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ОЦЕНКА ВЗАИМОСВЯЗИ ПОЛИМОРФИЗМА IL17A G-197A С ИММУНОЛОГИЧЕСКИМИ НАРУШЕНИЯМИ И СТРУКТУРНЫМИ ИЗМЕНЕНИЯМИ МОЗГА ПРИ ШИЗОФРЕНИИ

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Резюме. Шизофрения — хроническое психическое заболевание, которое вызывается сложной палитрой генетических, эпигенетических факторов и повреждающих воздействий окружающей среды. Шизофрения сопровождается структурными изменениями головного мозга, ассоциированными с клинической симптоматикой. К значимым патогенетическим компонентам шизофрении относятся иммунологические нарушения и системное воспаление, приводящие к нейровоспалению, которое является важным фактором в развитии структурных изменений мозга. Ранее нами показано, что повышение уровня интерлейкина-17А связано с морфометрическими изменениями мозга, активацией системного воспаления и Th2-звена адаптивного иммунитета при шизофрении. Генетический полиморфизм IL17A G-197A (rs2275913) может влиять на уровень секреции интерлейкина-17А. Целью данной работы было изучение ассоциаций между полиморфизмом IL17A G-197A, изменениями

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иммунитета и морфометрическими показателями мозга у больных для получения новых данных об иммунопатогенезе шизофрении. В основную группу вошли 60 человек с диагнозом «шизофрения» в возрасте от 18 до 42 лет. Контрольную группу составили 85 человек без когнитивных нарушений, сопоставимых с больными по полу и возрасту. Для определения концентрации цитокинов и хемокинов в сыворотке крови использовался мультиплексный анализ. Полиморфизм гена IL17A G-197A определяли методом полимеразной цепной реакции с электрофоретической детекцией продуктов амплификации. В результате проведенного исследования впервые был выявлен ряд взаимосвязей между генетическим полиморфизмом IL17A G-197A и показателями иммунитета у больных шизофренией. У носителей аллеля G наблюдалось значительное повышение IFNγ — ключевого цитокина Th1-звена адаптивного иммунитета, и IL-8 — хемокина, являющегося медиатором воспаления. Также у больных — носителей аллели G было отмечено повышение уровня хемокина CXCL16, который может стимулировать секрецию других провоспалительных хемокинов и участвует в активации Th1-звена адаптивного иммунитета. Кроме того, в данном исследовании была впервые обнаружена ассоциация гетерозиготного генотипа GA полиморфизма IL17A G-197A со снижением толщины коры головного мозга в ряде областей фронтальной коры при шизофрении. Изменения толщины коры в некоторых из этих областей, включая среднюю лобную извилину и орбитофронтальную кору, связано с патогенезом негативной симптоматики у больных. Полученные результаты свидетельствуют о важности иммуногенетических факторов в патогенезе шизофрении и показывают перспективность дальнейшего изучения полиморфизма IL17A G-197A на расширенных выборках больных как потенциального биомаркера иммунной дисрегуляции и морфометрических изменений мозга при шизофрении.

Ключевые слова: хемокины, цитокины, IL-17A, магнитная резонансная томография, однонуклеотидный полиморфизм, средняя толщина коры, шизофрения

ASSOCIATIONS OF IL17A G-197A SINGLE NUCLEOTIDE POLYMORPHISM WITH IMMUNOLOGICAL PARAMETERS AND STRUCTURAL CHANGES OF THE BRAIN IN SCHIZOPHRENIA

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Abstract. Schizophrenia is a chronic mental disorder that is caused by a complex palette of genetic, epigenetic and environmental factors. Some of the important components of its pathogenesis are systemic inflammation and the dysfunction of immunity, which lead to neuroinflammation, contributing to development of structural brain changes. Earlier we have shown that increase in interleukin-17A levels is associated with morphometric changes and immune dysregulation in schizophrenia. IL17A G-197A (rs2275913) genetic polymorphism is involved in determining interleukin-17A secretion. The goal of this work was to investigate the associations between rs2275913 polymorphism, immune disorders and structural neurovisualization findings in schizophrenia to provide new insights into the immunopathogenesis of this disease. 60 patients aged 18 to 42 years diagnosed with schizophrenia were enrolled. 85 healthy volunteers were included into the control group. Multiplex assay was used to determine cytokine and chemokine serum levels. Rs2275913 polymorphism was assessed by polymerase chain reaction with electrophoretic detection of amplification products. A number of relationships between rs2275913 polymorphism and the immune parameters in schizophrenia were revealed. Carriers of G allele showed significant increase in IFNγ, a key cytokine of Th1-link of adaptive immunity, and

IL-8, an inflammatory chemokine. Also, increased levels of CXCL16 were observed in patients carrying the G allele. CXCL16 activates secretion of other proinflammatory chemokines and is involved in activation of Th1 adaptive immunity. Associations of heterozygous GA genotype with reduced cortical thickness in a number of areas of the frontal cortex in schizophrenia were found. Changes in cortical thickness in some of these areas, including middle frontal gyrus and orbitofrontal cortex, can be relevant to the pathogenesis of schizophrenia. The results highlight the importance of immunogenetic factors in the pathogenesis of schizophrenia and indicate that the rs2275913 polymorphism requires further studies as a potential biomarker of immune dysregulation and morphometric brain changes in schizophrenia.

Keywords: chemokines, cytokines, IL-17A, magnetic resonance imaging, mean cortical thickness, schizophrenia, single nucleotide polymorphism

Introduction

Schizophrenia is a chronic mental disorder that is caused by a complex palette of genetic, epigenetic and environmental factors [5]. Symptoms of schizophrenia include disturbances in thinking, cognitive function, affects, emotional and psychomotor disorders. Schizophrenia is also characterized by structural brain changes that are associated with the severity and character of clinical symptoms, as well as with the duration of the disease [13].

The modern genetic, immunological, neuroimaging and other research methods allow to accumulate a large amount of data on the multiple factors of schizophrenia pathogenesis, which have not been fully deciphered yet. One of the most important components of the pathogenesis of schizophrenia is associated with dysfunction of immunity and systemic inflammation, which lead to the development of neuroinflammation and dysregulation of the immune response in the CNS [7]. Neuroinflammation is an important factor in the development of structural changes of the brain in schizophrenia. Therefore, it is important to study the role of immunogenetic factors that can influence systemic inflammation, immune dysregulation and inflammation in the development of morphometric changes of the CNS in schizophrenia.

In our previous studies, elevated levels of the cytokine IL-17A were found to have significant associations with morphometric changes of the brain in schizophrenia patients, and were also associated with systemic inflammation and activation of the Th2 type of the adaptive immune response [3].

The cytokine IL-17A plays a key role in protection against extracellular bacterial and fungal infections. However, overproduction of this protein is associated with immunoinflammatory and autoimmune diseases. The main source of IL-17A are Th17 cells, which induce local inflammatory processes in response to extracellular pathogens and autoimmune responses [1]. The pathogenetic role of IL-17A in neurodegenerative diseases and inflammatory CNS diseases is widely studied and is due to the fact that it can stimulate proinflammatory cytokine synthesis by microglial cells of the central nervous system (CNS), increase the permeability of the blood-brain barrier (BBB), permeate the BBB, support neuroinflammation and promote excessive activation of the glutamatergic neurotransmitter system. This leads to excitotoxic neuronal damage and has a depressing effect on neurogenesis in the hippocampus [2].

Therefore, it is relevant to study the factors influencing IL-17A levels in schizophrenia and their possible contribution to the development of morphometric changes of the brain in patients. The IL17A G-197A (rs2275913) genetic polymorphism is involved in determining IL-17A secretion. This SNP is located in the promoter region of the gene, near the nuclear factor of activated T cells (NFAT) binding motif. It has been suggested that substitution of nucleotide G for A in this position can lead to changes in IL-17A cytokine production [8]. Therefore, it is relevant to study the relationship of IL17A G-197A SNP with immunological disorders and morphometric parameters of the CNS in patients with schizophrenia [10].

The aim of this work was to investigate the associations between the IL17A G-197A polymorphism, immune disorders and the findings of structural brain MRI in schizophrenia patients to provide new insights into the immunopathogenesis of schizophrenia.

Materials and methods

The clinical sample consisted of 60 patients aged 18 to 42 years diagnosed with schizophrenia (F20.0) who were undergoing treatment at N.A. Alekseev Psychiatric Clinical Hospital No.1. 85 persons without cognitive impairment (31 men, 54 women), comparable with patients with schizophrenia by sex and age, were included into the control group. All

participants signed an informed voluntary consent form. The conduct of the study was approved by the local ethical committee of the National Research Center "Kurchatov Institute" (No. 5 of 05.04.2017).

The content and functional activity of lymphocyte subpopulations were analyzed by flow cytoflowmetry. Monoclonal antibodies for immunophenotyping manufactured by Becton Dickinson (USA) were used for cell staining.

A multiplex assay (Merck Millipore, Germany) was used to determine cytokine and chemokine concentrations in blood serum.

IL17A G-197A gene polymorphism was determined by PCR with electrophoretic detection of amplification products. Two parallel amplification reactions with two pairs of allele-specific primers were performed. PCR amplification products were separated in a 3% agarose gel. Ethidium bromide solution was used as a dye to visualize PCR products in the gel.

MRI brain scans were performed on a Siemens Magnetom Verio 3T magnetic resonance imager (Siemens GmbH, Germany). A 32-channel brain coil was used to acquire data. High-resolution anatomical data based on T1-weighted sequences (TR = 1900 ms, TE = 2.21 ms, 176 slices, voxel size $1 \times 1 \times 1$ mm^3) were obtained for gyrification, grey and white matter morphometry, and cerebrospinal volume for each subject. The obtained structural images were analyzed in Freesurfer program designed for processing and analysis of human brain MRI. This program allowed a complete morphometry of the brain. Based on the analyzed data, the index of local cerebral gyrification was calculated.

Excel (Microsoft, 2010) and STATISTICA 10 (Stat Soft, 2010) programs were used for statistical processing. The Shapiro-Wilk test was used to assess the normality of the distribution. Results were presented as means with 95% confidence intervals; when comparing two groups, the significance of differences was assessed using Student's test. In the case of discrete variables, Fisher's exact test was used to assess the significance of differences. Differences between variables were considered statistically significant at $p < 0.05$.

TABLE 1. FREQUENCY OF IL17A G-197A SNP IN PATIENTS WITH SCHIZOPHRENIA AND IN HEALTHY CONTROLS

Polymorphism	Group	Total number of patients	Homozygotes for the 1st allele		Heterozygotes		Homozygotes for the 2nd allele	
			n	%	n	%	n	%
IL17A G-197A (rs2275913)	Schizophrenia	85	29*	34.1	39*	45.9	17*	20.0
	Controls	100	80	80.0	19	19.0	1	1.0

Note. *, significant differences with the control group (p < 0.05).

TABLE 2. ASSOCIATIONS BETWEEN IL17A G-197A SNP, CYTOKINE, CHEMOKINE LEVELS AND CELL IMMUNITY PARAMETERS IN PATIENTS WITH SCHIZOPHRENIA

Parameter	GG	GA	AA	Controls
IFNγ, pg/mL	106.6±54.0 * p = 0.036	169.3±109.8 * p = 0.038	85.8±61.5	48.1±26.9
IL-8, pg/mL	71.5±32.7 * p = 0.028	89.2±36.9 * p = 0.005	56.6±50.9	26.3±14.6
CCL3, pg/mL	1194.8±2441.1	47.1±25.3 * p = 0.026	27.2±22.6	25.4±9.0
CXCL16, pg/mL	774.4±147.78	706.8±271.0 * p = 0.048	690.0±56.4	639.9±36.7
CD3⁻CD16⁺CD56⁺ (NK cells), %	12.3±2.7	10.0±2.3	16.1±4.1 * p = 0.04	11.9±1.9
CD3⁻CD8⁺CD16⁺CD56⁺ (CD8⁺ expressing NK cells), %	4.2±1.5	3.3±1.9	6.6±3.2 * p = 0.04	3.7±0.6

Note. *, significant differences with the control group (p < 0.05).

Results and discussion

The study to identify the IL17A G-197A (rs2275913) polymorphism of the IL17A gene revealed statistically significant differences in the frequency of this SNP between the schizophrenia patient group and the control group (Table 1).

As a result of this study, a number of relationships between the studied genetic polymorphism IL17A G-197A (rs2275913) and the immune parameters in schizophrenia patients were revealed for the first time (Table 2).

Thus, carriers of G allele of the investigated SNP showed significant increase in IFNγ, a key cytokine of Th1-link of adaptive immunity, and IL-8, a chemokine mediating inflammation. In AA homozygotes, these indices did not differ from the norm. However, they had an increased content of $CD3^-CD16^+CD56^+NK$ cells and of $CD8^+$ expressing $CD3^-CD8^+CD16^+CD56^+NK$ cells. According to the literature, this subpopulation of NK cells has an immunoregulatory function and may contribute to neuroprotection in brain diseases [6]. The association between IL17A G-197A SNP and $CD3^-CD8^+CD16^+CD56^+NK$ cells content has not been previously studied and requires further research.

In addition, carriage of the G allele of SNP IL17A G-197A was found to be associated with a tendency for elevated levels of the chemokine CCL3. This proinflammatory chemokine has a marked chemotactic effect on neutrophils, monocytes and macrophages. Previous studies involving this chemokine in patients with schizophrenia did not show significant differences with controls, which may have been due to insufficient statistical power of sampling [11].

Also, increased levels of CXCL16 were observed in patients carrying the G allele of SNP IL17A G-197A. This chemokine is expressed by mononuclear phagocytes after stimulation by the proinflammatory cytokines IFNγ and TNFα. It can activate the secretion of other proinflammatory chemokines and is involved in activation of the Th1 type of adaptive immune response [14].

According to our previous studies, elevated IL-17A levels are associated with marked immune abnormalities and with cortical morphometric changes in schizophrenia [4]. In this study, the G allele of SNP IL17A G-197A was shown to be associated with activation of systemic inflammation and signs of Th1 activation of the adaptive immune system in patients. It is possible that the effect of this SNP on the state

TABLE 3. MEAN CORTICAL THICKNESS IN PATIENTS WITH SCHIZOPHRENIA DEPENDING ON THE SNP ALLELE IL-17A G-197A

	AA		AG		GG		Controls	
Indicator	**m**	**σ**	**m**	**σ**	**m**	**σ**	**m**	**σ**
Caudal part of the middle frontal gyrus (right)	2.56	0.13	2.45*	0.12	2.58	0.14	2.66	0.14
Precentral gyrus (left)	2.49	0.12	2.46*	0.10	2.65	0.10	2.62	0.14
Rostral part of the middle frontal gyrus (left)	2.41	0.13	2.40*	0.09	2.46	0.11	2.54	0.13
Lateral orbitofrontal cortex (right)	2.72	0.14	2.66*	0.11	2.72	0.11	2.81	0.11
Rostral part of the middle frontal gyrus (right)	2.36	0.13	2.37*	0.10	2.39	0.11	2.53	0.16
Precentral gyrus (right)	2.45	0.19	2.40*	0.12	2.59	0.14	2.56	0.16
Pars orbitalis of the inferior frontal gyrus (IFG) (left)	2.79	0.20	2.75*	0.20	2.82	0.12	2.96	0.17
Pars triangularis of the inferior frontal gyrus (IFG) (left)	2.42	0.18	2.46*	0.14	2.49	0.07	2.60	0.14

Note. *, significance of differences $p < 0.005$ compared to the control group.

of immunity is due to changes in the local IL-17A secretion, although this requires further research.

Considering the results obtained in this study indicating the effect of SNP IL17A G-197A on the severity of immune disorders in patients, the association of SNP IL17A G-197A (rs2275913) with the average thickness of the large hemispheric cortex in schizophrenia was assessed (Table 3).

The data presented in Table 3 suggest an association of the heterozygous GA genotype of the SNP IL17A G-197A with reduced cortical thickness in a number of areas of the frontal cortex in schizophrenia. Changes in cortical thickness in some of these areas can be relevant to the pathogenesis of the disease, particularly to the development of negative symptoms in patients, which include apathy and abulia, as well as disturbances in memory, attention, thinking and speech. One such area is the middle frontal gyrus, which is divided into upper and lower parts by the middle frontal sulcus. Reduced middle frontal gyrus volume has been found to be associated with impaired episodic memory [9]. It is also known that the middle frontal gyrus is associated with reading, writing and numerical literacy skills, while the left middle frontal gyrus is also active in tasks requiring the actualization of verbal memory and word articulation, and supports the feedback system during verbal activity [15].

The orbitofrontal cortex is an area of the brain that plays an important role in the implementation of volitional functions and the regulation of behavior, as well as in emotional reinforcement in learning.

According to the literature, structural changes in the orbitofrontal cortex and disruptions in its functional connections with surrounding structures can lead to cognitive and behavioral disorders associated with impaired decision-making and emotion regulation. Decreased cortical thickness in these areas has been confirmed by other studies of brain morphometrics in schizophrenic patients, but the association of these changes with the SNP IL17A G-197A has been shown for the first time [12]. The findings indicate that SNP IL17A G-197A requires further research as a potential biomarker of adaptive immunity dysregulation and morphometric abnormalities in the brain in schizophrenia.

Conclusion

In conclusion, the results of this study demonstrate the association of increased chemokine levels and changed content of NK-cell subpopulations in schizophrenia patients with carriage of SNP IL17A G-197A (rs2275913) and also demonstrate the association of carriage of this polymorphism with morphometric changes in the cerebral cortex. The results indicate that SNP IL17A G-197A requires further studies on expanded samples of patients as a potential biomarker of immune dysregulation and morphometric abnormalities in the brain in schizophrenia. The findings can be translated into practice for use in predicting the course of the disease, the development of structural brain abnormalities, and the selection of therapy in schizophrenia.

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