International Journal of BioMedicine 3(4) (2013) 251-257

INTERNATIONAL JOURNAL OF BIOMEDICINE

CLINICAL RESEARCH

Parameters of Nonspecific and Specific Immune Resistance in Episodic Remittent Paranoid Schizophrenia Compared with Unfavorably Current Form of Episodic Paranoid Schizophrenia

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Abstract

Although the immune component of the pathogenesis of schizophrenia is well documented and recognized, the characteristics of the relationship between nonspecific and specific immune resistance and their correlation with the form and course of the disease continue to remain practically unexplored.

The aim of this study was to investigate the systemic relationships present between the multiple parameters of the immune system (cellular, humoral and phagocytic defenses, the serum levels of the antibodies to herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus and Epstein-Barr virus) in episodic remittent paranoid schizophrenia (ERPS) compared with unfavorably current form of episodic paranoid schizophrenia with progressive or stable deficit (EPSPSD).

Material and Methods: The study included 32 patients with ERPS (main group) and 30 patients with EPSPSD (control group). 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 the herpesviruses (HSV-1, HSV-2, CMV, EBV) were determined using the ELISA test. Total serum immunoglobulins, IgG, IgM, and IgA, were determined by immunoturbidimetry.

Results: In the main group, a combination of immune responses to the viruses studied was observed, while in the control group, an immune response to herpes simplex virus type 1 (HSV-1) - herpes simplex virus type 2 (HSV-2) - cytomegalovirus (CMV) association was found, as well as an immune response separately to Epstein-Barr virus (EBV). In both groups, the cellular immune deficit was noted to be more pronounced in the control group.

Conclusion: These results demonstrate a definite link between herpes infection and the immune resistance parameters of patients with the episodic paranoid schizophrenia. The results confirm the infectious theory of the diseases.

Keywords: *schizophrenia; immune system; herpesviruses; HSV-1; HSV-2; CMV; EBV.*

Introduction

Research is currently underway to determine the importance of pathology of immune response in the pathogenesis of schizophrenia. The imbalance of the T-helper cells, types 1 and 2, leading to T-cell immunity deficit and humoral activation, has been reported to be the main pattern of this disease. The link between the immune reactivity and clinical forms and course of the disease has now been revealed [1,2]. In particular, the low natural killer cell cytotoxic activity occurs right during the first episode of schizophrenia [3]. This parameter becomes normalized by the influence of serotonin [4]. Based on the analysis of numerous studies, the association of schizophrenia with an autoimmune process was discovered [5]. In particular, a tendency for the serum level

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of CIC to increase in schizophrenic patients was revealed. A direct correlation was noted between the CIC serum level and disease duration [6].

Several studies have described the activation of an innate immunity in the form of the high degranulating activity of the leukocyte elastase and functional activity of the alpha 1-proteinase inhibitor. The high degree of the leukocyte elastase activity and the high level of auto-antibodies produced in response to the nerve growth factor were found to correspond to the increase in the extent of the progression of the schizophrenia [7-9].

In our prior study [9], in patients revealing schizophrenia exacerbations, a clear tendency for the increased values in the titers of the neurotropic autoantibodies (IgG) in the "ELI-N-Test 12" (Russia - [10]) was revealed. The autoantibody complexes, whose titers were frequently elevated, reflected the connection between the autoimmune process in schizophrenia with neurodegeneration, demyelination and glial activation, as well indicated the signs of cerebral vasculitis described in other disciplinary approaches. However, the data indicating the presence of viral infections in patients with schizophrenia was also recorded [9]. This fact, in this context, is of particular interest because recent studies have reported an association of autoimmune diseases with the preceding infectious and inflammatory processes involving viruses, in particular, EBV [10-11].

The neurochemical changes in the brain structures associated with mental disorder are now being considered as one of the possible reasons for the immune disorders in schizophrenia [12]. A number of researchers tend to assume immune dysfunction as the primary disorder and presuppose their genetic nature [13,14]. Another hypothesis is the association of the immune pathology with the chronic infectious process in the prenatal period (one of the possibilities) accompanied by the transfer of the genetic material of an infectious agent along with the parental chromosomes [15-18]. Indeed, patients with schizophrenia revealed much higher antibody levels with respect to the neurotrophic infectious agents than do the healthy individuals [19-21]. This enabled the authors to conclude that these infectious agents played a possible significant role in the pathogenesis of schizophrenia. Besides, some data characterizing the correlation of the clinical and immunological parameters with the serum level of the antibodies to herpesviruses was obtained. Thus, positive correlations were established between the HSV-1 IgG antibody titers and the severity of the violations of some cognitive functions in schizophrenia [22, 23], as well as between the EBV IgG antibody levels and the severity of the psychotic symptoms in boys [24].

Some studies focused upon the various aspects of the immune response to CMV in patients with schizophrenia. Their results indicate a cellular immune deficit and low cytotoxic activity of the natural killer cells together with the tendency to reduce the degree of gamma interferon production in patients with the first-episode of juvenile schizophrenia [3, 25]. An association between the immunological parameters, CMV activity and the dynamics of therapy with psychotropic drugs was revealed [13].

In light of the correlation between the clinical and immunological parameters being clearly defined, the positive effect of immunomodulators (Cicloferon, Thymogenum and Aferon) has been associated with the therapy of schizophrenia exacerbations [12, 26]. The efficacy of the acyclovir derivatives in schizophrenia, however, is currently controversial [27, 28] Additionally, according to virologists [29, 30], cellular immunity deficit, which is formed in individuals with persistent herpes infections, is a well-known phenomenon.

The listed data indicate the possible role of the herpes virus infection as an etiopathogenetic factor determining the formation of multiple immune disorders leading to the impairment of the functioning of the brain structures and the subsequent development of the psychopathological symptoms.

The aim of this study was to investigate the systemic relationships present between the multiple parameters of the immune system (cellular, humoral and phagocytic defenses, the serum levels of the antibodies to HSV-1, HSV-2, CMV, and EBV) in episodic remittent paranoid schizophrenia (ERPS) compared with unfavorably current form of episodic paranoid schizophrenia with progressive or stable deficit (EPSPSD).

Material and Methods

The study included 32 patients with ERPS (F20.03) (main group) and 30 patients with EPSPSD (F20.00, F20.01) (control group). The patients were examined during their admission for inpatient treatment at the "Mental Health" clinic 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. 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). In total, 17 patients were admitted to a psychiatric hospital for the first time and had never taken psychotropic drugs. The other 19 patients had taken psychotropic drugs irregularly during the remission, although prior to entering the hospital, they had refrained from taking them.

Table 1.
Demographic and clinical characteristics of patients with schizophrenia

Variable		ERPS	EPSPSD	Total
Number of patients		32	30	62
Sex	Male	15	14	29
	Female	15	18	33
Age range, (yr)		18-51	18-58	18-58
Mean age,(yr)		29.6±8.85	31.5±9	30.5± 9.3
Duration of disease, (yr)		4.9±5	8.9±3	7±7.7
Main syndrome	Catatonic-paranoid	8	2	10
	Hallucinatory – Delusional	15	3	18
	Affective-Delusional	7	26	33

The syndromal psychiatric assessment of the patients in both groups at the time of examination is reflected in Table 1. The BPRS scale 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 the control group. Severe somatic diseases, organic diseases of the central nervous system, as well as alcohol and drug addiction were not identified in any of the cases studied. All the patients belonged to families holding a high socio-economic status.

Immunological methods

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 CIC level by spectrophotometry. The antibodies (Ab) against the herpesviruses (HSV-1, HSV-2, CMV, EBV) were determined using the ELISA test. Total serum immunoglobulins, IgG, IgM, and IgA, were determined by immunoturbidimetry.

Results were statistically processed using the software package Statistica 6.0 for Windows. *T*he mean (M) and standard deviation (SD) was deduced. For data with normal distribution, inter-group comparisons were performed using Student's t-test. The Mann-Whitney (U Test) was used to compare the differences between the two independent groups (for nonparametric data). Spearman's rank correlation coefficient was also used. Pearson's Correlation Coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A value of $P<0.05$ was considered statistically significant. Correlations were calculated for the quantitative indicators of immunity, regardless of whether they exceed the reference values.

Results and Discussion

We analyzed the quantitative values of the immune response as well as the correlation seen between them. Due to the small size of the groups, the significance of intergroup differences could not be determined. However, a comparison of the data has enabled the creation of an inferred picture of the immune response to mixed infection, including the various types of herpesviruses and those specific for episodic remittent paranoid schizophrenia compared with the unfavorably current form of episodic paranoid schizophrenia.

Analysis of the parameters of the specific immune resistance

The frequency of cases with a positive reaction for antibodies to the herpesviruses in the groups studied are shown in Table 2.

Table 2.

The frequency of cases with a positive reaction for antibodies to the herpesviruses in the groups studied.

Antibody	Virus	ERPS		EPSPSD		Total	
		n	%	n	%	n	%
IgG	HSV-1	25	81	16	59	41	64
IgM		1	3.5	2	37	3	4.7
IgG	HSV-2	4	14	0	0	4	6,3
IgM		0	0	0	0	0	0
IgM	CMV	1	3.5	4	14	5	7.8
IgG		9	31	9	33	18	28
IgG	EBV	29	96	25	92	54	84
IgM		0	0	0	0	0	0

The reaction was considered positive if the antibody level was greater than the reference value (Table 3).

In both groups of patients with schizophrenia, the seropositive cases to HSV-1 and EBV were dominant, and in a lesser degree to the CMV. In the main group, the elevated serum levels of the HSV-1 IgG antibodies were observed in 81% of the cases, the EBV IgG antibodies in 96% of the cases and the CMV IgG antibody in 31% of the cases. In the control group, the values of these parameters were 59%, 92% and 33%, 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 the main group 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 control group and 3.5% patients of the main group. The frequency of the elevated CMV IgG titers was similar in the groups (33% and 31%).

The data shown in Table 3 indicate higher levels of the serum HSV-1 and HSV-2 IgG antibodies in the main group and were compared with the control group, without finding any statistical significance. The EBV IgG antibody levels were significantly higher than the reference values (approximately four-fold) in both groups. It is important to note that almost all the parameters of the specific IgM antibodies were above zero. It should also be noted that according to modern virologists' findings, the levels of the specific IgM antibodies above zero clearly indicate an infectious process induced by the relevant agent.

Table 3.

The serum levels of the antibodies to the herpesviruses in the groups studied

Specific Ig (U/ml)	Herpesvirus	Reference values	ERPS	EPSPSD
IgG	HSV-1	<9 - neg. >9.8 – pos.	16.1±8.8	13.3±9.4
IgM		<1 – neg. >1 - pos.	0.8±0.2	0.77±0.2
IgG	HSV-2	<6 – neg. >6.8 – pos.	3.0±2.5	2.0±1.1
IgM		<1 – neg. >1 – pos.	0.76±0.21	0.71±0.2
IgM	CMV	<0.9 – neg. >1.1 –pos.	0.73±0.27	0.74±0.3
IgG		<6 – neg. >6 – pos.	5.0±3.8	5.2±3.9
IgG	EBV	<1 – neg. >1 – pos.	4.0±2.2	4.3±2.5
IgM		<1 – neg. >1 – pos.	0.81±0.03	0.8±0.06

Thus, these indicators of specific immune resistance in both the groups did not exclude the possibility of a mixed infection involving several herpesviruses, especially the HSV-1 and EBV. In the process of exacerbation in the main group, the role of HSV-2 was found to be more significant, whereas in the control group the CMV played a bigger role.

The data in Table 4 suggest the presence of EBV infection without any correlations with other infections in the main group of patients. In the control group, a significant number of correlations was revealed between the antibody levels to all the viruses studied, except for the EBV. Synchronous changes

in the serum levels of IgM and IgG antibodies in response to the HSV-1 and CMV may reveal the active infection caused by these viruses. The negative correlation between the IgM and IgG antibodies to HSV-2 may reflect the phase shift of the specific humoral immune response to this virus in the active phase of the process. Positive correlations between the values of the IgG antibodies to that of the HSV-1 and HSV-2, the IgG antibodies to the HSV-2 and CMV, the IgM antibodies to the HSV-1 and HSV-2 is most easily explained by the synergism of the viruses indicated. In the literature the possibility of a cross-immune response to these viruses is suggested [29], although the present study is limited for such conclusions.

Table 4.
Correlations between antibody (Ab) levels to herpesviruses in the patient groups

Variable	ERPS		EPSPSD	
Parameter 1	Parameter 2	r	Parameter 2	r
HSV-1 IgG Ab	-	-	HSV-1 IgM Ab	0.52*
			HSV-2 IgG Ab	0.46*
			CMV IgM Ab	0.42*
HSV-1 IgM Ab	-	-	HSV-2 IgM Ab	-0.47*
HSV-2 IgG Ab	-	-	HSV-2 IgM Ab	0.41*
	-	-	CMV IgG Ab	0.49*
HSV-2 IgM Ab	-	-	CMV IgG Ab	0.45*
EBV IgM Ab	EBV IgM Ab	-0.46*	-	-

*- $p<0.05$; ** - $p<0.005$

Thus, the data given above most likely describes the exacerbation of a mixed infection involving the HSV-1, HSV-2 and CMV, synergistically interacting with one another. This synergism is not observed for EBV due to the absence of appropriate correlations with the IgG antibodies. A large percentage of individuals with a high level of IgG antibodies to EBV (Table 2) and a high average value of IgG antibodies to the EBV (Table 3) with a lack of correlation between the levels of the IgG and IgM antibodies to EBV may indicate the presence of chronic EBV infection with stable values of the specific antibodies. Thus, the activation of the HSV-1, 2 and CMV interacting synergistically is probably developed against the background of the chronic course of the EBV infection.

It is important to pay attention to the conjugation of the antibody response to the various herpesviruses in the control group which probably indicates the joint activity of these viruses or a combination of their genetic material [33]. These data confirm the results of the experimental studies, which reveal the phenomenon of the interference viruses [29]. The data given in Table 4 indirectly indicate the cellular and phagocytic immune deficits in the control group against the background of the damaging effect of these viruses.

Analysis of the parameters of nonspecific immune resistance

Abnormalities in the immune status occurred in 80% of the patients in the main group and in 85% of patients in the control group. Deviations did not follow a specific characteristic pattern, except for the percentage of the lymphocytes. Thus, in the main group, 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 control group, lymphocytosis was detected almost twice as less frequently (26.3%). 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 control group occurred twice as often as in the main group (47.4% and 21.7%, respectively). In the control group, a slight increase in the CIC level was noticed in 40% of the cases and in 8% of the cases in the main group.

Thus, the data on the frequency of the abnormal values of nonspecific immunity in the patients studied reflect a combined character. The cases with the reduced parameters of cellular immunity are more common, especially in the control group. Overall, these results are consistent with Lobachyova [1] and other researchers regarding the nature of changes in the immunity in paranoid schizophrenia and their dependence upon clinical parameters.

Analysis of the relationships between the parameters of immune resistance

In the main group (Table 5), the correlation analysis revealed only a negative correlation present between the levels of the EBV IgM and IgG antibodies (r=-0.46), which could reflect the dynamics of change in the antibody formation (decrease of IgM synthesis and increase of IgG synthesis) in response to the active infectious process associated with EBV. In the main group, the presence of a significant number of correlations was noted between the nonspecific resistance parameters that might indicate their relative coordination, as well as sufficient immune reactivity as a whole (Table 5). The presence of the correlations between the parameters of cellular immunity with the IgM antibodies and CIC may indicate an acute infection. The correspondence of the quantitative values of these parameters to the reference values in a significant number of patients does not exclude the immune deficiency characteristic of the herpes infection [25, 29, 31].

The data from the control group reflect the acute infectious process. Its originality lies in the combination of significant correlations between the parameters of cellular immunity with an insufficient number of correlations between the parameters of the other components of immunity. In particular, no correlation between the IgG antibodies and PhI, CIC, as well as between the percentage of B-lymphocytes and nonspecific immunoglobulins is seen. Such features of the immune response may be due to the EBV influence on the immunocompetent cells [29, 34], and correspond to a high level of EBV IgG antibody in the control group (Table 3). Moreover, the lack of correlation between the CIC and PhI may imply an immunological tolerance to the infective agents [24]. The absence of elevated CIC levels may also reflect the functional defects of the phagocytic system. It should be noted that the correlations between the cellular immunity parameters were numerically quite small and the incoordination between the components of the immune system was more pronounced in the control group when compared with those of the main group. In the main group, the increased level of the HSV-1 IgM antibodies was associated with the increased synthesis of the IgG antibodies (Table 6). This phenomenon could be explained

Table 5.

Correlations between parameters of nonspecific immune resistance in the patient groups

Variable	ERPS		EPSPSD	
Parameter 1	**Parameter 2**	**r**	**Parameter 2**	**r**
T- lymphocytes, %	T- helpers, %	0.59*	T- helpers, %	0.72**
	T-killers/ suppressors, %	0.6**	T-killers/ suppressors, %	0.62**
	Phagocytic index	0.54**	-	-
	-	-	T-helpers/μl	0.86**
	-	-	T-killers/ suppressors/μl	0.75**
	-	-	Natural killers/μl	0.57*
T- lymphocytes/μl	T-helpers/μl	0.93**	-	-
	T- killers/ suppressors/μl	0.94**	T- killers/ suppressors/μl	0.87**
	Natural killers/μl	0.68**	Natural killers/μl	0.79**
	B- lymphocytes/μl	0.8**	B- lymphocytes/μl	0.71**
	IgM	-0.6**	-	-
	Phagocytic index	0.53**	-	-
	Lymphocytes, %	0.58**	Lymphocytes, %	0.6**
	Lymphocytes 10x^9/l	0.91**	Lymphocytes 10x^9/l	0.75**
	-	-	IgA	-0.56*
T- helpers, %	IgM	-0.45*	-	-
T-helpers/μl	T- killers/ suppressors/μl	0.82**	-	-
	Natural killers/μl	0.78**	Natural killers/μl	0.64**
	B- lymphocytes/μl	0.85**	B- lymphocytes/μl	0.76**
	IgM	-0.63*	-	-
	Phagocytic index	0.5*	-	-
	Leukocytes 10x^9/l	0.64*	Leukocytes 10x^9/l	0.58*
	Lymphocytes, %	0.52*	Lymphocytes, %	0.73**
	Lymphocytes 10x^9/l	0.94**	Lymphocytes 10x^9/l	0.95**
T- killers/ suppressors,%	B- lymphocytes/μl	0.44**	-	-
T- killers/ suppressors/μl	Natural killers/μl	0.57**	Natural killers/μl	0.57*
	B- lymphocytes/μl	0.8**	-	-
	Leukocytes 10x^9/l	0.59*	-	-
	IgM	-0.5*	-	-
	Phagocytic index	0.4*	-	-
	Lymphocytes, %	0.5*	Lymphocytes, %	0.67*
	Leukocytes 10x^9/l	0.63*	Leukocytes 10x^9/l	0.59*
	Lymphocytes 10x^9/l	0.81**	Lymphocytes 10x^9/l	0.96**
Natural killers/μl	B- lymphocytes/μl	0.6**	B- lymphocytes/μl	0.79**
	IgM	-0.48*	-	-
	Lymphocytes, %	0.47*	Lymphocytes, %	0.5*
	Lymphocytes 10x^9/l	0.71**	Lymphocytes 10x^9/l	0.76**
	-	-	Leukocytes 10x^9/l	0.5*
Natural killers, %	-	-	Natural killers/μl	0.57*
	-	-	B-лимфоциты %	0.47*
Phagocytic index	Lymphocytes 10x^9/l	0.47*	Lymphocytes 10x^9/l	0.85**
	Leukocytes 10x^9/l	0.43*	Neutrophils 10x^9/l	0.84**
Lymphocytes, %	Neutrophils 10x^9/l	-0.53*	Neutrophils 10x^9/l	-0.53*
B- lymphocytes,%	Phagocytic index	0.53**	-	-
B- lymphocytes/μl	Phagocytic index	0.5**	-	-
	Leukocytes 10x^9/l	0.5**	-	-
	Lymphocytes, %	0.54**		-
	Lymphocytes 10x^9/l	0.78**	-	-
IgM	Lymphocytes 10x^9/l	-0.56**	-	-
CIC (3% PEG)	Leukocytes 10x^9/l	0.6**	-	-
	Neutrophils 10x^9/l	0.5*	-	-
Leukocytes 10x^9/l	Lymphocytes 10x^9/l	0.61**	-	-
	Neutrophils 10x^9/l	0.86**	-	

* - p<0.05;

** - p<0.005

by the presence of the humoral response to the activation of the HSV-1 infection; moreover, the frequency of cases with elevated HSV-1 IgG antibodies in this group was high (81%). However, the correlation with the total pool of IgG antibodies and lack of the correlation with HSV-1 specific IgG antibodies more likely support the assumption regarding the provocation of the HSV-1 infection with the other pathogens. Such an interpretation is consistent with the data considering the participation of pathogens such as toxoplasma, rubella, influenza, and other infectious agents in the pathogenesis of schizophrenia [18, 19, 35].

Table 6.

Correlations between parameters of specific and nonspecific immune resistance in the patient groups

Variable	ERPS		EPSPSD	
Parameter 1	**Parameter 2**	**r**	**Parameter 2**	**r**
HSV-1 IgM Ab	IgG Ab	0.46*	-	-
	-	-	Natural killers,%	-0.55*
HSV-2 IgM Ab	T- lymphocytes, %	0.63**	T- lymphocytes, %	0.5*
	T- helpers, %	0.57**	-	-
	B- lymphocytes,%	0.47*	-	-
	Phagocytic index	0.64**	-	-
	-	-	IgA Ab	-0.48*
HSV-2 IgG Ab	CIC (3% PEG)	-0.42*	CIC (3% PEG)	-0.52*
CMV IgM Ab	-	-	Natural killers,%	-0.5*
EBV IgG Ab	-	-	IgA Ab	0.51*

*- p<0.05; ** - p<0.005

The main group of patients showed signs of activation of all the components of immunity in response to the HSV-2, viz., correlations between the levels of serum HSV-2 and the CIC content, the serum levels of HSV-2 IgM antibodies and the percentage content of the T-lymphocytes, T-helper cells, B-lymphocytes, and PhI.

In accordance with the data in Tables 5 and 6, the immune response of the main group of patients was more harmonious and focused upon the acute HSV-2 infection, although indirect signs of intercurrent infection, which activated the HSV-1, were also observed.

In light of the above observation, the negative correlation noted between the EBV IgM antibodies and the EBV IgG antibodies in the absence of their relation with the parameters of non-specific immunity is very interesting. This correlation indicates the presence of acute EBV infection. Under conditions of EBV infection, this statistical autonomy can be explained by the activation of the humoral immunity under induced T-cell apoptosis [32]. Signs of this phenomenon in conjunction with the frequency of EBV seropositivity may indicate persistent EBV infection. Further, it is important to consider the possibility of the presence of various intercurrent infections and the specific disruption of the immune response related to them.

For the control group, the polymorphic immune response to the mixed viral infection was more typical, viz., the signs of acute inflammation associated with the HSV-2 activation (a negative correlation between the serum levels of HSV-2 IgM and IgA antibodies, the HSV-2 IgG antibodies and CIC, a positive correlation between the serum levels of HSV-2 IgM

antibodies and the percentages of the T-lymphocytes). The negative correlation between the serum level of HSV-1 IgM antibodies and the percentage of the neutrophils may indicate the depression of the effector stage of the immune response when phagocytosis is activated, as well as the production of T-suppressors is increased.

The positive correlation between the serum levels of the EBV IgG antibodies and the EBV IgA antibodies most likely reflects the presence of the EBV infection with virus replication in the epithelial cells. The negative correlation between the serum levels of the CMV IgM antibodies and the percentage of the natural killer cells indicates the activation of phagocytic immunity during the period of the acute infectious process.

Thus, in patients with an acute episode of Episodic Remittent Paranoid Schizophrenia, the exacerbation of persistent infection of a mixed nature accompanied by the significant role of the herpesviruses was revealed. The immune response was characterized by the relative integrity of reactivity and coordination in the operation of various units of immunity. However, the signs of heterogeneity were also marked. In particular, if the response to the HSV-2 is quite harmonious, the response to the HSV-1 and EBV infection will be predominantly humoral. The symptoms of immunity deformation (general insufficiency of the immune response intensity and the local insufficiency of cellular immunity) described may be associated with the persistence of the herpesviruses.

Analysis of the nonspecific and specific immune resistance parameters in patients with an unfavorable course of episodic paranoid schizophrenia revealed signs of the chronic infectious process involving the association of the herpesviruses (HSV-1, HSV-2, CMV) and VEB against the backdrop of deficiency in the cellular and phagocytic immune response, as well as its disorganization.

Conclusion

The results of this study indicate the presence of mixed infection involving several herpesviruses (HSV-1, HSV-2, CMV, EBV) against the background of partial immunosuppression in those patients with paranoid schizophrenia in both groups.

With persistence, the tropism of the herpesviruses discussed to the immunocompetent cells contributes to the development of secondary immune deficiency. The origin of the primary immune deficiency, however, continues to remain unclear. The hypotheses of hereditary and viral immune deficiency can be combined with the possibility of the integration of viral genetic material into the host DNA with subsequent transfer by succession; the phenomenon of immune imprinting should also be considered [10, 17].

Our study revealed several inter-group differences regarding the nature of the interaction of the herpesviruses with the macroorganism, the interaction between viruses, and the characteristic features of immune deficiency. Thus, if the patients in the main group possessed several “superimposed” immune responses to different pathogens (including EBV) in acute infectious processes, the control group of patients revealed the association of the HSV-1, HSV-2, and CMV with a synergistic effect. The immune response in the control group is perceived as being rarer due to the greater and more severe lack of all the components of immunity and the violation of consistency between them. These features correspond to the signs of chronic EBV infection and the presence of opportunistic CMV infection.

The results of the study enable us to conclude regarding the connection between specific herpesviruses with the clinical features of schizophrenia. Thus, in both groups, the HSV-2 was found to be the most important in the pathogenesis of disease exacerbation. The nature of the EBV infection reveals a connection with the type of schizophrenia. It should be noted that EBV infection enhances the stability of the infected B-lymphocytes to apoptosis and their potential to stimulate polyclonal autoantibody formation [31]. The results of our study support that a marked trend towards the development of the autoimmune processes with an increase in the duration of schizophrenia associated with EBV infection. The results thus obtained can consider the herpesviruses as an important etiopathogenic factor of various clinical forms of episodic schizophrenia. These findings are consistent with the previously mentioned results, which revealed the variation in the severity of the psychopathological symptoms according to the serum levels of the antibodies to the herpesviruses [20].

The present study determines the relevance of a multidisciplinary approach to the study of schizophrenia based on the etiopathogenic role of the viral factors and the advisability of the inclusion of antiviral and immunomodulatory drugs in the treatment algorithm of schizophrenia.

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