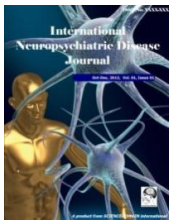

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The Role of Herpes Family Viruses in the Pathogenesis of Paranoid Schizophrenia: the Data of Multidimensional Correlations of Immunological, Morphological and Clinical Characteristics

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

The majority of current researches of participation of herpes viruses in pathogenesis of schizophrenia are aimed at detection of increased specific antibodies level. Works studying polymodal system connections between antibodies to herpes viruses, other immunity parameters, structural brain changes and psychopathology symptoms in schizophrenia do not occur practically. The aim was to investigate the systemic relationships present between parameters of the immune system, including the level of serum antibodies to herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), cytomegalovirus (CMV), and Epstein-Barr virus (EBV), structural anomalies of brain and clinical symptoms of schizophrenia.

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Material and Methods: The study included data of investigation of 30 patients with episodic paranoid schizophrenia with progressing and stable defect and positive symptoms in remissions (EPSPSD) (main group) and 32 patients with episodic remittent paranoid schizophrenia (ERPS) (controls). We determined the leukocyte content, the lymphocyte subpopulations and the leukocyte phagocytosis in PHAGOTEST with fluorescein (FITC)-labeled opsonized bacteria and calculated the phagocytic index (PhI), the circulating immune complexes (CIC) level by spectrophotometry. The antibodies against herpes viruses were determined using the ELISA test. Total serum immunoglobulins, IgG, IgM, and IgA were determined by immunoturbidimetry. Clinical psychiatric examination, BPRS and MRI examination were used.
Results: MRI-signs of brain structures abnormalities, including hemodynamic disorders and developmental brain anomalies, were identified. Levels of IgG to studied herpes viruses were increased, levels of IgM to all studied herpes viruses differed from 0. The interactions of morphological, clinical and immunological parameters were defined.
Conclusion: These results demonstrate a definite link between herpes infection and the immune, clinical and morphological parameters of patients with the episodic paranoid schizophrenia with progressing and stable defect. The results confirm the infectious theory of the diseases.

Keywords: Schizophrenia; herpes viruses; HSV-1; HSV-2; CMV; EBV; structural MRI; MRI.-angiography; lymphocyte subpopulations; multidimensional immunological characteristics.

1. INTRODUCTION

As it`s known, schizophrenia refers to so called multifactorial diseases. The role of genetic factors in the mechanisms of disease development has been proven, but the implementation of genetic predisposition to the disease is carried out by environmental factors [1,2]. Infectious factors can be related to the number of them, although their role may be more complex. In particular, there is virogene theory of schizophrenia [3], taking into account the ability of the viruses to integrate into the human DNA and to be inherited. Viruses, including herpesviruses, can affect gene expression and induce changes in the immune system. Also, being neurotropic, Herpesviruses can damage the nervous tissue and cause disorders of neurotransmitter metabolism. Listed properties of herpes family viruses identified usefulness of studying their contribution to the pathogenesis of schizophrenia.

The majority of the current researches of participation of herpes viruses in pathogenesis of schizophrenia is aimed at detection of increased specific antibodies level. In some studies, their connection with some clinical symptoms is shown [4]. The progressive cingulate and cerebellum reduction associated with the virus herpes type 1 persistence in schizophrenia were demonstrated [5,6]. Positive correlations were established between the EBV IgG antibody levels and the severity of the psychotic symptoms in boys [7]. An association between the CMV activity, immunological deficit and the dynamics of therapy with psychotropic drugs was revealed [8].

The disbalance of the T-helper cells, types 1 and 2, leading to T-cell immunity deficit and humoral activation in schizophrenia [9], is a well-known phenomenon in individuals with persistent herpes infections [10].

However, works studying polymodal system connections between antibodies to herpes viruses levels, other immunity parameters and structural changes in the brain and psychopathology symptoms in schizophrenia do not occur practically.

Research aim was to study the interactions between the parameters of the immune system, including those associated with a specific immune response to the herpes viruses (the level of serum antibodies to HSV-1, HSV-2, CMV and EBV), structural anomalies of the brain and clinical symptoms of schizophrenia.

2. MATERIALS AND METHODS

The data of investigation of 62 schizophrenic patients were the materials of study. 2 groups of patients were examined during their admission for inpatient treatment at the “Mental Health” clinic (Moscow) in connection with the acute exacerbations of schizophrenia or the very first manifestation of the disease between 2009 and 2011. The clinical diagnosis of schizophrenia was conducted in accordance with the ICD-10 criteria. We chose to compare the most

distinguished types of schizophrenia, suggesting them to have clear differences in pathogenesis; these differences can be used to find the way to control the course of the disease.

The main group consisted of 30 patients with episodic paranoid schizophrenia with progressing and stable defect and positive symptoms in remissions (EPSPSD) (F20.01, F20.02). Controls included 32 patients with episodic remittent paranoid schizophrenia (ERPS) (F20.03).

The patients ranged from 18 to 58 years in age, with patients between 18 and 39 years being more prevalent (n=57). The average duration of the disease from the first manifestation did not exceed 9 years (Table 1).

1. Clinical psychiatric examination included interview about current state, anamnesis taking and observations.

The syndromal psychiatric assessment of the patients in both groups at the time of examination is reflected in Table 1. The BPRS scale (Bech P., Kastrup M., Rafaelsen O.J., 1986) was used to assess the severity of the psychopathology. The average global assessment of severity of the psychopathological symptoms was 3.4±2.3 points in the main group and 4.8±0.5 points in controls. Severe somatic diseases, organic diseases of the central nervous system, alcohol and drug addiction were not identified in any of the cases studied.

2. MRI examination (structural MRI and MRI-angiography): 1.5 T tomograph (Siemens, Germany) in the vascular mode without contrast in T1, T2, TIRM, MR-myelography in three orthogonal planes with a section thickness of 5 mm and intersection intervals of 1.5 mm. For visualization of intracranial arteries we used time-of-flight MR angiography with subsequent 3D reconstruction, a comparative assessment of the diameter of the Willis arteries was performed on the basis of the original images. For visualization of the pachymeninx sinuses we used phase-contrast angiography in the sagittal and coronary planes.

Informed consent for participation was taken in all cases.

3. Immunological method: parameters of immune status, levels of IgM and IgG to HSV-1, HSV-2, CMV, EBV by ELISA method using monoclonal antibodies. Sets of Vector-Best were used. Values were considered negative in case of relative density below CutOf.
4. Statistical processing: Calculating the correlation coefficient ($p \leq 0,05$), Mann-Whitney U-test ($p \leq 0,05$) in the Statistica 6.0 program for Windows (StatSoft, USA).

3. THE RESULTS

3.1 Morphological Abnormalities of the Brain

MRI-signs of brain structures abnormalities, including hemodynamic disorders and developmental anomalies of the brain, are shown in Table 2.

Table 1. Demographic and clinical characteristics of patients with schizophrenia

Schizophrenia forms (ICD-10)		EPSPSD (N=30)	ERPS (N=32)	in total (N=62)
Gender	Male	15	14	29
	Female	15	18	33
Age (years)		31.5±9	29.6±8.9	30.5± 9.3
Duration of illness (years)		8.9 ±3	4.9±5	7± 7.7
Leading syndrome (%)	Catatonic-paranoid	27	6	16
	Hallucinatory delusional	50	9	29
	Affective delusional	13	85	55

Table 2. MRI-signs of brain structures abnormalities in examined groups

MRI-signs (%)	EPSPSD(main group)	ERPS (controls)	In total
The frequency of MRI-signs of brain structures reduction.			
Subarachnoid space dilation	65.5	51.6	57.4
Cortex sulci enlargement	23.3	9.7	16.4
Focuses of dystrophy *	10	32.3	21.3
Ventricular enlargement	63.3	19	50.8
The frequency of MRI-signs of brain structures stigmas.			
Native abnormality of structure of brain arteries*	33.3	10.4	21.3
Brain development anomalies	13.3	6.4	10
The frequency of MRI-signs of cerebral vascular and hemodynamic impairment.			
Perivascular space dilation total	77	66.7	65.6
- in basal ganglia*	40	75	57.5
Perivascular cysts	13.3	6.5	9.8
Venous circulation disorder	23.3	16	19.7
The pathology of venous sinuses reflecting change of blood stream speed	43.3	35.5	39.3

*$p \leq 0,05$

MRI-data suggest a more diffuse and chronic nature of the vascular pathology in paranoid episodic schizophrenia, and the greater importance for its formation of predisposition anatomical anomalies causing the persistent inadequacy of its compensatory abilities. The phenomena described are consistent with greater clinical severity in paranoid episodic schizophrenia, brain tissue reduction development, topography of which largely depends on the topography of vascular anomalies.

3.2 Abnormalities of the Immune Status Parameters

Abnormalities in the immune status occurred in 85% of the patients in the main group and in 80% of patients of controls. Deviations did not follow a specific characteristic pattern, except for the percentage of the lymphocytes. In the main group, lymphocytosis was detected almost twice as less frequently (26,3% and 47,8% correspondently). Patients with lymphocytosis "have accumulated" the cases of other elevated parameters of cellular immunity. The remaining patients with normal lymphocyte levels revealed the accumulation of cases of other reduced parameters of cellular immunity. In particular, the reduction in the number of the T- helper cells in the main group occurred twice as often as in controls (47.4% and 21.7% respectively). In controls, lymphocytosis was noted in 47.8% of the cases and lymphopenia in 21% of the cases. These patients also revealed other signs of T-cell deficiency. In the main group, a slight increase in the CIC level was noticed in 40% of the cases and in 8% of the cases in controls.

3.3 Abnormalities in the Serum Levels of Antibodies to Herpes Viruses

The maximum number of patients showed a positive response to IgG to HSV-1, EBV, and to a lesser to CMV. It is important to mention that nonzero values of IgM to all herpes viruses are observed in both groups of patients. It indicates the presence of acute infectious process [11].

In both groups of patients, the seropositive cases to HSV-1 and EBV were dominant, and in a lesser extent, to the CMV. In the main group, the elevated serum levels of the HSV-1 IgG antibodies were observed in 59% of the cases, the EBV IgG antibodies in 92% of the cases and the CMV IgG antibody in 33% of the cases. In controls, the values of these parameters were 81%, 96% and 31%, respectively.

The serum levels of the HSV-1 IgM antibodies exceeded that of the reference value in a few cases, whereas the serum levels of the IgM antibodies to the other viruses matched the reference values. The serum levels of the HSV-2 IgM antibodies corresponded to the reference values in both groups. The positive titers of the HSV-2 IgM antibodies were observed only in controls in 14% of the patients. On the other hand, positive titers of the CMV IgM antibodies were detected in 14% of the patients in the main

group and 3.5% patients of the control group. The frequency of the elevated CMV IgG titers was similar in the groups 33% and 31%).

In main group direct and indirect interactions between the antibody levels to all herpes viruses, except for EBV, were identified. It evidences the massiveness of infection. In controls, on the contrary, interactions between antibody levels to EBV are identified only.

3.4 The Relationship between Immunological, Morphological and Clinical Characteristics

Intercorrelation coefficients of all the parameters in each group were calculated. In addition, the correlation coefficients between all the parameters of different groups were calculated. Groups of parameters with the highest correlation coefficients we named complexes.

The complexes of statistically connected clinical, immunological and morphological parameters were following: “partial-depressive”, “affective” and “psychotic” complexes in both forms of schizophrenia and “catatonic” complex in unfavorable form (table 3).

The relationship between abnormal MRI-signs and clinical and immunological parameters were determined by comparison of clinical and immunological parameters of patients with abnormal MRI-sign, and without it by Mann-Whitney U-test ($p \leq 0, 05$).

Interaction of components of the “partial-depressive” complex in main group (EPSPSD) may indicate the acute infection of HSV-1. MRI-signs can be associated with the inflammatory process. The connection of indicators of acute infection (IgM to HSV-1, NK and B-lymphocytes) with MRI-signs of venous circulation disorder may indicate cerebral vasculitis.

Most of the severity of “guilt” parameter in patients without ventricular enlargement can be explained by inflammatory edema of the brain tissue, as evidenced by sinuses pathology and venous discirculation. Edema of the brain tissue and subependima can mask ventricular enlargement.

The “partial-depressive” complex in controls (ERPS) reflects the acute HSV-2 infection, as indicated by the positive connection of the level of IgM to HSV-2 with indicators of cellular, humoral and phagocytic immunity. The levels of IgM to HSV-2 are associated with the perivascular spaces dilation of subcortical area, which corresponds to the high content of virus in the perivascular glia. The asymmetry of the sigmoid sinuses signal reflects a diffuse disturbance of venous outflow. Distention of perivascular spaces of subcortical area indicates to degeneration of perivascular microglia in these areas [12]. Since microglial cells are immunocompetent, their degeneration leads to the decrease of local immunity.

Thus, both complexes reflect acute infection, but in the first case of HSV-1, and in the second – of HSV-2.

In the first case, the immune response is mainly limited by humoral link and in the second – is more harmonious and includes all links of immunity. Morphological changes in both cases are related mainly to the impact on the brain and its vascular system of viruses and intoxication.

In the second case, there are mechanisms of delimitation of infection in the form of dilation of perivascular spaces. In the first case there is no such a mechanism, and there are signs of reduction nervous tissue and more severe development of vasculitis.

“Affective” complex in main group (EPSPSD) reflects different aspects of a mixed infection of HSV-2, CMV and EBV. Extension of cerebral sulci reflects the reduction of nervous tissue, probably under the influence of the virus (negative relation of IgG to HSV-2). Positive relation with the number of T-helpers and cytotoxic cells can testify about regeneration processes in this zone.

The “Affective” complex in controls (ERPS) reflects the expanded immune response to acute HSV-2, with the spread of the inflammatory process in the brain structures that form the walls of the lateral ventricles (hippocampus, thalamus, caudate nucleus and the corpus callosum), accompanied by a reduction of nervous tissue.

Affective complex in both groups shows the development of acute herpetic infection. In main group (EPSPSD) it gets mixed nature. The immune response is predominantly humoral. In controls (ERPS) the complex reflects HSV-2 infection with a harmonious immune response. In both cases, the painful process spreads to new areas of the brain and is accompanied by a reduction of brain tissue.

Table 3. The composition of the clinical - paraclinical complexes in studied groups.*

Form of schizophrenia	EPSPSD (main group)		ERPS (control group)	
The name of complex	BPRS parameters	Immunological and morphological parameters	BPRS parameters	Immunological and morphological parameters
1. “Partial-depressive” complex	“Guilt”	HSV-1 IgM*, B-lymphocytes (%), Natural killers (%), venous circulation disorder, ventriculi enlargement, pathology of sinuses.	“Somatic concern”	HSV-2 IgM*, IgA (g/l), Cytotoxic cells(%), T-lymphocytes (%), T-helpers (%), B- lymphocytes (%), phagocytic coefficient(%), distention of perivascular spaces of subcortical area, asymmetry of the sigmoid sinuses signal
2. “Affective” complex	“Anxiety”, “Hostility”, “Tension”, “Excitement”, “Depression”, “Motor retardation”, Total BPRS value.	HSV-2 IgM*, HSV-2 IgG(IU/ml), EBV IgM*, EBV IgG*, CMV IgG*, IgA(g/l), T- lymphocytes %, Neutrophils (10x9/l), T-helpers(μl), cytotoxic cells(μl), cortex sulci enlargement, perivascular space dilation in basal ganglia and in the parietal lobes white matter.	“Anxiety”, “Tension”, “Guilt”, “Depression”.	HSV-2 IgM*, CIC, phagocytic coefficient(%), T- lymphocytes %, T-helpers %, B- lymphocytes %, natural killers%, lateral ventricles asymmetry, subcortical perivascular space dilation.
3. “Psychotic” complex	“Unusual thought content”, “Hallucinations”, “Suspiciousness”,	HSV-1 IgM*, HSV-2 IgG(IU/ml), EBV IgM*, IgM(g/l),	“Unusual thought content”, “Hallucinations”, “Suspiciousness”,	HSV-2 IgM*, EBV IgM*, EBV IgG*, phagocytic coefficient(%),

	"Grandiosity".	IgG(g/l), CIC, Natural killers %, B-lymph (μl), Ventricli enlargement, venous circulation disorder, asymmetry of the sigmoid sinuses signal.	"Grandiosity", "Hostility", "Uncooperativeness".	ventriculi enlargement, perivascular space dilation, venous circulation disorder.
4. "Catatono-disorganized" complex	"Mannerisms and posturing", "Conceptual disorganization".	T-helpers(μl), cytotoxic cells(μl), T-lymphocytes(μl), diffuse perivascular cysts.	----------	

**the ratio of positivity*

***For correlation between immunological and BPRS parameters 0,4 ≤R≤ 0,86; p<0,05.*

"Psychotic" complex in main group (EPSPSD) reflects mixed acute HSV-1 and 2 and EBV infection, accompanied by a reduction of brain structures and hemodynamic disorders. Immune response is humoral. The presence of CIC in the structure of complex may indicate apparent viral load.

The complex identifies relation of individual symptoms of the syndrome with various infectious agents. In particular, hallucinatory delusional symptoms are associated with HSV-2 and accompanied by a reduction of the structures forming the walls of lateral ventricles and the third ventricle. Delusion of grandeur is associated with EBV and are accompanied by vascular disorders and neuroreduction of the third ventricle walls (optic thalamus, etc.).

"Psychotic" complex in controls (ERPS) reflects mixed HSV-2 and EBV infection, which is accompanied by hemodynamic disorders and reduction of midline structures of the brain. The immune response is partial; its cellular link is not represented.

"Psychotic" complexes in both forms of schizophrenia indicated to mixed acute herpetic infection, disintegration of the immune response with the apparent lack of a cellular component, expressed hemodynamic disorders and reduction of nervous tissue in the ventricular system. If such a mechanism of infection delimitation as perivascular spaces dilation is included in the complex in remittent form, then it is not included in the complex in episodic paranoid schizophrenia with progressing and stable defect and positive symptoms in remissions.

«Catatono-disorganized » complex reflects viral effects on the brain in immunodeficiency (negative correlation with the number of T-lymphocytes). It is known that herpes viruses are able to break the interneuron and neuromuscular connections that can be expressed in disorders of thought and muscle tone. Disorders of venous circulation, leading to formation of perivascular cysts are also typical for herpes virus infection [13]. Thus, these connections between the symptoms of "mannerisms and posture" and "conceptual disorganization" find a logical explanation.

4. DISCUSSION

Our data confirm the results of studies that show the immunopathological changes in patients with schizophrenia [9]. They also correspond to the data [4-7] revealing in schizophrenia increased titers of antibodies to viruses of the herpes family. Established vascular disorders (perivascular spaces dilation) correspond to recent pathomorphological studies data which found similar abnormalities in patients with schizophrenia on postmortem material and presumably linking these disorders with viral infection [14].

Our study revealed that the presence and severity of positive psychopathological symptoms of schizophrenia, parameters of immune status and levels of antibodies to studied herpes viruses, as well as MRI-anomalies typical for the inflammatory process are linked into a united system. The sequence of complexes in the direction of increasing severity of mental state from rudimentary-depressive to psychotic one correspond to the stages of development of herpetic infection with the inclusion of new herpes viruses and increasing of decompensation processes. In episodic paranoid schizophrenia with progressing and stable defect and positive symptoms in remissions, these processes occur in the context of more immune deficiency and massive viral load.

Results of research attach greater importance to viral hypothesis of schizophrenia [3], as based on the fact that the phasing of schizophrenic symptomatology corresponds to viral process phasing and concomitant immune response. Regressive changes in brain tissue, correlated with infectious inflammatory process, can be considered as degenerative.

The results of our work determine the feasibility of the following approaches to treatment: antimicrobic therapy, immunocorrection, normalization of hemodynamic, detoxication, metabolic therapy and correction of biorhythms. These activities may be accompanied by psychopharmacology or be separately.

Antimicrobic therapy includes drug, vegetal or wave antiviral therapy and treatment of an accompanying infection, including the parasitic one. Immunocorrection includes immune-proofreaders and diet therapy for increase of immunity of a gastrointestinal path and activation of immunocompetent cells. Hemodynamic therapy includes normalization of a vascular tone, strengthening of a vascular wall and normalization of rheological blood properties.

5. CONCLUSION

The research in patients with paranoid schizophrenia found:

1. MRI-signs of vascular disorders such as the perivascular spaces dilation, perivascular cysts, impaired venous microcirculation, deterioration of the venous sinuses signal, congenital vascular pathology (anomalies in the structure of cerebral arteries, abnormal development of the brain). MRI-signs of reduction of nervous tissue: enlargement of the brain lateral and 3 ventricles, subarachnoid spaces enlargement, cortical sulci enlargement.
2. Immunological changes: a tendency to failure of cellular link of immunity, a slight increase in the levels of CIC, increased levels of IgG, non-zero values of IgM to herpes viruses (HSV1, HSV-2, CMV, and EBV).
3. Vascular and morphological anomalies in episodic paranoid schizophrenia with progressing and stable defect and positive symptoms in remissions were more prominent as compared with remittent form.
4. The correlations between morphological, immunological and clinical parameters.
5. Dimensioned correlations reflect compliance of the phasing of infection process with dynamics of development of schizophrenia.
6. Neurodegenerative nature of brain tissue reduction is caused by infectious and inflammatory and hemodynamic changes.

6. LIMITATION

Limitations of the study were: no morphometry and no study related infections.

ETHICAL APPROVAL

The study included data of standard medical investigation that does not require the ethical approval.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Owen MJ, Cardno AG, O`Donovan MC. Psychiatric genetics: Back to the future. Molecular Psychiatry. 2000;5:22–31.
2. Orlova VA. Clinico-genetic investigations of schizophrenia (current state and perspectives of the development. Russian Psychiatry J. 2003;1:31-35.
3. Crow TJ. The virogene Hypothesis of psychosis. Current Status. In: Kurstak E, editor. Psychiatry and Biological Factors. New York: Plenum. 1991;9-21. Available:http://www.dissercat.com/content/kliniko-immunologicheskie-zakonomernosti-adaptatsii-bolnykh-shizofreniei
4. Yolken RH, Torrey EF, Lieberman JA, Yang S, Dickerson FB. Serological evidence of exposure to Herpes Simplex Virus type 1 is associated with cognitive deficits in the CATIE schizophrenia sample. Schizophr Res. 2011;128(1-3):61-5.
5. Prasad KM, Eack SM, Goradia D, Pancholi KM, Keshavan MS, Yolken RH, et al. Progressive gray matter loss and changes in cognitive functioning associated with exposure to herpes simplex virus 1 in schizophrenia: A longitudinal study. Am J Psychiatry. 2011;168(8):822-30.
6. Schretlen D, Vannorsdall T, Winicki J, et al. Neuroanatomic and cognitive abnormalities related to herpes simplex virus type 1 in schizophrenia. Schizophr Res. 2010;118(1-3):224–231.
7. Wang H, Yolken RH, Hoekstra PJ, Burger H, Klein HC. Antibodies to infectious agents and the positive symptom dimension of subclinical psychosis: The trails study. Schizophr Res. 2011;129(1):47-51.
8. Brusov OS, Kaleda VG, GI Kolyaskina, Lavrov VF, et al. Cytomegalovirus infection as a factor of resistance to treatment with neuroleptics in adolescence patients with first-episode of endogenous psychosis. Psychiatry. 2007;4:62-71. [Article in Russian].
9. Lobachyova OA. Clinical and immunological patterns of adaptation in patients with schizophrenia. Abstract of ScD Thesis. Tomsk; 2011. [Russian]. Available:http://www.dissercat.com/content/kliniko-immunologicheskie-zakonomernosti-adaptatsii-bolnykh-shizofreniei

10. Gavrisheva NA, Antonova TV. Infectious process. Clinical and pathophysiological aspects. St. Petersburg: ELBI-SPb; 2006. [Russian].
11. Alimbarova LM, Garayev MM. Laboratory methods in diagnosis of herpes infections. In: Lvov DK, Barinskiy IF, Garaeva MM, Alimbarova LM, editors. Actual Problems Herpesvirus Infections. Moscow. 2004;8-25. [Russian].
12. Wierzba-Bobrowicz T, Lewandowska E, Kosno-Kruszewska E, et al. Degeneration of microglial cells in frontal and temporal lobes of chronic schizophrenics. Folia neuropathologica. Association of Polish Neuropathologists and Medical Research Centre, Polish Academy of Sciences. 2004;42(3):157-65.
13. Barinsky IF, Mahmudov FR. Herpes. Baku, "Victory"; 2013. [Russian].
14. Uranova N, Zimina IV, Vikhreva OI, et al. Ultrastructural damage of capillaries in the neocortex in schizophrenia. The World Journal of Biological Psychiatry. 2010;11:567–78.

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