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LEVELS OF NEUROTROPIC AUTOANTIBODIES IN PATIENTS WITH SCHIZOPHRENIA

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ИЗУЧЕНИЕ УРОВНЕЙ НЕЙРОТРОПНЫХ АУТОАНТИТЕЛ У БОЛЬНЫХ ШИЗОФРЕНИЕЙ

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Plasma levels of IgG autoantibodies to the NMDA-receptors, human S-100 protein, and dopamine Type 2 receptors were detected in 26 males suffering from schizophrenia. Half of the patients had their levels of autoantibodies to the NMDA-receptors above average values, while in the rest of the group the antibody level was within norm. Following that, the patients were divided into two groups: Group 1 with a higher level of antibodies to the NMDA-receptors, Group 2 – with their normal levels of antibodies to the NMDA-receptor. The patients in the Group 1 also revealed significantly elevated levels of autoantibodies to the dopamine Type 2 receptors as well as to the S-100 protein in their blood plasma. Psychometric testing involving the PANSS scale showed that the positive symptoms' values in the Group 1 were below those in the Group 2 while the negative symptoms' values in the Group 1 were higher. Respectively, the composite index, which is determined as the difference between the positive and the negative scores, was lower in the Group 1 and higher in the Group 2.

Key words: schizophrenia, autoantibodies, NMDA-receptors, dopamine receptors, S-100 protein

Определяли содержание в плазме крови IgG аутоантител к NMDA-рецепторам, к белку S-100 человека и к дофаминовым рецепторам 2 типа у 26 мужчин, больных шизофренией. Уровень аутоантител к NMDA-рецепторам был выше нормальных значений у половины больных, у остальных – содержание антител было

нормальным. В связи с этим больных разделили на две группы: первая – с повышенным уровнем антител к NMDA-рецепторам, вторая – с нормальным их содержанием. У больных первой группы было также обнаружено существенное повышение в плазме крови уровней аутоантител к дофаминовым рецепторам 2 типа и к белку S-100. Психометрическое тестирование по шкале PANSS показало, что значения показателя позитивной симптоматики у больных первой группы были ниже, чем во второй группе. Показатель негативной симптоматики был меньше во второй группе, чем в первой. Соответственно композитный индекс, определяемый как разность позитивного и негативного баллов, был ниже в первой и выше во второй группе больных шизофренией.

Ключевые слова: шизофрения, аутоантитела, NMDA-рецепторы, дофаминовые рецепторы, белок S-100

In the latest decade, the development of autoantibodies to proteins in various human and animal tissues has been seen as a natural process [6, 7, 9]. On the other hand, a growth in the level of autoantibodies may witness some tissue lesion and an immune response to such changes, which might be employed successfully for early detection of the developing pathology [7, 9]. There is a discussion going on regarding employing such diagnostic approach for predicting and evaluating the efficiency of medication therapy, including for treating cases of schizophrenia [2, 7]. There is intense study of the role that glutamatergic mechanisms have in the development of behavioral and psychotic issues in case of schizophrenia [1, 4, 5]. There has been an increase detected in the level of autoantibodies to the NR2-subunit of NMDA-receptors [2].

At the same time, a number of works show that in case of brain damage a reliable indicator revealing the severity of the injury may be increased levels of the S-100 proteins as well as a growth in the titres of autoantibodies to S-100 [7]. Based on this, it was of interest to conduct a comprehensive evaluation of the levels of neurotropic autoantibodies in patients with schizophrenia because these factors may be supposed to have a role in the pathology development.

The aim of this study was to investigate the influence of the level of autoantibodies to the NMDA-receptors and S-100 protein on the patients with schizophrenia.

Material and Methods. The study involved 26 patients with schizophrenia, aged 20–40, all males. The patients had their peripheral dark blood taken within the first fortnight of their inpatient hospitalization in a psychiatric clinic. The bloodwork involved detection of IgG autoantibodies to the NMDA-receptors, to the human S-100 protein, and to dopamine Type 2 receptors (DA2). The levels of the autoantibodies were detected via a test-system developed at the Research Company IMMUNOTEX, LLC (Russian Federation). This system was designed to identify the levels of the IgG antibodies (U/ml) to the NMDA-receptors, to the S-100 protein, as well as to human DA2 receptors.

The method is based on the immunological reaction between antibodies in patients' blood serum and the antigens to the NMDA-receptors, S-100, and DA2-receptors [human recombinant antigens were used – glutamate receptor N-Methyl-D-Aspartate 2A (GRIN2A), dopamine D2-receptor (DRD2), S100 Calcium Binding Protein A1 (Cloud-Clone Corp., USA)], immobilized on the sample well surface of a plastic plate, followed with detection of the developing immune complex with peroxidase-conjugated monoclonal antibodies to

human IgG immunoglobulin. The fermentation activity was detected by the change in the chromogenic mix coloring. The results of the analysis were registered with a vertical-scanning photometer (wave length – 450 nm). The values of the IgG antibodies to the NMD-receptors, the S-100 protein, and the DA2-receptors were accepted as normal if falling in the range of up to 10 U/ml. The study was carried out employing an automatic immunoenzyme detector LAZURITE (Dynex Technologies Inc., USA).

All the patients also underwent psychometric testing with the PANSS scale with positive and negative symptoms evaluated, composite index assessed, identification of anergy clusters, disturbance of thinking and excitation, as well as with evaluation of the paranoid cluster and the cluster of depression. Besides, an extra cluster was also identified, which reflects the risk of aggressive and auto-aggressive activities [3]. The duration of the disease was detected as well.

The obtained data was processed using the software package of Statistica 7 and Microsoft Excel. The Mann – Whitney test was used to determine the significance of the differences in view of the distribution type. Differences were accepted as statistically meaningful at $p < 0.05$. The values are provided as a median (Me) and as an interquartile range (25th; 75th percentile). Spearman's rank correlation test was also carried out in order to identify the link between the indicators for autoimmune status of the patients and the psychometric test data.

Results and Discussion. Immunological check-up of patients with schizophrenia showed that the level of antibodies to the NMDA-receptors in their blood plasma was significantly above that in healthy people (normal value accepted at up to 10 U/ml). However, individual evaluation of plasma autoantibodies to the NMDA-receptors showed that some of the patients had their antibody levels within the normal range (44.4 % of the cases). 55.6 % of the patients had the same indicator elevated and significantly above the norm – up to 10 U/ml. Given that, in view of the special interest taken in increased levels of autoantibodies to the NMDA-receptors, the patients were broken into two groups; Group 1 – with their blood antibodies within norm, and Group 2 – with that level elevated. In Group 1 the level of the antibodies was 41.7 (22.8; 58.1) U/ml, while in Group 2 this index was significantly lower – 4.0 (2.3; 4.6) U/ml.

The level of the autoantibodies to the DA2-receptors in Group 2 was mildly above the normal range (up to 10 U/ml). The patients of Group 1, in turn, had the level of antibodies to the DA2-receptors significantly higher ($p < 0.01$) (Table).

Table
Levels of autoantibodies in blood plasma and psychometric values on the PANSS scale in patients with schizophrenia showing normal (Group 1) and elevated (Group 2) levels of autoantibodies to the NMDA-receptors*

Group of patients	Autoantibodies to NMDA-receptors U/ml	Autoantibodies to DA2-receptors U/ml	Autoantibodies to S-100 protein U/ml	Positive symptoms	Negative symptoms	Composite index
1 (n=11)	41.7 (22.8; 58.1)	33.0 (26.2; 66.0)	19.2 (12.8; 25.0)	25 (24; 27)	31 (23; 35)	-5 (-11; -3)
2 (n=15)	4.0 (2.3; 4.6)	11.9 (2.4; 33.0)	3.1 (1.3; 19.5)	27 (26; 29)	25 (13; 32)	4 (-6; 20)
p	<0.01	<0.01	<0.01	<0.05	>0.05	<0.05

* – values are provided as a median and an interquartile range (25th & 75th percentiles); n – number of patients in groups; p – level of reliability for significant differences between the groups of patients (Mann – Whitney test).

The blood plasma levels of autoantibodies to the S-100 protein in Group 2 were lower than in Group 1 (3.1 U/ml (1.3; 19.5) vs. 19.2 (12.8; 25.0) (p<0.01), respectively).

Therefore, the patients with higher levels of autoantibodies to the NMDA-receptors in their blood plasma also had higher levels of autoantibodies to the DA2-receptors and the S-100 protein.

The age difference between the two groups of the patients with schizophrenia was minimal. However, the patients in Group 2 had somewhat longer history of the disease – Group 1 with 9.0 (3.0; 10.0) years; Group 2 – 12.0 (6.0; 15.0) years (p>0.05).

The groups had their psychometric test outcomes differing, too. Testing showed that the values of the positive symptoms in Group 1 were lower – 25.0 (24.0; 27.0) than in Group 2 – 27.0 (26.0; 29.0) (p<0.05). The negative symptoms index, however, was slightly lower in Group 2 – 25.0 (13.0; 32.0) against 31.0 (23.0; 35.0) in Group 1. As a result, the composite index, which is determined as the difference between the positive and the negative scores, was significantly lower in Group 1 (-5.0 (-11.0; -3.0) and higher in Group 2 (4.0 (-6.0; 20.0) (p<0.05) of patients with schizophrenia.

Evaluation of general psychopathological symptoms presentation and assessment of the anergy cluster yielded no difference in the outcomes. There were

no differences identified among the groups on the disturbed thinking cluster, excitation cluster, paranoid cluster and the clusters of depression, aggression, and auto-aggressive actions.

A correlation analysis showed that there was a mild positive connection between the values for the levels of autoantibodies to the NMDA-receptors and the serum concentrations of antibodies to the S-100 protein and the DA2-receptors (for S-100 r= 0.47, p<0.05; for DA2 r= 0.53, p<0.05). During that, there was a strong positive connection detected between the levels of the antibodies to the S-100 protein and the DA2-receptors (r= 0.84; p<0.01).

A connection was identified between the levels of autoantibodies and the indices of the psychometric testing (the PANSS scale). Thus, a mild positive correlation was detected between the level of antibodies to the NMDA-receptors and the values for the positive and the negative symptoms (r= -0.48, p<0.05; r= 0.58, p<0.05, respectively). As for the composite index, however, there was a mild negative correlation identified (r= -0.59, p<0.05), while for the anergy cluster the correlation was mild and positive (r= 0.4, p<0.05).

A mild and positive correlation was also found between the values for the negative symptoms and the level of autoantibodies to the S-100 protein (r= 0.4, p<0.05) and the plasma concentration of autoantibodies to the DA2-receptors (r= 0.48, p<0.05). Note to be made of a negative correlation, even though slight, between the composite index of the PANSS scale and the level of antibodies to the S-100 protein (r= -0.34) and the DA2-receptors (r= -0.37).

A mild positive correlation was there between the disease duration and the level of antibodies to the NMDA-receptors (r= 0.35) and the S-100 protein (r= 0.34).

Given the above, high levels of autoantibodies to the NMDA-receptors in patients with schizophrenia coincide with a prominent negative syndrome subject to the psychometric evaluation with the PANSS scale. The negative syndrome is known to be a predictor for a more severe course of the disease as well as for lack of efficiency offered by anti-psychotic medications [8]. Such patients must also have more severe disturbances in the dopaminergic mechanisms as well as neuron-glia and glial-glia connections, another evidence to which may be found in a high level of antibodies to the DA2-receptors and to the S-100 protein.

Conclusions. Consequently, patients with schizophrenia who have negative syndrome prevailing in the clinical presentation, when evaluated with the PANSS scale reveal significant elevation in the levels of autoantibodies to the NMDA-receptors, the DA2-receptors, and the S-100 protein.

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STUDY OF THE SPECTRUM OF DENTAL COMPOSITES BIOLOGICAL ACTIVITY IN MODEL EXPERIMENTS IN VITRO

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ИССЛЕДОВАНИЕ СПЕКТРА БИОЛОГИЧЕСКОЙ АКТИВНОСТИ СТОМАТОЛОГИЧЕСКИХ КОМПОЗИТОВ В МОДЕЛЬНЫХ ОПЫТАХ IN VITRO

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The nature of the effect of composite dental materials, based on methacrylate and oxirane, on the structural and functional properties of the blood cells of healthy subjects was investigated in model experiments in-vitro. There were revealed the changes of structural and functional characteristics of red blood cells, indicating the membrane damaging effect of the monomer composites. It is shown that incubation of blood with unpolymerized material causes expressed deformation of the membrane, erythrocyte aggregation. Methacrylate based composites have a more pronounced negative potential due to biodegradation that requires strict compliance with the polymerization conditions. Oxirane based materials are bioinert after polymerization, which allows recommending them for wider application. The study substantiated the feasibility of using of the developed experimental model for biological testing of dental filling materials.

Key words: monomers, dental composites, biological activity, blood, red blood cells

Проведено исследование характера влияния композитных стоматологических материалов на основе метакрилата и оксирана на структурно-функциональные свойства клеток крови клинически здоровых лиц в модельных опытах in-vitro. Выявлены изменения структурно-функциональных характеристик эритроцитов, свидетельствующие о мембраноповреждающем действии мономеров композитов.

Показано, что инкубация крови с неполимеризованными материалами вызывает выраженную деформацию мембран, агрегацию эритроцитов. Композиты на основе метакрилата вследствие биодegradации обладают более выраженным негативным потенциалом, что требует строгого соблюдения режимов полимеризации. Материалы на основе оксирана после полимеризации биоинертны, что позволяет рекомендовать их для более широкого применения. Проведенное исследование обосновало целесообразность использования разработанной экспериментальной модели для биотестирования стоматологических пломбировочных материалов.

Ключевые слова: мономеры, стоматологические композиты, биологическая активность, кровь, эритроциты