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Features of the functioning of innate immunity in children with chronic idiopathic urticaria

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ABSTRACT

Aim. To study the features of the functioning of innate immunity in children with chronic idiopathic urticaria.

Materials and methods. The study included 28 children of both sexes aged 6–16 years with chronic idiopathic urticaria (CIU). The median age of the patients was 8 years (p = 0.045). Clinical research methods included an analysis of complaints and anamnestic data, as well as an objective examination of the child (dynamics of urticaria, severity of itching, the presence of angioedema). Immunological techniques included determination of the number of monocytes expressing $CD14^+CD282^+$, $CD14^+CD284^+$, $CD14^+CD289^+$, the number of peripheral blood lymphocytes expressing $CD3^+CD16^+$, the levels of immunoglobulin (Ig) E, lactoferrin, interferon (IFN) γ, interleukin (IL)-4, and IL-6, and a nitroblue tetrazolium test.

Results. In the course of the study, an increase in the expression of Toll-like receptors TLR2 and TLR4 by monocytes, a decrease in the expression of TLR9 by monocytes, a significant rise in lactoferrin levels, a slight decrease in the number of natural killer (NK) cells, a decrease in microbicidal activity and adaptive reserves, a rise in IgE levels, a decrease in IL-4 levels, and an increase in IFNγ and IL-6 were revealed in children with CIU.

Conclusion. The immunological changes revealed during the study indicate multidirectional expression of Toll-like receptors, disturbances in the work of the cellular components of innate immunity, and a launch of a proinflammatory cytokine cascade in children with CIU, which can serve as a mainstay for the development of new schemes for personalized therapy of CIU in children.

Keywords: chronic idiopathic urticaria, children, innate immunity

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Conformity with the principles of ethics. All study participants or their parents signed an informed consent. The study was approved by the local Ethics Committee at RostSMU (Protocol No. 10/21 of 27.05.2021).

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Особенности функционирования врожденного иммунитета у детей с хронической крапивницей

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РЕЗЮМЕ

Цель. Изучить особенности функционирования врожденного иммунитета у детей с хронической крапивницей (ХК).

Материалы и методы. В исследование включены 28 детей обоих полов в возрасте от 6 до 16 лет с хронической идиопатической (спонтанной) крапивницей. Медиана возраста – 8 лет (p = 0,045). Клинические методы исследования: анализ жалоб, анамнестических данных, объективный осмотр ребенка (динамика уртикариев, выраженности кожного зуда, наличие ангиоотеков). Иммунологические методы исследования: определение количества моноцитов, экспрессирующих $CD14^+CD282^+$, $CD14^+CD284^+$, $CD14^+CD289^+$, количества лимфоцитов периферической крови, экспрессирующих $CD3^+CD16^+$, содержания иммуноглобулина Е, уровня лактоферрина, интерферона (IFN) γ, интерлейкина (IL) 4 и 6, проведение теста с нитросиним тетразолием.

Результаты. В ходе исследования у детей с ХК выявлено повышение экспрессии моноцитами Toll-рецепторов TLR2 и TLR4, подавление экспрессии моноцитами TLR9, значительное увеличение уровня лактоферрина, незначительное сокращение количества NK-клеток, снижение микробицидной активности и адаптационных резервов, повышение уровня IgE, IFNγ и IL-6, уменьшение уровня IL-4.

Заключение. Выявленные в ходе исследования иммунологические изменения свидетельствуют о разнонаправленной экспрессии Toll-рецепторов, нарушениях в работе клеточного звена врожденного иммунитета, запуске цитокинового каскада воспаления у детей с хронической идиопатической крапивницей, что может послужить основой для разработки новых схем персонифицированной терапии ХК у детей.

Ключевые слова: хроническая крапивница, дети, врожденный иммунитет

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Chronic urticaria (CU) is a current problem in pediatrics due to increasing incidence, frequently developing resistance to treatment methods, and negative impact on children's and adolescents' quality of life (impaired sleep, poor school performance) [1, 2]. The prevalence of CU in the general population varies between 0.1 and 1.5% [3, 4]; according to different researchers, it may increase up to 3% among children and adolescents [5–8].

It is known that CU is characterized by spontaneously developing blisters and / or angioedema persisting for more than 6 weeks [9]. Clinical manifestations of CU are similar in all patients, while the pathogenesis of the disease is varied. However, the leading pathogenetic factor in half of the cases cannot be determined, and such CU is considered to be idiopathic or spontaneous [10, 11].

Since the role of innate immunity in the pathogenesis of urticaria is poorly understood, it seems promising to study the features of its functioning in children with chronic urticaria [12]. At the same time, treatment efficacy is predominantly determined by the possibility of conducting pathogenetically grounded, targeted therapy, which becomes truly effective only when the mechanisms of CU are revealed [13, 14].

The aim of the study was to investigate the features of the functioning of innate immunity in children with chronic idiopathic urticaria (CIU).

MATERIALS AND METHODS

Twenty-eight children of both sexes aged 6–16 years with CIU were examined. The median age was 8 years (p = 0.045). Inclusion criteria were clinical manifestations of urticaria (skin rash, itching, angioedema) lasting more than 6 weeks. Exclusion

criteria were signs of an acute infectious disease, signs of chronic disease exacerbation, a positive autologous serum skin test, elevated serum levels of thyroid peroxidase antibodies, and treatment with systemic glucocorticoids within one month before the examination. The control group included 30 almost healthy boys and girls aged 6–16 years (median age was 9 years) without chronic diseases. The patients were examined on the first day of admission before the initiation of inpatient therapy.

The studies were carried out according to the principles of the Declaration of Helsinki developed by the World Medical Association (WMA) "Ethical principles for medical research involving human subjects" amended by the 52nd WMA General Assembly (2000) and "Principles of Clinical Practice in the Russian Federation", approved by the Order of the Ministry of Health of Russia No.266 of 19.06.2003.

Clinical research methods included an analysis of complaints and anamnestic data, as well as an objective examination of the child (dynamics of rash, severity of itching, the presence of angioedema). Immunological techniques included determining the number of monocytes expressing $CD14^+CD282^+$, $CD14^+CD284^+$, $CD14^+CD289^+$ by flow cytometry with monoclonal antibodies (Caltag Laboratories, USA), determining the number of peripheral blood lymphocytes expressing $CD3^+CD16^+$ using the FC500 laser flow cytometer (Beckman Coulter Inc., USA), measuring the levels of immunoglobulin (Ig) E by the Manchi technique (Microgen, Russia), determining the levels of lactoferrin, interferon (IFN) γ, interleukin (IL)-4, and IL-6 (Cytokine, Russia) by enzyme immunoassay, and performing a nitroblue tetrazolium test (DIA-M, Russia). All laboratory tests were performed once. An informed consent was obtained from parents of children under 15 years and from adolescents 15 years of age and older to conduct clinical research and draw blood from veins.

For quantitative variables, the data were presented as the median and the interquartile range *Me* (Q_1; Q_3), maximum and minimum values *Min; Max*. The Mann – Whitney test was used to compare the medians in the groups. The differences were considered statistically significant at $p < 0.05$. All calculations were performed using R Foundation for Statistical Computing 3.2 software (Austria).

It was found that all children in the experimental group had typical presentation of chronic urticaria exacerbation (rash and itching), in 12 children (42.9%), urticaria was accompanied by angioedema.

RESULTS

The results of studying innate immunity parameters in children with CIU and in the control group are presented in the Table.

Table

Comparison of quantitative parameters of innate immunity in children with CIU and in the control group

Parameter	CIU, *n* = 28		Control group, *n* = 30		*p* (Mann –Whitney test)
	Me (Q_1; Q_3)	*Min; Max*	*Me* (Q_1; Q_3)	*Min; Max*	
$CD14^+CD282^+$, %	38 (26; 45.5)	18; 88	28.5 (27; 32)	22; 34	0.003
$CD14^+CD284^+$, %	45.5 (39; 52.5)	24; 60	7 (5; 8)	5; 9	< 0.001
$CD14^+CD289^+$, %	1.7 (1.5; 1.9)	1.2; 2.6	30.3 (26.8; 33.2)	22.3; 36.5	< 0.001
Lactoferrin, ng / ml	4,378 (2,189; 5,004)	1,087; 6,581	985 (750; 1,084)	582; 1,158	< 0.001
$CD3^+CD16^+$, %	8 (5; 11)	4; 7	10 (7; 13)	5; 16	0.062
IgE, g / l	173 (104; 197)	10.9; 477	45 (38; 75)	34; 88	< 0.001
Spontaneous nitroblue tetrazolium test (NBT), c.u.	96 (84; 112)	67; 167	102 (98; 105)	89; 112	0.077
Stimulated NBT-test, c.u.	143 (114; 162)	87; 200	180 (174; 192)	172; 203	< 0.001
Stimulation coefficient, units	1.3 (1.2; 1.7)	1.2; 2.4	1.8 (1.75; 1.9)	1.7; 1.96	< 0.001
IFN γ, pg / ml	16 (11.1; 18)	8.9; 23.3	5.8 (5.29; 7.5)	4.25; 8.7	< 0.001
IL-4, pg / ml	2.08 (1.9; 2.48)	1.1; 2.8	5.3 (4.2; 11.3)	3.8; 13.7	< 0.001
IL-6, pg / ml	9.89 (2.83; 48.7)	1.71; 67.5	4.98 (4.12; 5.35)	3.5; 5.72	0.154

In children with CIU, we revealed a statistically significant increase in TLR4 expression by monocytes by more than 6 times compared with the control group and extremely low values of TLR9 expression by monocytes – a decrease by almost 18 times. At the same time, the level of TLR2 expression by monocytes was increased by 1.3 times compared with the control group. In the group of children with CIU, a 4.5-fold rise in the level of lactoferrin was recorded compared with the control group. The number of natural killer (NK) cells in the blood of children with CIU was reduced by 1.3 times compared with the control

group. The median of total serum IgE in children with CIU was 3.8 times higher than in the control group. Children with CIU showed a decrease in the values of spontaneous NBT test associated with reduced adaptive reserves of phagocytes combined with decreased values of stimulated NBT test, which was manifested through a significantly low stimulation coefficient. The level of IFNγ was elevated by 2.8 times compared with the control values. At the same time, the content of IL-4 was reduced by more than 2 times compared with the control group. The level of IL-6 exceeded the control values by 2 times, although it was not statistically significant.

DISCUSSION

Studies describing the role of Toll-like receptors (TLRs) in the pathogenesis of CIU published by foreign researchers are few [15]. In our study, we noted an increase in TLR2 and TLR4 expression by monocytes in children with CIU, which is in line with the data published by Russian authors. So, E.V. Sorokina et al. (2020) found that the TLR2 and TLR4 levels were 6 and 4 times higher, respectively, in patients with CIU lasting at least 6 months than in the group of healthy individuals, while the duration of the disease did not affect TLR9 expression [16]. Our study showed a decrease in expression of TLR9 by monocytes in children with CIU compared with the control group. Similar results were obtained in the comparative study published by foreign authors who revealed functional failure of TLR9 expressed by dendritic cells in patients with CU compared with the control group [17].

The properties of serum lactoferrin as one of the transferrin family proteins involved in transport and metabolism of iron are fully described in the literature [18]. Due to this unique ability, lactoferrin exerts its antioxidant and membrane stabilizing effects [19]. We did not find available literature on the contribution of lactoferrin to the pathogenesis of CIU. In our study, a significant increase in the lactoferrin level in children with CIU may be explained by its anti-inflammatory effect – by iron binding in the focus of inflammation, which eventually reduces cell damage by oxygen free radicals and decreases the intensity of inflammation.

Currently, NK cells, in addition to their direct cytolytic effects, are known to exert a regulatory effect on immune responses through secretion of cytokines, chemokines, and growth factors [20]. We did not find any information on the contribution of NK cells to the mechanism of CIU development in the available literature. Pathological presentation of urticaria is characterized by a perivascular infiltrate consisting of lymphocytes, monocytes, mast cells, eosinophils, and neutrophils [21]. A slight decrease in the number of NK cells in the blood of children with CIU in our study may be due to their migration to the focus of inflammation.

We did not find information about the role of phagocytosis in the genesis of CIU in the literature. There are a few works devoted to the study of phagocytosis in allergic diseases. Thus, the study by E.G. Moiseeva et al. (2005) showed a decrease in the intensity of phagocytosis in allergic inflammation, which is regarded as a stage of its depletion [22]. In our study, we revealed low microbicidal activity and a decrease in adaptive reserves in children with CIU, which also characterizes diminishment of phagocytosis.

Determination of IgE level in various variants of urticaria development has always been of great interest for researchers. Thus, A. Kessel et al. (2010) revealed an increase in the level of IgE in patients with CU compared with the control group [23]. In a comparative study, K.L.Chang et al. (2011) found that in children with CU, an increase in IgE levels was not as intense as in patients with acute urticaria [24]. Besides, increased IgE values were found in patients who had CIU with concomitant atopic diseases [16]. The results of our study on determining the level of IgE in children with CIU comply with the results of the works discussed above.

Changes in the cytokine profile play an important role in the pathogenesis of somatic symptom disorders, including the pathogenesis of CIU. IL-4 is often called an anti-inflammatory cytokine, as it is able to suppress the immunostimulatory effect of Th1 and reduce TNF and IFNγ synthesis. However, according to A.S. Simbirtsev (2021), IL-4 is a typical proinflammatory and proallergic cytokine with a wide spectrum of biological activity, which is involved in the functioning of innate and adaptive immunity [25]. The decrease in the serum IL-4 level in children with CIU revealed in our study demonstrates possible reduction or suppression of synthesis of this cytokine.

The role of IL-6 in severe CU and its direct relationship with acute-phase proteins and the fibrinolytic system are shown in the study by A. Kasperska – Zajac (2011) [26]. Other foreign researchers also consider that IL-6 plays one of the key roles in immune and inflammatory responses and can be a biomarker of CU activity [27–29]. The role of IFNγ in the patho-

genesis of CU was also confirmed by foreign scientists. Thus, a positive relationship was found of basophil activation and an increase in TLR4 expression on mast cells with an increase in the serum IFNγ level in CIU [30]. The results of our study also revealed overproduction of proinflammatory cytokines IFNγ and IL-6 in children with CIU, which, in our opinion, can be considered not only as a marker of the inflammatory response intensity, but also as a predictor of CIU in children.

CONCLUSION

The immunological changes revealed in the study indicate multidirectional expression of TLRs, disturbances in the work of cellular components of innate immunity, and a launch of a proinflammatory cytokine cascade in children with CIU. This, in turn, causes activation of regulatory components of inflammation and adaptive defense mechanisms of the body, which results in a chronic course of idiopathic urticaria. An integrated approach to the study of innate immunity will provide a more complete understanding of the immunopathogenesis of CU and may serve as a mainstay for the development of new targeted treatment strategies for this disease in children.

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Authors contribution

Maltsev S.V. – collection of data for analysis, drafting of the article. Sizyakina L.P. – critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Lebedenko A.A – conception and design, analysis and interpretation of the data.

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