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Features of the Inflammatory Response in Juvenile Depression with Attenuated Symptoms of Schizophrenic Spectrum

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ORIGINAL ARTICLE

Summary

Background: early nosological qualification of juvenile depression and detection of specific phenomena of schizophrenic spectrum in its structure makes it possible to identify the onset of an endogenous process and to provide timely therapeutic intervention. This is facilitated by an integrated approach based on a thorough psychopathological assessment of patients and the determination of individual immunological blood parameters**. The aim** was to identify markers of inflammation in juvenile depression with attenuated symptoms of the schizophrenic spectrum (ASSS) in relation to the characteristics of their clinical manifestation and response to therapy. **Patients and methods:** a total of 50 patients, aged 16 to 25 years with the first depression, of which 26 people with attenuated psychotic symptoms (APS) and 24 patients with attenuated negative symptoms (ANS) were examined. The control group consisted of 19 healthy volunteers. The activity of leukocyte elastase (LE) and α_1-proteinase inhibitor (α_1-PI), as well as the level of autoantibodies (AB) to S100β and myelin basic protein (MBP) in blood plasma were measured. The ratio of LE and α_1-PI activity was determined as the leukocyte inhibitory index (LII). Clinical, psychometric (HDRS, SOPS, SANS scales) and immunological examinations were performed at admission to the hospital and at discharge. **Results:** different profiles of immunological indices in patients with juvenile depression with ASSS, reflecting different variants of the inflammatory response to the pathological process were revealed. Only 24% of patients, regardless of the identified clinical groups, were characterized by a balanced immune response. The inflammatory response in 76% of the examined patients was characterized by varying degrees of insufficiency of the neutrophils functional activity against the background of an increase in the activity of α_1-PI, i.e. reduced LII. In 44% of cases, a decrease in LII was also accompanied by an increase in the level of antibodies to S100β. The relationship between immunological profiles with clinical severity of depression with APS and ANS and response to therapy was confirmed. **Conclusions:** the obtained results extend the understanding of the pathogenetic mechanisms of juvenile depression with ASSS and indicate various variants of the inflammatory response associated with these pathological conditions.

Keywords: juvenile depression; attenuated symptoms of the schizophrenic spectrum; positive and negative symptoms; inflammatory and autoimmune markers.

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INTRODUCTION

Currently, the focus of researchers' attention is directed to the prevention of mental illnesses, including those, related to the schizophrenic spectrum. The search for opportunities for their early recognition and therapeutic intervention will allow suspending, or even stopping the course of the endogenous process and maintaining a high level of quality of life [1]. According to the data of retrospective studies of schizophrenic patients some nonspecific psychopathological symptoms were detected already in early adolescence, i.e. more than 10 years before the onset of psychosis [2].

At the pre-manifest stage, which falls on adolescence [3], depressive symptoms proper (60%) [4], self-harm (49%) and suicidal thoughts (66%) [5] are often revealed, which can also occur within the framework of a depressive syndrome. Thus, juvenile depression require a thorough psychopathological analysis in relation to their nosological qualifications. The detection of individual phenomena of the schizophrenic spectrum in their structure, the main of which, according to the modern model of schizophrenia, include positive and negative symptoms [6] will allow suggesting the onset of endogenous process.

From a biological point of view, one of the pathogenetic links of the first psychotic attack that develops in adolescence is neuroinflammation, associated with the development of inflammatory reactions in the bloodstream [7, 8]. This process is accompanied by an increase in blood levels of various humoral (plasma) inflammatory mediators, as well as molecules, released from cells during the development of an inflammatory response [9, 10].

The results of our own research have repeatedly shown an increase in a number of immunological parameters (inflammatory and autoimmune markers) in the blood of patients with schizophrenia and affective disorders [11–13], as well as the presence of correlations of the level of these markers with the acuteness and severity of the psychotic state of patients [14]. In this work the enzymatic activity of the proteolytic enzyme of neutrophils, leukocyte elastase (LE), and the functional activity of its inhibitor, α_1-proteinase inhibitor (α_1-PI), which is simultaneously a protein of the acute phase of inflammation and is synthesized in the liver, were determined as inflammatory markers. The level of autoantibodies to neuroantigens S100β and MBP, which characterizes the activation of acquired (specific link) immunity and, as was shown earlier, accompanying the most severe course of the pathological process in the brain, was considered as autoimmune markers [15].

The aim of the study was to identify markers of inflammation in juvenile depression with attenuated symptoms of the schizophrenic spectrum (ASSS) in relation to the characteristics of their clinical manifestation and response to therapy.

A comprehensive clinical and biological approach to the study of juvenile depression will allow us to determine the pathogenetic patterns of their development, justify the assessment of the severity of the condition, and also contribute to early nosological verification and optimization of therapy.

PATIENTS AND METHODS

The study was carried out on the basis of the Department of Adult Psychiatry (Head — MD, PhD, Professor V.G. Kaleda) together with the Laboratory of Neuroimmunology (Head — MD, PhD, Professor T.P. Klyushnik), FSBSI MHRC (Director — MD, PhD, Professor T.P. Klyushnik). A total of 50 patients, aged 16 to 25 years (mean age 19.4 ± 2.4 years) with first depression with attenuated (weakened) psychotic and negative symptoms of the schizophrenic spectrum were examined. The "subthreshold" degree of severity, on the one hand, made them available for detection, and, on the other hand, did not allow diagnosing within the framework of schizophrenia (F32.1, F32.2, F32.28, F32.8 according to ICD-10). All patients were admitted to clinic of the FSBSI MHRC from 2016 to 2019. Inclusion criteria were as follows: adolescence (16-25 years), first depression, voluntary informed consent to participate in the study. The exclusion criteria included: comorbid mental pathology, the presence of anamnestic data on mental disorders, distinct psychotic symptoms, allowing the diagnosis of psychotic depression with congruent (F32.33) and incongruent (F32.34) affect delusions, clinically significant chronic medical and neurological diseases, as well as the presence of infectious, inflammatory and autoimmune illnesses within 2 months before the start of the examination. According to the specificities of the psychopathological structure of juvenile depression, two clinical groups of patients were identified: the 1st group (26 subjects; 52%) — with attenuated psychotic symptoms (APS), which, from the psychopathological point of view, were separate symptoms of delusional and hallucinatory registers, weakened in severity or in terms of duration and not reaching the degree of "true" psychotic, and the 2nd group (24 patients; 48%) — with rudimentary negative symptoms, differing in partiality and potential reversibility, which did not allow them to be classified as classic negative symptoms and justified their definition as attenuated (ANS) [16]. From a psychopathological point of view, ASSS in the structure of juvenile depression in both clinical groups were considered as equivalent to positive and negative symptoms pathognomonic for schizophrenia and were regarded as a risk factor for the development of schizophrenia.

Clinical, psychopathological and psychometric examination according to the scales for assessing the severity of depressive symptoms (Hamilton Depression Rating Scale — HDRS), prodromal symptoms (Scale of Prodromal Symptoms — SOPS) and negative symptoms (Scale for Assessment of Negative Symptoms — SANS) were carried out twice: upon admission to hospital and at discharge at the stage of remission formation.

The mean duration of depressive state in all studied patients was on average 20.5 ± 16.5 months (the 1st group — 13.7 ± 11.7 months; the 2nd group — 28.5 ± 18.1 months). However, psychopathological examination revealed, that the development of distinct clinical signs of depression, as a rule, was preceded by an initial stage, represented by undescribed affective fluctuations, individual symptoms of a neurosis-like, psychopathic level and a decrease in the level of social and labor adaptation. The duration of depression, taking into account the initial stage, averaged 33.4 ± 16.8 months (the 1st group — 28.5 ± 16.5 months; the 2nd group — 39.1 ± 15.4 months). The healthy controls made up 19 volunteers matched in age with the patient group (mean age 20.7 ± 1.4 years).

In the blood plasma of patients of both clinical groups and the control group, a number of immunological parameters were studied. The enzymatic activity of LE was determined by the enzymatic spectrophotometric method (Ultrospec 5300 spectrophotometer (Amercham)) using the substrate N-tert-Butoxy-carbonyl-L-alanine-4nitrophenyl ester (ICN Biomedical Inc.) [17]. The functional activity of α_1-PI was measured by a spectrophotometric method based on the interaction of an inhibitor with trypsin using N-α-Benzoyl-L-arginine ethyl ester hydrochloride (ICN Biomedical Inc.) as a substrate

Table 1. Immunological indicators of blood plasma in patients with juvenile depression with ASSS and in the control group, Me (IQR)

Groups	Immunological indicators				
	LE activity, nmol/min × ml	α_1-PI activity, IU/ml	LII	Ab to S100β, OD	Ab to MBP, OD
Clinical group (juvenile depression with ASSS) (n = 50)	239.8* (213.8–261.4) p < 0.001	43.6** (36.9–51.7) p < 0.001	5.55* (4.4–6.7) p = 0.008	0.69 (0.63–0.78) p = 0.593	0.68 (0.60–0.79) p = 0.361
Control group (n = 34)	207.4 (196.4–218.8)	33.3 (30.2–35.6)	6.45 (5.85–6.7)	0.68 (0.61–0.77)	0.72 (0.65–0.82)

*p < 0.01; **p < 0.001 — significant differences with controls.

[18]. The measurement was carried out using SWIFT 1000 Reaction Kinetics software (Version 2.03, Biochrom Ltd). To quantitatively determine the level of autoantibodies to S100β proteins (AB to S100β) and myelin basic protein (AB to MBP), a variant of the enzyme immunoassay developed by T.P. Klyushnik et al. was used [19]. The measurements were carried out on a Multiskan RC multichannel spectrophotometer (Labsystems, Finland). The ratio of LE and α_1-PI activity was determined as the leukocyte inhibitory index (LII).

The choice of these inflammatory markers is determined by the role of neutrophils in the development of inflammatory reactions. Activation of neutrophils and an increase in the enzymatic activity of their proteolytic enzymes, and, first of all, LE, is the most important component of inflammatory reactions and changes in vascular permeability (including blood-brain barrier vessels in brain diseases) [20]. The acute phase protein α_1-PI acts as an inhibitor of the destructive proteolytic potential of LE [21]. It has been shown that the ratio of proteases and their inhibitors — the leukocyte-inhibitory index largely determines the course and outcome of the inflammatory response [22, 23]. An increase in the level of antibodies to neuroantigens is considered as a factor indicating a more severe pathological process in the brain associated with destructive changes [24].

The study was conducted in compliance with the rights, interests and personal dignity of the participants in accordance with the Declaration of Helsinki by the World Medical Organization in 1964 and revised in 2013. The study was approved by the Local Ethics Committee of the FSBSI MHRC (protocol No. 281 of 05.05.2016).

Statistical analysis was carried out using Statistica 10.0 and IBM SPSS Statistics 26 software. Since the analyzed sample did not correspond to the normal distribution, when checking the normal distribution of indicators using the Shapiro–Wilk test, the data obtained were analyzed using nonparametric statistical methods. The results are presented as Median (Me) and Interquartile Range (IQR, Q1–Q3). Inter-group comparison was performed using the Kruskal–Wallis test, pairwise comparison of groups — the Mann-Whitney test. The contingency of indicators was assessed using the χ^2-Pearson test. Comparison of related samples was carried out using the Wilcoxon test. The search and assessment of possible correlations was carried out using the ρ-Spearman correlation coefficient. To select groups in the structure of the studied sample, cluster analysis was used. For the correct use of cluster analysis, preliminary standardization of the variables was carried out by calculating the Z-contribution, or the standardized contribution,according to the formula:

$$Z_i = (x_i - \bar{x})/\sigma,$$

where x_i is the value of this observation; $\bar{x}$ — average, σ — standard deviation. The minimum significance level was p < 0.05.

RESULTS AND ITS DISCUSSION

The primary immunological examination of patients with juvenile depression with ASSS, carried out upon admission to the hospital, revealed a statistically significant increase in the activity of LE and α_1-PI inflammation markers, as well as a decrease in LII compared with control (p < 0.01, p < 0.001 and p < 0.01, respectively). The level of antibodies to S100β and MBP neuroantigens was within the reference values (p > 0.05). The results are shown in Table 1.

Correlation analysis revealed statistically significant associations for a number of analyzed parameters in the clinical group of juvenile depression with ASSS: an inverse correlation of the HDRS score with the functional activity of α_1-PI (ρ = −0.39; p = 0.005), a direct correlation of the total HDRS score with LII (ρ = 0.502; p = 0.0002). In addition, a correlation was found between the

Table 2. Characteristics of immunological clusters by values of related indicators LII and the level of autoantibodies to S100β, Me (IQR)

Indicator	Clusters			Control	*p*
	1st (*n* = 12)	2nd (*n* = 22)	3rd (*n* = 16)		
	Me (IQR)	Me (IQR)	Me (IQR)	Me (IQR)	
LII	6.9* (6.8–7.55)	5.55 (4.7–6.2)	4.35 (3.95–5.2)	6.45 (5.9–6.7)	$p^{1-2-3} < 0.001$* $p^{1-2} < 0.001$* $p^{1-3} < 0.001$* $p^{2-3} = 0.121$
AB to S100β	0.63 (0.56–0.67)	0.80* (0.75–0.85)	0.63 (0.60–0.65)	0.65 (0.6–0.71)	$p^{1-2-3} < 0.001$* $p^{1-3} = 1.0$ $p^{1-2} < 0.001$* $p^{2-3} < 0.001$*

*$p < 0.001$ — significant differences between clusters.

level of AB to S100β and MBP (ρ = 0.716, $p < 0.001$). The revealed clinical and biological connections, presumably, indicate the pathogenetic role of the analyzed markers of inflammation in the development of juvenile depression with ASSS. At the same time, significant variability was observed for each of the analyzed immunological indicators: indicators in the sample structure were found that fell the upper and the lower limits outside the control range. The proportion of patients with LE, α_1-PI and LII activity values higher than Q_3 in the control group was 72%, 84% and 22%, respectively. Low values of the studied markers (below Q_1 of the control group) for LE and LII were observed in 16% and 56% of cases, respectively. Hyperimmune sera containing a high level of antibodies to the neuroantigens S100β and MBP were found in 30% and 22% of patients, respectively.

The revealed variability of immunological parameters served as the basis for carrying out a two-stage cluster analysis — a method of statistical data processing that allows identifying clusters in the structure of the studied sample population based on the similarity (measures of connectivity) and differences between patients for specified variables.

Cluster analysis showed that the most likely number of clusters identified in the clinical group is three. The most informative for clustering were two variables — the LII value and the level of AB to the neuroantigen S100β. 24% (12 people) of the examined patients entered the 1st cluster, 44% (22 people) — into the 2nd cluster, 32% (16 people) — into the 3rd cluster. The ratio of the largest cluster to the smallest one was 1.83. The measure of cluster connectivity and separation is 0.6.

The results of comparing the obtained clusters by clustering variables are presented in Table 2.

The results of cluster analysis indicate, that the 1st cluster is characterized by a significant increase in LII compared to the control ($p < 0.05$), as well as a "normal" level of AB to S100β, while the 2nd and the 3rd clusters are characterized by a reduced LII in relation to the control ($p < 0.05$). The 2nd cluster is also distinguished by an increased level of autoantibodies to the S100β protein ($p < 0.05$). Thus, the identified clusters differ in multidirectional changes in the leukocyte inhibitory index and the level of activation of autoimmune reactions relative to the normative values, which indicates different types of inflammatory response in the examined patients.

Statistically significant increase in LII ($p < 0.05$) determined by an increase in both the enzymatic activity of LE (244.1 (238.2–270.0) nmol/min × ml) and the functional activity of its inhibitor (35.5 (32, 2–37.0) IE/ml) (the 1st cluster) in comparison with the control ($p < 0.001$, $p = 0.065$, respectively), characterizes the pro-inflammatory potential and is regarded as a manifestation of a balanced immune response aimed at restoring disturbed brain homeostasis. It was shown earlier that this type of inflammatory reaction is associated with a pathological process of mild to moderate severity and a relatively favorable course of the disease [25].

Reduced LII for the rest of the examined patients (the 2nd and the 3rd clusters) ($p < 0.05$ and $p < 0.001$) in relation to the control is determined mainly by an insufficient increase in LE activity — 235.5 (208.4–261.4 nmol/min × ml) and 241.2 (186.2–253.8 nmol/min × ml). At the same time, the functional activity of its inhibitor was significantly increased — 43.3 (37.3–52.2 IU/ml) and 50.6 (48.3–53.4) IU/ml ($p < 0.05$, $p < 0.001$, respectively), the synthesis inducer of which are IL-6, IL-11, LIF [26]. The most pronounced decrease in the leukocyte-inhibitory

Table 3. Distribution of patients from identified clinical groups of juvenile depression with ASSS by immunological clusters

Groups		Clusters			Total
		1st	2nd	3rd	
1st group Depression with APS (*n* = 26)	number	10	11	5	26
	%	38.5	42.3	19.2	100
2nd group Depression with ANS (*n* = 24)	number	2	11	11	24
	%	8.3	45.8	45.8	100
Total (*n* = 50)	number	12	22	22	50
	%	24	44	32	100

Table 4. Results of comparing the distribution of patients with different clinical variants of juvenile depression with ASSS by immunological clusters

Statistic methods	Value	Degrees of freedom	*p*
Pearson Chi-square	7.515	2	0.023*
Likelihood ratio	8.048	2	0.018*
Linear-by-Linear Association	2.164	1	0.141
The NUMBER of observations	50		

*$p < 0.05$ — statistical significance.

ratio compared to the control ($p < 0.001$) and the 1st cluster ($p < 0.001$) is observed in the 3rd cluster ($p < 0.001$, $p < 0.001$, respectively).

Due to the fact that LE activity characterizes the activation of neutrophils, it can be assumed that the observed decrease in LII is associated with insufficient functional activity of these immune cells, which against the background of an increase in the level of α_1-PI is a sign of a different degree of imbalance in the inflammatory response. Earlier it was shown that this type of inflammatory reaction is associated with asthenic symptom complex in endogenous mental diseases and is a sign of an unfavorable course of the pathological process [27]. A possible reason for the functional insufficiency of neutrophils can be a genetic predisposition, as well as "depletion" of neutrophils due to a long-term current chronic pathological process. The presence of an increased level of antibodies to S100β in patients with reduced LII compared to the control (the 2nd cluster) (0.80 (0.72–0.89 IU ml, $p < 0.05$)) is an additional sign of a more severe and unfavorable course of the disease.

Thus, in the course of clustering in the clinical group of juvenile depression with ASSS, three immunological clusters were identified, significantly differing in the profile of immunological parameters (LE, α_1-PI, LII and AB to S100β). The biological meaning of these differences, presumably, is associated with the features of the course of the inflammatory reaction and characterizes the varying severity of the pathological process. A balanced immune response is observed only in patients of the 1st cluster. The 2nd and the 3rd clusters are characterized by varying degrees of "depletion" of the cellular link of the immune system, which is reflected in an insufficient increase in LE activity (against the background of a high activity of its inhibitor).

The results shown in Table 3 indicate that patients with APS (the 1st group) were distributed mainly

Table 5. Psychometric assessment of patients with juvenile depression with ASSS in the selected immunological clusters at admission, Me (IQR)

Immunological clusters	SOPS positive subscale	SOPS negative subscale	SOPS total score	HDRS total score	SANS total score
1st (n = 12)	11 [10–13]	16 [15–19]	46 [46–50]	27 [27–34]	49 [42–51]
2nd (n = 22)	8 [6–10]	20 [17.5–21]	48 [41–50]	26 [21.5–32]	61 [49.5–69]
3rd (n = 16)	8 [5.5–12.5]	22 [20–24]	52 [43.5–59.5]	27 [22.5–32.5]	70 [59.5–81.5]
p^{1-2-3}	p = 0.023	p = 0.078	p = 0.294	p = 0.542	p = 0.005¤
p	p^{1-2} = 0.982	p^{1-2} = 0.444	p^{1-2} = 0.450	p^{1-2} = 0.423	p^{1-2} = 0.242
	p^{1-3} = 0.016	p^{1-3} = 0.037*	p^{1-3} = 0.557	p^{1-3} = 0.292	p^{1-3} = 0.014*
	p^{2-3} = 0.101	p^{2-3} = 0.095	p^{2-3} = 0.122	p^{2-3} = 0.872	p^{2-3} = 0.113

*p < 0.05 — significant differences between clusters.

between the 1st and the 2nd clusters, and patients with ANS (the 2nd group) between the 2nd and the 3rd clusters. Thus, only a quarter of the examined patients (24%), who made up the 1st immunological cluster, are characterized by a balanced immune response and, presumably, a more favorable course of the pathological process. The rest of the patients (76%) are characterized by the type of inflammatory response associated with varying degrees of deficiency of neutrophil activity, combined in 44% of cases with pronounced autoimmune reactions to neuroantigens (protein S100β), which is considered as a unfavorable of the course of the disease.

The results of comparing the features of the clinical course of juvenile depressions with ASSS and the type of immune response (by LII and the autoimmune component) indicate that similar immunological profiles correspond to different identified groups of juvenile depression, as well as similar clinical conditions are characterized by different immunological profiles. Comparison of the frequency of distribution of patients with identified clinical groups of juvenile depression by immunological clusters revealed statistically significant differences (p = 0.023) (Table 4).

Further, the severity of clinical symptoms of patients was compared according to the SOPS, HDRS and SANS scales in the selected immunological clusters. The results of the comparison are shown in Table 5.

Intergroup comparison of the profiles of immunological parameters characteristic of different clusters with the severity of psychometric assessment of the patient's condition revealed statistically significant differences in the positive (p < 0.05) and negative SOPS subscales (p = 0.078 at the trend level), as well as on the SANS scale (p < 0.05).

Further pairwise comparison of clusters revealed significant differences in the severity of positive SOPS symptoms in patients of the 1st cluster compared with the 3rd cluster (p < 0.05). The greatest severity of negative symptoms was observed in patients included in the 3rd cluster, most of whom, as shown above, were patients with ANS. Statistically significant differences in comparison with the 1st cluster were revealed not only on the negative SOPS subscale (p < 0.05) and on the SANS scale (p < 0.05), but also on the subscales of affective flattening and SANS alogy (SANS 8 and 13) (p < 0.05 and p < 0.05, respectively), as well as by the severity of psychopathic symptoms (p < 0.05), which, according to clinical data, was more common in the structure of depression with ANS (p < 0.05). An important result is also the revealed significantly longer course of the state in patients with depression with ANS (p < 0.05), which is consistent with the above assumption about the possible depletion of the neutrophilic link of immunity in these patients.

Examination of patients after the therapy showed that the positive dynamics of immunological parameters was observed mainly in patients who made up the 1st and the 3rd clusters (Table 6), in whom an autoimmune component was not detected, which is also consistent with the statement that autoimmune

Table 6. The level of statistical significance of dynamics of LII and the level of AB to S100β in immunological clusters after pharmacotherapy (Wilcoxon's method)

Immunological clusters	*p*	
	LII	AB to S100β
1st	0.004*	1.0
2nd	0.636	0.131
3rd	0.007*	0.093

*$p < 0.05$ — significant differences between clusters.

reactions characterize the most severe and relatively resistant to therapy course of the disease.

Thus, in the course of the study, differences in the profiles of immunological parameters, constituting three clusters, were revealed in patients with juvenile depression with ASSS, which reflects different variants of the immune (inflammatory) response to the pathological process in the brain of these patients. The identified clinical groups of juvenile depression were unevenly distributed among the identified immunological clusters: patients with APS were distributed mainly between the 1st and the 2nd cluster, and patients with ANS — between the 2nd and the 3rd cluster.

Only a quarter (24%) of patients with various types of juvenile depression are characterized by a balanced immune response that helps resolve the pathological process. This position is confirmed by the relative normalization of immune parameters after the therapy ($p < 0.05$). The inflammatory response in the majority of the examined patients (76%), regardless of the identified groups of juvenile depression with ASN, was characterized by insufficient enzymatic activity of LE — a marker of neutrophil activation against the background of an increased level of α_1-PI, i.e. reduced leukocyte inhibitory index. In some patients (44%), decreased LII compared with control was also accompanied by an increase in the level of autoantibodies to neuroantigens. In these patients, despite the improvement in the clinical condition (according to psychometric scales) after the treatment ($p < 0.001$), there was no significant change in the analyzed immunological parameters ($p > 0.05$), which may indicate the continuing course of the pathological process and the achievement of therapeutic remission of a low quality.

During the clinical and immunological comparison, the relationship between the isolated immunological profiles and the severity of the clinical condition of patients with APS and ANS was confirmed. The best therapeutic response is characteristic of patients with a balanced immune response ($p < 0.05$) without an autoimmune component ($p > 0.05$).

CONCLUSIONS

Thus, the results obtained expand the existing understanding of the pathogenetic mechanisms of juvenile depression with ASSS and indicate different variants of the inflammatory response associated with these pathological conditions. It has been shown that similar immunological profiles correspond to different identified groups of juvenile depression, and, on the contrary, similar clinical conditions are characterized by different immunological profiles.

Determination of inflammatory and autoimmune markers in the blood of patients with juvenile depression with ASSS and the identification of various features of the inflammatory response can significantly supplement the results of clinical examination of patients in terms of assessing the severity of their clinical condition, possible predicting the further course of the disease, and response to ongoing therapy.

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