

TABLE 1. INDICATORS OF CYTOKINES IN BLOOD SERUM IN CHILDREN DEPENDING ON THE PRESENCE OF GASTROESOPHAGEAL REFLUX DISEASE

Cytokine	Gastroesophageal reflux disease + (n = 42)			Gastroesophageal reflux disease – (n = 100)			p
	Me	$Q_{0.25}$	$Q_{0.75}$	Me	$Q_{0.25}$	$Q_{0.75}$	
IL-2	0.1	0.1	0.2	0.1	0.1	0.4	0.791
IL-4	1.5	0.8	2.0	1.2	0.6	1.8	0.304
IL-6	0.1	0.1	0.1	0.1	0.1	0.1	0.363
IL-8	16.4	0.1	73.9	17.4	0.1	89.6	0.985
IL-18	117.9	64.5	215.9	129.0	74.2	182.0	0.968
IL-1β	0.1	0.1	0.1	0.1	0.1	0.1	0.762
IFNα	0.1	0.1	1.3	0.1	0.1	1.5	0.747
TNFα	0.1	0.1	0.1	0.1	0.1	0.1	0.621
IL-10	0.1	0.1	0.1	0.1	0.1	0.1	0.442

Note. n, number of children; p, level of significance.

TABLE 2. FREQUENCY OF GASTROESOPHAGEAL REFLUX DISEASE IN CHILDREN WITH A FAMILY HISTORY OF PEPTIC ULCER DISEASE

Family history of peptic ulcer disease	Gastroesophageal reflux disease	
	n	%
Yes (n = 57)	22	38.6
No (n = 85)	20	23.5
p	0.054	

Note. n, number of children; p, level of significance.

syndrome, abdominal migraine, etc.). The absence of differences obviously indicates a certain commonality of dysfunction of regulatory systems, regardless of the nosology of functional pathology.

In children with a family burden of peptic ulcer, GERD was determined much more often (Table 2), which is probably a consequence of their increased acidity of gastric contents. In the presence of motor disorders of the gastroesophageal region, this leads to its damaging effect on the mucous membrane of the esophagus, which leads to the occurrence of clinical manifestations of heartburn.

The presence of a family predisposition to peptic ulcer was associated not only with an increase in the clinical manifestations of GERD, but was also reflected in the cytokine regulation of the disease. In particular, the course of GERD in the presence of a family history of peptic ulcer disease was associated with increased replication of both IL-4 and IFNα (Table 3).

The increase in IFNα replication ($p = 0.001$) in the blood serum of children with GERD with a family burden of peptic ulcer is obviously aimed at enhancing immune responses involving the whole body to damage. This is due to its functional role in the body: participation in the immune response. At the same time, the considered cytokine has not only immunomodulatory and antiviral effects, but also antibacterial activity due to the ability to induce the activity of enzymes with antibacterial activity in the damaged cell [8].

IL-4 performs a diverse function in the body: it reduces macrophage activity; activates the replication of such cytokines as TNFα, IL-6; regulates proliferative processes [7]. Enhancement of IL-4 replication ($p = 0.027$), obviously, enhances various metabolic and immune processes in the body, one of the main purposes of which is to maintain homeostasis of proliferative processes in the esophageal mucosa under conditions of hyperproduction of hydrochloric acid in the

TABLE 3. INDICATORS OF CYTOKINES IN BLOOD SERUM IN CHILDREN WITH GASTROESOPHAGEAL REFLUX DISEASE, DEPENDING ON THE PRESENCE OF A FAMILY HISTORY OF PEPTIC ULCER DISEASE

Family history of peptic ulcer disease	Cytokine	GERD + (n* = 22; n** = 20)			GERD – (n* = 35; n** = 65)			p
		Me	$Q_{0.25}$	$Q_{0.75}$	Me	$Q_{0.25}$	$Q_{0.75}$	
Yes	1. IL-2	0.1	0.1	0.3	0.1	0.1	0.5	0.578
	2. IL-4	1.7	1.4	2.4	1.2	0.5	1.8	0.035
	3. IL-6	0.1	0.1	0.1	0.1	0.1	0.1	0.869
	4. IL-8	15.4	0.1	73.0	8.3	0.1	44.7	0.895
	5. IL-18	132.1	66.6	213.5	113.0	79.1	149.6	0.442
	6. IL-1β	0.1	0.1	0.1	0.1	0.1	0.1	0.914
	7. IFNα	1.1	0.1	1.9	0.2	0.1	1.5	0.200
	8.TNFα	0.1	0.1	0.1	0.1	0.1	0.1	0.604
	9. IL-10	0.1	0.1	0.1	0.1	0.1	0.1	0.672
No	10. IL-2	0.1	0.1	0.2	0.1	0.1	0.1	0.984
	11. IL-4	1.1	0.1	1.9	1.2	0.6	1.8	0.427
	12. IL-6	0.1	0.1	0.1	0.1	0.1	0.1	0.679
	13. IL-8	16.4	0.1	91.7	21.6	0.1	89.8	0.996
	14. IL-18	99.6	9.6	228.9	146.6	44.2	231.1	0.414
	15. IL-1β	0.1	0.1	0.1	0.1	0.1	0.1	0.441
	16. IFNα	0.1	0.1	0.1	0.1	0.1	1.3	0.142
	17. TNFα	0.1	0.1	0.1	0.1	0.1	0.1	0.573
	18. IL-10	0.1	0.1	3.7	0.1	0.1	0.1	0.143
p	1-10	0.832			0.293			
	2-11	0.027			0.915			
	3-12	0.865			0.770			
	4-13	0.712			0.638			
	5-14	0.562			0.306			
	6-15	0.142			0.184			
	7-16	0.001			0.097			
	8-17	0.172			0.269			
	9-18	0.500			0.483			

Note. GERD, Gastroesophageal reflux disease; n, number of children; n*, number of children with a family history of peptic ulcer disease; n**, number of children without a family history of peptic ulcer disease; p, level of significance.

stomach, which is characteristic of people with family burden for peptic ulcer disease. In addition, in children with a family history of peptic ulcer, there was an increase in serum IL-4 in children with GERD compared with children who did not have clinical signs of GERD ($p = 0.035$).

Conclusion

When a family history of peptic ulcer is aggravated in schoolchildren with gastritis associated with GERD, a number of links in the cytokine network (IL-4, IFNα) transition to the systemic level of regulation.

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