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ПОКАЗАТЕЛИ ВРОЖДЕННОГО И ПРИОБРЕТЕННОГО ИММУНИТЕТА В ОЦЕНКЕ ТЯЖЕСТИ КЛИНИЧЕСКОГО СОСТОЯНИЯ ПАЦИЕНТОВ С ДЕТСКОЙ ШИЗОФРЕНИЕЙ

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Резюме. Результаты предыдущих исследований убедительно свидетельствуют о патогенетической роли иммунной системы в развитии шизофрении. При обследовании пациентов с шизофренией подросткового-юношеского и молодого возраста показано, что активность/уровень некоторых показателей врожденного и приобретенного иммунитета коррелирует с остротой и тяжестью патологического процесса в мозге больных. Выявление особенностей иммунной системы у пациентов с шизофренией детского возраста во взаимосвязи с тяжестью их клинической симптоматики, помимо потенциального терапевтического аспекта, может служить основой для ранней диагностики этих состояний, а также мониторинга и прогноза дальнейшего развития заболевания.

Цель исследования – сопоставление клинических и иммунологических показателей у детей с шизофренией для оценки возможности использования изучаемых иммунологических параметров для определения степени активности патологического процесса. Обследовано 62 пациента (39 мальчиков и 23 девочки) от 4 до 17 лет с детской шизофренией. Психическое состояние больных оценивалось психопатологическим и психометрическим методами (с использованием шкал PANSS и CGI-S). Иммунологические показатели определяли в сыворотке крови, взятой из пальца. Активность лейкоцитарной эластазы (ЛЭ) и α1-протеиназного ингибитора (α1-ПИ) определяли спектрофотометрическим методом. Для определения уровня аутоантител к S-100B и ОБМ использовали иммуноферментный анализ.

В результате проведенного исследования выявлена активация врожденного (по показателям активности ЛЭ и α1-ПИ) и приобретенного (по уровню аутоантител к S-100B и ОБМ) в сыворотке крови детей с шизофренией. При проведении корреляционного анализа показана значимая положительная связь между комплексной оценкой уровня активации иммунной системы пациентов и тяжестью их состояния по шкале CGI-S ($r = 0,64$, $p < 0,0001$), а также выраженностью психопатологической симптоматики по подшкале негативных симптомов шкалы PANSS ($r = 0,34$, $p = 0,0077$).

Выявленные взаимосвязи свидетельствуют о возможности использования комплекса изучаемых иммунологических показателей (активности ЛЭ и α1-ПИ, а также аутоантител к нейроантигенам) в качестве дополнительного лабораторного метода обследования для объективизации клинического состояния детей с шизофренией.

Ключевые слова: шизофрения детская, маркеры воспаления, активность лейкоцитарной эластазы, аутоантитела к нейроантигенам

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INNATE AND ACQUIRED IMMUNITY INDICES IN ASSESSING THE CLINICAL SEVERITY OF PATIENTS WITH CHILDHOOD SCHIZOPHRENIA

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Abstract. The results of previous studies suggest pathogenetic role of immune system in the development of schizophrenia. Examination of adolescent and young adult schizophrenic patients showed that the activity/level of distinct parameters of innate and acquired immunity correlates with acuity and severity of pathological process in the brain. Presumably, evaluation of immune system characteristics in patients with childhood schizophrenia, concerning severity of their clinical symptoms, along with potential therapeutic aspect, may be the basis for early diagnosis of these conditions, and monitoring and prognosis of the further progression of the disease.

The objective of our study was to compare clinical and immunological indices in children with schizophrenia to analyze the possibility of using these parameters for determination of the degree of activity of the pathological process. Sixty-two patients (39 boys and 23 girls) from 4 to 17 years of age with childhood schizophrenia were examined. Psychopathological and psychometric methods (PANSS and CGI-S scales) were used to assess mental state of the patients. Immunological parameters were determined in blood serum taken by fingerprick. Activity of leukocyte elastase (LE) and α1-proteinase inhibitor (α1-PI) was determined by spectrophotometric method. To determine the level of autoantibodies to S-100B and MBP, we used enzyme immunoassay.

The study revealed activation of innate (by activity of LE and α1-PI) and acquired (by the level of autoantibodies to S-100B and MBP neuroantigens) immunity markers in blood serum of children with schizophrenia. Correlation analysis showed the significant positive correlation between complex evaluation of activation level of the immune system and severity of the patients' state on the CGI-S scale ($r = 0.64$, $p < 0.0001$), as well as severity of negative symptoms according to the PANSS scale ($r = 0.34$, $p = 0.0077$).

The revealed correlations suggest an opportunity for using immunological parameters (LE and α1-PI activity, and antibodies to neuroantigens), as the additional laboratory criteria for the assessment of clinical state in patients with childhood schizophrenia.

Keywords: childhood schizophrenia, inflammation markers, activity of leukocyte elastase, autoantibodies to neuroantigens

Introduction

According to modern concepts, the inflammatory response is the most important physiological mechanism of chronic non-infectious diseases, including schizophrenia [3, 6, 11]. A large number of studies in the serum of patients with schizophrenia revealed improvement of various mediators of inflammation, acute phase proteins, and molecules involved in the increase in vascular permeability [8, 9, 12].

Inflammatory mediators are synthesized by cells of the innate (nonspecific) immune system (neutrophils, monocytes / macrophages, dendritic and NK cells, and others). The activation of Toll-like receptors on the surface of immunocompetent cells is caused not only by different exogenous (microorganisms, viruses, and et al.), but also by endogenous agents, that are the products of the degradation of the body's tissues, which occurs in various pathological processes in the brain [1].

It is also known that in mental diseases in the blood of some patients can be identified autoantibodies to various molecular components of the brain, including neuron-specific proteins. Autoantibodies are immunoglobulin molecules synthesized by cells of acquired immunity (B lymphocytes).

Identification of inflammatory mediators and antibodies to neuroantigens in the blood of patients suffering from schizophrenia may be important in the pathogenesis of the disease assessment, adaptation of therapeutic programs for these patients, and may also improve the reliability of early detection of the disease, provide laboratory monitoring of disease development and its prognosis.

Previously, during the many years of clinical and immunological study of adolescents and young patients with schizophrenia, we have demonstrated that the enzymatic activity of leukocyte elastase, a protease contained in the azurophil granules of neutrophils, is positively correlates with the acuity of the clinical status of patients. The level of autoantibodies to neuroantigens S-100B and myelin basic protein (MBP) is related to the severity of their condition [4, 5].

However, similar studies on patients with childhood schizophrenia have not been performed. At the same time, it is important that the age-related features of the immune system may significantly contribute to the realization of neuro-immune interactions not only in the norm but also in the development of pathological states of the nervous system.

The objective of the study was to compare clinical and immunological indices in children with schizophrenia to analyze the possibility of using these parameters in the determination of the degree of activity of the pathological process.

Materials and methods

The study was carried out in the Department of Child Psychiatry together with the Laboratory of Neuroimmunology of the FSBSI "Mental Health Research Centre" (Moscow, Russia) in the 2012-2015. The study involved 62 patients (39 boys and 23 girls from 4 to 17 years) with schizophrenia. The mean age of onset of the disease in all patients was 3.2±2.7 years. The mean duration of the disease was 7.5±3.4 years. The mental status of patients was assessed by psychopathological and psychometric methods using psychometric scales PANSS and CGI-S.

The criteria for inclusion of patients in the study were: the presence of a psychotic episode; a continuous malignant course leading patients to the hospitalization; the need for medication therapy of patients; informed consent of a parent or guardian of the child to participate in the study; compliance with modern standards of biomedical ethics in examining patients.

Exclusion criteria were: clinical and laboratory signs of inflammatory and infectious or autoimmune disorders, diagnosed within 1-2 months before the survey, as well as the post-vaccination period.

Based on the differences in clinical symptoms, patients were divided into 2 groups. The 1st group included 47 patients (29 boys and 18 girls from 4 to 16 years; mean age 10.9±3.2 years) with a diagnosis of "childhood schizophrenia" – F20.8xx3 by ICD-10 (1994), adapted to the Russian Federation in 1999. In the clinical picture of patients of the 1st group, hyperkinetic, less often hypokinetic and partial productive catatonic disorders were identified in combination with the negative symptoms (regression, severe autism). Later, the negative symptoms began to dominate. Patients developed deficits in the cognitive, energy (acquired by fatigue), and emotional spheres. The thinking was concrete with a reduced level of generalization, and a lack of abstraction. As the severity of the condition decreased, patients retained residual catatonic disorders in the form of subcortical protopathic motor stereotypies displacing purposeful movements.

The 2nd group consisted of 15 patients (10 boys and 5 girls aged 8 to 17 years; mean age 12.5±4.5 years) with a diagnosis of "schizotypal disorder" (F21.x) according to ICD-10. The group of patients was heterogeneous in the positive symptoms, and the depth of the developing personality defect. According to the leading positive symptoms, all the patients were divided into two subgroups. The 1st subgroup included 10 patients (F21.3) with leading neurosis (anxiety-phobic, obsessive-compulsive) disorders. Negative disorders in children of this subgroup were confined to personal changes schizoid range, distortion, and the immaturity of the higher mental functions, retaining the ability to learn, socialization. The 2nd subgroup consisted of 5 patients (F21.4) with positive psychopathic disorders with aggression towards others, self-aggression, withdrawal, vagrancy, with eating disorders, affective disorders, accompanied by personality changes autism range with high sensitivity, pedantry, psychophysical infantilism.

The control group included 44 healthy children corresponding to patients by age and sex. The age of patients with schizophrenia did not differ from a control group ($p = 0.09$), as well as from patients with schizotypal disorder ($p = 0.1$).

The immunological parameters were determined in blood serum which was carried out from the finger. Formed elements were pelleted by centrifugation at 3000 rpm/min (700 g) for 15 minutes at 22 °C. Then the serum was collected, which was used for the analysis or immediately after preparation, or stored at a temperature 2 °C to 8 °C not more than a day or frozen at -18 °C to -24 °C for a month before analysis.

The following immunological parameters were studied: the enzymatic activity of leukocyte elastase (LE) (serine protease, which is a marker of the degranulating activity of neutrophils – one of the major cellular components of innate immunity); functional activity of α1-proteinase inhibitor (α1-PI) (an acute-phase protein is synthesized in the liver, the role of which is to limit the proteolytic activity of LE and to regulate of inflammatory response); the autoantibodies to S-100B and MBP produced by B lymphocytes (acquired immunity).

The enzymatic activity of LE was determined by an spectrophotometric method using the specific substrate N-tert-butoxy-carbonyl-alanine-β-nitrophenyl ester (BOC-Ala-ONp), and evaluated in

TABLE 1. INTERPRETATION OF ASSESSING THE SEVERITY OF THE DISORDERS ON THE PSYCHOMETRIC SCALES PANSS AND CGI

PANSS P	PANSS N	PANSS G	CGI-S	Degree of the the severity of the disorders
7-11	7-10	16-27	1-2	Norm, borderline, mild
12-18	11-20	28-49	3-4	From moderate to marked
19-30	21-45	50-70	5-6	From marked to severe
31 and >	46 and >	71 and >	6-7	From severe to the most severe

Note. The highest score on any of the PANSS subscales determines the patient's CGI severity score. In some cases, the CGI score may be higher than the PANSS subscale score, based on the patient's condition (anorexia, delusional disorders, etc.).

TABLE 2. PSYCHOMETRIC ASSESSMENT OF PATIENTS WITH CHILDHOOD SCHIZOPHRENIA AND SCHIZOTYPAL DISORDER (PANSS AND CGI SCALES) Me ($Q_{0.25}$-$Q_{0.75}$)

Diagnosis (ICD-10)	PANSS P	PANSS N	PANSS G	CGI-S	Degree of the severity of the disorders
Childhood schizophrenia (F20.8xx3) (n = 47)	20 (17-22)	45 (37-47)	54 (48-56)	6 (6-6)	From moderate to the most severe
Schizotypal disorder (F21.x) (n = 15)	16 (12-18)	18 (16-23)	51 (43-54)	5 (4-5)	From moderate to marked

TABLE 3. IMMUNOLOGICAL INDICES IN PATIENTS WITH CHILDHOOD SCHIZOPHRENIA AND SCHIZOTYPAL DISORDER, Me ($Q_{0.25}$-$Q_{0.75}$)

Groups	LE activity, nmol/min × ml	α1-PI, IU/ml	AAB to S-100B, OD	AAB to MBP, OD
Control (n = 44)	194.4 (172.8-208.4)	32.5 (28.2-36.1)	0.69 (0.62-0.79)	0.66 (0.58-0.72)
Childhood schizophrenia (n = 47)	245.2** (218.6-255.0)	43.7** (38.5-50.2)	0.85** (0.73-1.01)	0.72* (0.60-0.84)
Schizotypal disorder (n = 15)	230.7** (218.2-267.8)	42.7** (37.7-51.7)	0.76 (0.69-0.80)	0.70 (0.58-0.81)

Note. Statistical differences with control: *, $p < 0.05$; **, $p < 0.00001$.

nmol/min × ml (the sensitivity is 40 nmol/min × ml) [2]; functional α1-PI activity was detected by the spectrophotometric method and in inhibitory units/ml (IU/ml) (the sensitivity is 5 IU/mL) [10]. The level of autoantibodies to S-100B and MBP was determinated by immunosorbent assay [7] using antigen S-100B and MBP (Sigma, USA). The autoantibody titer was estimated by optical density (OD).

Statistical analysis was performed using nonparametric statistical software Statistica-10 (StatSoft., Inc, USA). The data in the Tables 2, 3 and text are presented as Medians – Me ($Q_{0.25}$-$Q_{0.75}$). Intergroup differences were determined using the Mann–Whitney test. To evaluate the clinical and immunological relationships using the correlation coefficient of Spearman. We used a confidence level: $p \leq 0.05$.

Results and discussion

On the scale PANSS adapted to children's age, we evaluated the positive (P), negative (N), general psychopathological symptoms (G). Furthermore, within each subscale, the severity of related disorders (Table 1) was determined. This "categorical" assessment of symptoms on the PANSS subscales is ne-

cessary to compare psychometric data with a comprehensive assessment of patients' immune system state.

The CGI scale (Clinical Global Impression Scale) score in points corresponds to different general severity of the disease: the 1st subgroup – mild disorders with scores from 1 to 2; the 2nd subgroup 2 – 3-4 points (from moderate to marked); the 3rd subgroup – 5-6 points (from marked to severe); the 4th subgroup 6-7 points (from severe to the most severe).

From the data presented (Tables 1, 2), it can be seen that in the group of patients with a diagnosis of "childhood schizophrenia" prevailing negative disturbances which may indicate a predominate and cognitive deficiency of this cohort of patients, as well as an unfavorable outcome of the disease. In the group of patients with a diagnosis of "schizotypal disorder" the negative changes are minimal, these patients have the highest overall score on a scale of general psychopathological symptoms (affective, obsessive, psychopathic condition, etc.).

Table 3 presents the results of a study of immunological parameters in children with schizophrenia and schizotypal disorder. In the group of children with schizophrenia a statistically significant increase in activity of LE ($p < 0.0001$), α1-PI ($p < 0.0001$), as well as the level of antibodies to S-100B ($p < 0.0001$), and MBP ($p < 0.05$) was revealed compared to the control group.

The group of children with schizotypal disorder was also characterized by a significant increase in the activity of LE ($p < 0.0001$) and α1-PI ($p < 0.0001$) compared to the control. But the level of autoantibodies to neuroantigens remained in the control range ($p > 0.05$).

To identify possible relationships between clinical and biological indicators the patients with schizophrenia and schizotypal disorders were integrated into a single group: weak positive correlations were found between the activity of LE and the severity of negative symptoms on the PANSS scale ($r = 0.28$, $p = 0.05$) and between the level of antibodies to S-100B and scores on the CGI-S scale ($r = 0.29$, $p = 0.02$). We also revealed a negative correlation between the functional activity of α1-PI and the level of autoantibodies to the S-100B ($r = -0.30$, $p = 0.04$), and a positive correlation between the autoantibodies to the S-100B and MBP ($r = 0.47$, $p = 0.0001$), reflecting, possibly, existing functional relationship between innate and acquired immunity.

Thus, this sample of patients with childhood schizophrenia and schizotypal disorders was found activation of inflammatory (by LE and α1-PI activity) and autoimmune (the level of autoantibodies to neuroantigens) reactions. Results obtained corresponds to the previously obtained ones during the examination of patients' adolescent and young age [4, 5].

However, there was no evidence of pronounced linkages between individual immunological parameters and clinical features of patients on psychometric scales.

The study of clinical and immunological relationship revealed a high significant positive correlation between the complex assessment of the level of activation of patients' immune system and the severity of their clinical condition on the CGI-S scale ($r = 0.64$, $p = 0.000001$), as well as the correlation with the severity of negative symptoms assessed to the PANSS scale ($r = 0.34$, $p = 0.0077$).

It is known, that innate and acquired immunity are the two interacting parts of a single system that ensures the development of an immune response to a violation of homeostasis. The innate immunity is the evolutionarily more ancient primary "protective echelon" that implements its function by inflammation and phagocytosis, ensuring the elimination of pathogens or endogenous molecules that enter the bloodstream at the destructive processes in the body's tissues, in the first few minutes/hours after their appearance when the mechanisms of acquired immunity are not yet available. Acquired immunity is the second phase of the protective reaction of the organism, which is realized by the synthesis of specific antibodies or autoantibodies. The presence of neuroantigens characterizes the most severe and progressive pathologic state in which the restoration of homeostasis can not be achieved only by inflammatory mechanisms [12].

Conclusion

The results indicate the involvement of the immune system in the pathogenesis of schizophrenia and schizophrenia spectrum disorders in children.

The most severe and progressive pathological conditions in patients with childhood schizophrenia are accompanied by activation of both innate (LE and α1-PI activity) and acquired (autoantibodies to S-100B and MBP) immunity. In patients with schizotypal disorders, the activation of only innate immunity was revealed.

The correlations between a comprehensive assessment of the level of activation of the immune system and the severity of the patients' clinical state confirm the relationship of the studied immune markers with the activity of the pathological process in the brain. The results suggest an opportunity for using these immune indices as the additional laboratory criteria for the assessment of the clinical state of children with schizophrenia, which is important for the diagnosis, monitoring and prognosis of the disease.

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