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The relationship of morphometric changes of the brain with IL-6 levels, systemic inflammation and immune disturbances in the patients with schizophrenia

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Abstract

Schizophrenia is a chronic disease characterized by psychosis, behavioral, cognitive and social impairments. It is accompanied by structural and functional changes in the brain. To confirm the significance of morphometric changes, it is important to establish relationships between structural changes in the brain, clinical symptoms, and the level of biomarkers reflecting the pathogenesis of the disease, including immunological markers. The aim of this work was to assess the relationship of interleukin-6 (IL-6) levels with systemic inflammation, immune activation and with the results of neuroimaging in schizophrenia. The study included 60 patients with schizophrenia, 25 healthy volunteers. MRI scanning and the assessment of key immunological parameters was performed. It was found that the patients had significant negative correlations between IL-6 levels and a number of structural MRI indicators. Patients with a marked increase in IL-6 levels (> 15 pg / ml) had a reduced mean curvature in the left lingual gyrus and a reduced gyrification index in the left fusiform gyrus compared with the control group. The level of IL-6 was

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associated with signs of systemic inflammation and immune activation in the patients. Thus, in this work, an immunological profile in schizophrenia associated with an increase in IL-6 and with morphometric changes of the brain was characterized for the first time. In further studies, we plan to evaluate morphometric changes in patients with various immunological phenotypes of schizophrenia, clinical course of the disease, and factors of genetic predisposition.

Keywords: Type your keywords here, separated by semicolons ;

1. Introduction

Schizophrenia is a debilitating and chronic disease that is accompanied by psychosis and a wide range of behavioral, cognitive and social impairments [1]. In 2017, about 20 million cases of schizophrenia were registered in the world [2]. The prevalence of this disease in Russia is about 1%, in most cases young people get affected (the peak incidence is between 15 and 35 years). Schizophrenia is characterized by a high level of disability: for example, in 2017, the indicator of the average number of years lived with disability (YLD), which characterizes the total "disease burden", was about 12,657,900 for schizophrenia [2]. The diagnosis of schizophrenia is mainly based on phenomenological observations and clinical descriptions. Although these descriptions are reliable, they are not based on reliable instrumental survey data [3]. Schizophrenia is characterized by heterogeneity of symptoms, responses to treatment and outcomes, which reflects the presence of different subtypes within the disease, but clinical observations alone do not allow the formation of precise subgroups that identify etiological and pathological differences [4]. Modern therapy for schizophrenia does not change the course of the disease, remaining largely symptomatic. In patients with severe negative symptoms, treatment is usually ineffective. The negative symptoms of schizophrenia include impaired motivation, loss of interest (for example, detachment, anhedonia or a decrease / loss of the ability to enjoy activities, asociality), and others. These symptoms are a major component of schizophrenia and account for a significant proportion of long-term morbidity and poor functional outcome in the patients [5].

Many links in the pathogenesis of schizophrenia are still unclear. In deciphering the central mechanisms of the disease, the development of neuroimaging methods played an important role. It should be noted that intravital brain imaging revolutionized the understanding of the pathogenetic foundations of schizophrenia, allowing to obtain convincing evidence that schizophrenia is a neuropsychiatric disorder [6].

In general, it has been shown that the disease is accompanied by structural and functional changes in the brain. The areas of the brain most often affected in schizophrenia are the anterior and posterior parts of the cerebral cortex and the limbic system. There are indications of involvement of the temporal and frontal lobes, the limbic system (in particular, the cingulate gyrus, amygdala, and hippocampus), cerebellum, and thalamus. There is evidence that the posterior cingulate gyrus, medial prefrontal cortex, and a number of other areas are involved in the neuropathophysiology of schizophrenia. Many zones still need to be deciphered for participation in the development of certain symptoms of schizophrenia [6].

According to some researchers, schizophrenia can be caused by changes in functional circuits in the brain, and not just by structural abnormalities in some area of the brain. Some of the most interesting results from structural MRI and fMRI studies in schizophrenic patients include a decrease in gray matter volume (frontal lobe) and a decrease in brain activity and volume [7]. The ventricles and basal nuclei in the brain of schizophrenic patients are often larger than usual, while the hippocampus and amygdala are smaller [8].

Despite the almost 30-year history of neuroimaging studies, significant differences persist in the detected changes in the structure and functional activity of the brain, obtained by different groups of scientists. There are also differences in the data of brain scans during the first episode, in chronic, naive and treated patients with schizophrenia. Nevertheless, many changes, structural changes and fMRI data are reproduced in homogeneous groups of patients with schizophrenia. However, there is still no translation of the results of neuroimaging studies into clinical practice, including their use in predicting the course of the disease, in the choice of therapy and its monitoring. One of the significant reasons for this situation is the lack of in-depth associative clinical and visualization studies in patients with schizophrenia. Currently, there are separate works aimed at finding

relationships between certain clinical symptoms in schizophrenia and morphometric changes in the brain. Thus, it was revealed that auditory hallucinations in patients are associated with functional and anatomical disorders in the areas responsible for auditory perception (primary and secondary auditory cortex), as well as with disorders of the structures responsible for the reproduction of speech sounds, including the opercular part of the inferior frontal gyrus and the anterior insular zone of the inferior frontal gyrus [8-11].

Given the pathogenetic and clinical heterogeneity of schizophrenic spectrum disorders, to confirm the significance of morphometric changes, it is important to establish relationships between structural changes in the brain, clinical symptoms, and the level of biomarkers reflecting the pathogenesis of the disease. We believe that the search for relationships between changes in the structure and functional activity of the brain according to fMRI data with peripheral markers of systemic inflammation, activation and dysfunction of immunity will provide new knowledge and a new level of understanding of the mechanisms of the disease for both fundamental neuroscience and clinical psychiatry and the subsequent translation of neuroimaging methods into practical activity of psychiatrists.

Among the pathogenetically significant biomarkers, the level of which is altered in schizophrenia, the indicators of immunity should be noted. Currently, clinical, immunological, genomic, transcriptomic studies and the study of the postmortal brain have accumulated convincing data on the presence of neuroinflammation in patients with schizophrenia, as well as systemic inflammation and activation of the immune system in the periphery [12-16]. The interrelation of changes in immunological parameters with the prognosis of schizophrenia and the nature of symptoms was found [14, 15, 17, 18]. However, their place in the pathogenesis of schizophrenia, the role in the complex relationships between the brain with altered activity, neuroinflammation and peripheral factors of inflammation, endocrine and immune regulation remain unclear. Questions about the correlation of morphometric disorders, neuroimmune changes and different clinical forms of schizophrenia, the course of the disease and the characteristics of the response to treatment (resistance to therapy, cognitive disorders, chronicity, etc.) remain open.

Among the immunological biomarkers, the cytokine IL-6, a mediator of the immune system and inflammation, has attracted much attention. IL-6 is synthesized not only in the cells of the immune system, but also in the central nervous system and normally has a neurotrophic effect, promotes neurogenesis and memory consolidation [19]. It is one of the key cytokines that plays an important role in triggering the systemic inflammatory response, pyrogenic reactions, and functions of adaptive immunity [20]. An increase in the level of IL-6 in the central nervous system, which can be observed, in particular, in neuroinfections, autoimmune diseases, mental illnesses, has a damaging effect on neurons and glial cells, and promotes neurodegeneration (see, for example, a review [19]). The possible role of the systemic level of IL-6 as an indicator of immune activation and a potential prognostic marker in patients with schizophrenia is not well understood. According to the results of one of the recent studies, the serum level of IL-6 has a negative correlation with indicators of cognitive functions in outpatients with schizophrenia ($r = -0.395$), while the level of other cytokines studied in that work (IL-2, IL-4, IL-10, IL-17A, TNF-α, IFNγ) was not associated with cognitive functioning [17]. According to the results of another study, in hospitalized patients with schizophrenia after a course of antipsychotic therapy, an increased level of IL-6 decreased to normal values, which correlated with a decrease in the severity of positive and negative symptoms according to the PANSS scale [18]. These data indicate that, at least in some patients with schizophrenia, the level of IL-6 may act as a potential marker of the severity of cognitive impairment and the effectiveness of therapy. The relationship between an increase in IL-6 in the patients with the level of other indicators of immunity and markers of systemic inflammation, and with structural changes in the brain has also been insufficiently studied. Thus, many features of the immunological profile in schizophrenia associated with increased IL-6 remain unclear. In this regard, the aim of this work was to assess the relationship of IL-6 levels with markers of systemic inflammation and immune activation, as well as with the results of neuroimaging in schizophrenic patients to search for the IL-6-associated phenotype of paranoid schizophrenia.

2. Materials and methods

60 patients with paranoid schizophrenia and 25 healthy volunteers were enrolled into the study.

MRI scanning was performed at the National Research Center Kurchatov Institute (Moscow, Russia) on a Siemens Magnetom Verio 3T magnetic resonance tomograph (Siemens GmbH, Germany). A 32-channel brain coil was used to acquire the data. For gyrification, morphometry of gray and white matter, cerebrospinal fluid volume,

high-resolution anatomical data were obtained for each subject based on the 3D T1-weighted sequence (TR = 1900 ms, TE = 2.21 ms, 176 slices, voxel size 1x1x1 mm^3). Freesurfer is an open source software package for the processing and analysis of MRI of the human brain. All structural images obtained within the framework of this project were analyzed on the supercomputer of the National Research Center "Kurchatov Institute" in the Freesurfer program. This program allowed for the removal of the skull from images, subcortical and cortical segmentation, reconstruction of the cortical surface, assessment of cortical thickness and complete brain morphometry. Also, on the basis of the data obtained after analysis in the Freesurfer program, the index of local cerebral gyrification was calculated. Additionally, the volume of the cerebellum and its divisions was calculated.

Determination of the main parameters of innate and adaptive immunity, the systemic level of key mediators of the immune system - cytokines (IL-4, IL-6, IL-8, IL-10, IFNγ), as well as other markers of inflammation (C-reactive protein (CRP), cortisol, circulating immune complexes (CIC), immunoglobulins IgA, IgM, IgG was performed using the enzyme-linked immunosorbent assay (ELISA). Reagent kits manufactured by Cytokin, Russia, St. Petersburg (IL-4, IL-6, IL-10, IFNγ), "Vector Best", Russia, Novosibirsk (IL-8), "HEMA", Russia were used.

The study was approved by the local ethics committee of the National Research Center "Kurchatov Institute" (No. 5 dated 04/05/2017). All participants were familiarized with the details of the experiment and signed a voluntary informed consent sheet, a questionnaire and consent to the processing of personal data.

The software Exel (Microsoft, 2010) and STATISTICA 10 (StatSoft, 2010) were used for statistical processing. Group results were presented as medians with 25^{th} and 75^{th} percentiles or as means ± 95% confidence intervals. The distribution normality was assessed using the Shapiro-Wilks test. To assess the significance of differences in immunological parameters, the Mann-Whitney test was used, considering the differences between the parameters to be statistically significant at $p < 0.05$. To assess the significance of differences in morphometric indicators that had normal distribution, the Student's test was used. The differences between the indicators were considered to be statistically significant at $p < 0.05$. To assess the correlations, the Pearson's correlation coefficient was used.

3. Results

Analysis of the relationship between the serum levels of immune and neurobiological factors and the results of structural and functional imaging revealed that the patients had a significant ($p < 0.05$) negative correlation between the level of IL-6 and a number of structural MRI indicators. Thus, there was a correlation between the level of this cytokine and the folding index, gyrification index, surface area and volume of gray matter in the area of the right lingual gyrus (-0.27, -0.24, -0.24, -0.26). In addition, the level of IL-6 was negatively correlated with the surface area and volume of the cortex in the region of the left calcarine sulcus (-0.20, -0.17). The relationship between the level of this cytokine and the mean curvature, Gaussian curvature, internal curvature index and internal folding index in the region of the left lingual gyrus was found (-0.41, -0.37, -0.37, -0.34). Thus, in patients with schizophrenia there was a significant ($p < 0.05$) negative correlation of IL-6 level with morphometric parameters of the right lingual gyrus cortex, left lingual gyrus cortex and a number of structures of the limbic system (Table 1).

Patients with a marked increase in IL-6 levels (> 15 pg/ml) had a reduced mean curvature in the left lingual gyrus ($p < 0.002$) and a reduced gyrification index in the left fusiform gyrus ($p < 0.005$) compared with the control group.

The relatively small value of the detected correlations may be associated with the heterogeneity of patients in morphometric changes, given that the most pronounced morphometric changes were observed at IL-6 levels> 15 pg / ml. In addition, the results could be influenced by the heterogeneity of patients in terms of genetic predisposition to schizophrenia and genetically determined characteristics of IL-6 production, heterogeneity in the characteristics of brain morphogenesis, and acquired risk factors for schizophrenia. In further studies, we plan to evaluate morphometric changes in patients with various immunological phenotypes of schizophrenia, clinical features of the course of the disease, and factors of genetic predisposition.

Table 1. Correlation of IL-6 level with morphometric parameters of the cerebral cortex in schizophrenia.

Morphometric parameters	Correlation coefficient (*R*)
Folding index, right lingual gyrus	-0.27

Gyrification index, right lingual gyrus	-0.24
Surface area, right lingual gyrus	-0.24
Volume, right lingual gyrus	-0.26
Surface area, left calcarine sulcus	-0.20
Volume, left calcarine sulcus	-0.17
Mean curvature, left lingual gyrus	-0.41
Gaussian curvature, left lingual gyrus	-0.37
Internal gyrification index, left lingual gyrus	-0.37
Internal folding index, left lingual gyrus	-0.34

The mean level of IL-6 in schizophrenic patients was 10 times higher than in healthy volunteers (21.69 ± 9.15 pg / ml and 2.07 ± 1.62 pg / ml, respectively, p <0.005). The greatest increase in the content of IL-6 (more than 15 pg / ml) was observed in 21 out of 60 patients with schizophrenia. At the same time, the level of the cytokine IL-6 had a relationship with the content of a number of other main cytokines and indicators reflecting the activation of the adaptive immune response and systemic inflammation. Thus, patients with IL-6 levels above 15 pg / ml had significantly higher concentrations of a number of cytokines of innate and adaptive immunity, total immunoglobulin G, and acute phase CRP protein than patients with IL-6 levels below 15 pg / ml. In particular, the level of CRP was increased 5 times: the median (25% quartile; 75% quartile) was 15.8 mg / l (2.0; 35.8), while in patients without an increase in IL-6 it was 3.0 mg / l (1.1; 9.0) (p <0.05), and in the control group - 0.5 mg / l (0.3; 1.7) (p <0.005). The median level of total IgG in patients with IL-6> 15 pg / ml was 14.3 g / l (13.1; 15.7), which was significantly higher than in the control group, in which it was 12.5 g / l (10.2; 14.5) (p <0.05). In patients with IL-6 level <15 pg / ml, inflammatory changes were less pronounced and less frequent, therefore there were no significant differences with the control group in terms of total IgG content.

Thus, the level of IL-6, a key mediator of systemic inflammation, correlated with morphometric parameters on MRI and was associated with signs of systemic inflammation in patients with paranoid schizophrenia. Based on the results obtained, it can be concluded that there is a schizophrenia phenotype associated with high production of IL-6, which is characterized by immune activation (humoral immunity, cytokines of natural and adaptive immunity) and systemic inflammation. The second conclusion is that peripheral factors of inflammation are related to structural changes in the brain and the pathogenesis of schizophrenia. These conclusions require an expansion of the sample to confirm them.

4. Discussion

As mentioned above, the cytokine IL-6 has neurotrophic functions in the brain tissue, but its increased level, along with other factors, can cause neuronal damage. What are the ways of the influence of the increased IL-6 content in the blood in some patients with schizophrenia on neuroinflammation (activity of glia, astrocytes) and damage in the brain? It is known that pro-inflammatory mediators transmit an inflammatory (activating) signal to microglia in the brain through the nerve endings of the vagus nerve and through acting on the epithelium of the blood-brain barrier (BBB). In addition, with increased BBB permeability (genetic predisposition, exposure to inflammatory factors and endotoxins), IL-6 can enter the brain, causing inflammatory reactions [19]. In the presence of neuroinflammation, IL-6 can be one of the factors of its chronicity, adversely affecting the dynamics of the disease. In addition, IL-6 can play a direct role in the development of cognitive impairments in patients: a number of studies have shown that it is involved in the development of neurodegeneration [21]. It is also known that IL-6 may play an important role in autoimmune pathology. It is assumed that in some cases autoimmunity may be involved in the pathogenesis of schizophrenia [22]. According to the data of a meta-analysis, the levels of cytokines IL-6, TNFα and receptor antagonist IL-1RA in acute schizophrenia is increased, which is consistent with our data [15]. In chronic schizophrenia, the same meta-analysis showed increased levels of IL-1β and IL-6. Acute schizophrenia was defined as hospitalization due to a psychotic episode, chronic schizophrenia was defined as an examination of patients on outpatient treatment.

Only a small number of articles are devoted to the study of the relationship between indicators of immunity and the results of neuroimaging in schizophrenia.

In our work, it was revealed for the first time that morphometric changes in a number of areas of the cerebral cortex are associated in the patients with schizophrenia with the level of IL-6. According to the literature, in many of these zones there are structural changes in patients with schizophrenia, and in some zones the changes are associated with the severity of clinical symptoms. Thus, in schizophrenic spectrum disorders, a decrease in the volume of the left fusiform gyrus was found, which was associated with a decrease in the ability to recognize faces and emotions, as well as more pronounced negative symptoms [23]. It has also been shown that the severity of neurological microsymptoms in schizophrenia (in contrast to healthy volunteers) correlates with a decrease in the volume of gray matter in the left lingual gyrus [24]. Thus, morphometric changes in the left lingual gyrus may be clinically significant in schizophrenia. Our results show for the first time a connection between morphometric changes in the left lingual gyrus in schizophrenic patients with increased IL-6.

Thus, within the framework of this study, for the first time, in terms of associations with morphometric data and characteristic changes in immunity parameters, the immunological profile in schizophrenia associated with an increase in IL-6 was characterized. Taking into account the fact that an increased level of IL-6 was a marker of pronounced immuno-inflammatory activation in the patients examined by us, the data obtained on the relationship between the level of IL-6 and the morphometric characteristics of the brain in schizophrenia can be considered as indicating the adverse effect of excessive immune activation on structural changes in the brain in schizophrenia. Based on the results of the work and on the literature data, it seems appropriate to further study the associations of changes in the morphometric characteristics of the brain in schizophrenia with the immunological profiles of the disease and clinical manifestations. The results of such studies are important for the search for new markers for predicting the course of schizophrenia and for new therapeutic targets in various immunoinflammatory profiles of schizophrenia.

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