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Changes of Cytokines Levels with Proinflamatory Activity (IL-1B, TNFa) and with Antiinflamatory Properties (IL4, IL-10) in Patients with Different Types of Paranoid Schizophrenia

Изменение уровня цитокинов с провоспалительной активностью (IL-1β, TNFα) и с противовоспалительными свойствами (IL-4, IL-10) при разных типах течения параноидной шизофрении

Abstract

Schizophrenia is a topicalissue of the modern medicine. In this study the levels of cytokines with pro- and anti-inflammatory activity were studied in patients with different courses of paranoid schizophrenia (with continuously progressive type (F 20.00), episodic course with an incresing defect (F20.01) and with episodic course with stable defect (F 20.02). A clinical and psychopathological examination of 98 patients with paranoid schizophrenia was performed. In 30 (30.6%) patients paranoid schizophrenia was diagnosed, in 34 (34.7%) patients – (F 20.01) and in another 34 (34.7%) patients – (F20.02). The age of patients was 21 to 60 years old, among them there were 43 males (43.9%) and 55 females (56.1%). After performing the immunology study there were the increase of blood serum concentration levels established of all studied cytokines, especially proinflamatory. It was found that the greater increase of studied cytokines was observed in patients with continuously progressive type of disease, and the smallest changes were found in episodic course with stable defect.

Keywords: paranoid schizophrenia, cytokines, pathogenesis.

Резюме

Шизофрения – актуальная проблема для современной медицины. В статье изучена концентрация цитокинов с провоспалительной активностью (IL-1ß, TNFα) и цитокинов с противовоспалительными свойствами (IL-4, IL-10) у лиц с разными типами течения параноидной шизофрении (непрерывно-прогредиентным типом течения (F20.00), эпизодическим течением с нарастающим дефектом (F20.01) и эпизодическим течением со стабильным дефектом (F20.02)). Было проведено клинико-психопатологическое обследование 98 пациентов с параноидной шизофренией. У 30 (30,6%) пациентов была диагностирована параноидная шизофрения (F20.00), у 34 (34,7%) пациентов – F20.01 и F20.02 – у 34 (34,7%). Возраст пациентов составлял от 21 до 60 лет, женщин было 55 (56,1%), мужчин 43 (43,9%). В ходе иммунологического исследования было установлено повышение концентрации в сыворотке крови уровня всех изученных цитокинов,

особенно провоспалительных. Установлено, что наибольшее увеличение уровня изученных цитокинов наблюдалось при непрерывно-прогредиентном типе течения данного заболевания, наименьшее – при эпизодическом течении со стабильным дефектом.
Ключевые слова: параноидная шизофрения, цитокины, патогенез.

■ INTRODUCTION

Despite significant successes in medicine, the problem of mental health is very relevant at the present time [1, 2]. Mental disorders make a significant contribution to the overall picture of diseases, due to social maladaptation and a significant deterioration in the quality of life of patients, as well as their relatives, and, in some cases, due to decrease in the life expectancy of patients [3]. According to the data of modern statistical studies, the incidence of such a mental disorder as paranoid schizophrenia (PS) has a steady tendency to a constant increase, as well as the formation of resistant forms of this pathologyin patients [4, 5].

Proceeding from the above, the issues of detailed study of the pathogenesis of PStowards developing effective treatment regimens is up-to-date task. In recent years, scientists have found a significant effect of neuroimmune mechanisms in the pathogenesis of schizophrenia, in particular, the changes of levels of certain cytokines (CK) in this disease [5–10]. But up to the present time the questions concerning the study of the level of the CK with pro and anti-inflammatory activity in persons with different types of PS state remain unclear, which determines the topicality of our study.

■ OBJECTIVE

To study the concentration of the CK with pro-inflammatory activity (IL-1ß, TNFα) and CK with anti-inflammatory properties (IL-4, IL-10) in individuals with different types of PSstate.

■ MATERIALS AND METHODS

A clinical, psychopathological and immunological examinations of 98 patients with PS were performed. The diagnosis of PS with a continuously progressive course (F20.00) was established in 30 (30.6%) patients, PS with an episodic course and an increasing defect (F20.01) – in 34 (34.7%) patients and with episodic course with a stable defect (F20.02) – in 34 (34.7%) patients. The patients' age ranged from 21 to 60 years (mainly from 31 to 50 years old (57.1%), the average age of patients was 31.5±8.5 years, 55 (56.1%) among women, 43 (43.9%).

A special immunological study included evaluation of the concentration of pro- and anti-inflammatory CKs (IL-1ß, TNFα, IL-4, IL-10) in blood serum using the solid-phase ELISA method on the MULTISKAN ASCENT analyzer manufactured by LABSYSTEMS (Finland).

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics 20 licensed program using variational statistics methods, determination of mean values (M), error in mean (m). The probability

of variant changes in case of a normal distribution in the samples was determined by Student t-test. We used a significance level of 0.05 (two sided) for almost all statistical tests.

■ RESULTS

We analyzed the features of the clinical course of PS in patients with different types of disease course. During psychopathological study, the examined patients showed typical disorders of PS, which included both positive and negative psychopathological symptoms. Autism, the reduction of the energy potential, the fall of mental activity, emotional deficiency, the phenomena of drift were attributed to negative psychopathological phenomena.

Autistic disorders were observed in 79 (80.6%) patients, i.e. in the majority of patients who were under observation.

Emotional deficiency was characterized by a gradual loss of brightness of emotions, a decrease in their diversity, the development of paradoxical emotional reactions. Emotional reactions become meager, usually in the early stages of the disease and gradually steadily progress. In 52 (53.1%) examined patients emotional deficiency was detected.

Loss of interest in life, indifference, inactivity were noted in 41 (41.8%) patients and were defined by us as a reduction of the energy potential.

In 36 (36.7%) of the examined patients, during the progressive course of the disease, the so-called drift phenomena were observed, which were manifested by apathy, passivity of the patient, which made it impossible to construct the so-called "life line". Such patients passively took instructions from strangers who held leading positions in society, could abuse alcohol and drugs, although the patients themselves did not have the slightest inclination for this.

Summarizing the above, it should be noted that all of the negative disorders described by us differed from each other in a fairly wide range. Depending on the type of PScoursethe disorders also were represented in a wide range – from subtle, slightly noticeable psychic features to expressed ones, which indicated a significant progression of the pathological process.

Positive psychopathological symptoms included disorders of thinking, asthenic disorders, psychopathic, affective, hallucinatory-delusional and catatonic symptom complexes.

Thinking disorders were noted in 45 (45.9%) patients and concerned various aspects of the process - the content of thoughts, speed and flow of thought formation, the lack of reality of thinking.

The asthenic syndrome manifested in 33 (33.7%) patients and was characterized by constant fatigue, increased fatigue, weakening or even loss of the patient's ability to prolonged physical and intellectual stress. Also, these patients had expressed affective lability mainly with a decrease in mood and tearfulness, irritability and hyperesthesia.

The affective syndrome was characterized by patient's mood disorder. The total number of patients with this syndrome was 47 (48.0%). Depending on the nature of the ascertaining affect, depressive disorders were diagnosed in 32 (68.1%) patients and manic disorders – in 15 (31.9%) patients. Clinically depressive syndrome manifested in a depressed mood, as well as intellectual and motor inhibition. Diagnostic criterion of manic

syndrome was an increased mood, acceleration in the patient associative processes, as well as an excessive desire for various kinds of movements, unmotivated influx of strength and energy.

Hallucinatory disorders were noted in 49 (50.0%) patients with PS and were characterized by an influx of intense visual, auditory or tactile hallucinations, of which auditory ones were the most typical. In 76 (77.6%) patients with PSthere was a delusional syndrome manifested by systematized interpretative delirium. Catatonic syndrome was diagnosed in 4 (4.1%) patients and was characterized as a condition in which disturbances of motion were a privaling symptom.

In all the examined patients the development of a personality defect is closely related to various productive syndromes and symptoms.

Table 1 shows the quantitative structure of the negative and positive syndromes, which were noted in the PS patients with the different types of the pathological process.

Providing immunological study we analyzed the blood levels of the CK with a proinflammatory activity (IL-1ß, TNFα) and levels of CK with anti-inflammatory properties (IL-4, IL-10) in patients with PS (Table 2).

Obtained data shows that before the start of conventional treatment in the group of patients with continuously progressive type of PS course (F20.00) the IL-1 concentration increased in the serum in average in 3.7 times comparing to the corresponding normal values (19.3±1.0 pg/ml) and averagely was 71.2±1.6 pg/ml ($P<0.001$). In patients with episodic course with an increasing defect of the PS (F20.01) before the start of therapy, the concentration of IL-1β was slightly less increased and averaged 55.4±1.5 pg/ml, which was 3.11 times above the normal values ($P<0.001$). In patients with an episodic course with a stable defect (F20.02) of PS, during this study period the concentration of IL-1β was on average 48.9±1.4 pg/ml, which was 2.5 times higher than the norm ($P<0.001$).

The mean concentration of proinflammatory TNFα in this period of the study accounted 169.2±2.9 pg/ml in the group of patients with continuously

Table 1
Structure of the negative and positive psychopathological manifestation in patients with different types of PS courses

Syndromes	F 20.00 (n=30)		F 20.01 (n=34)		F 20.02 (n=34)	
	abs.	%	abs.	%	abs.	%
Autism	27	90	30	88.2	22	64.7
Emotional deficit	17	56.7	17	50	18	52.9
Reduction of the energy potential	13	43.3	14	41.2	14	41.2
Drift phenomena	12	40	12	35.3	12	35.3
Thought disorder	15	50	15	44.1	15	44.1
Asthenic	10	33.3	11	31.4	12	35.3
Affective	7	23.3	16	47.1	24	70.6
Psychopathy-like	4	13.3	5	14.7	5	14.7
Hallucinatory	18	60	18	52.9	17	50
Delusional	24	80	26	76.5	26	76.5
Catatonic	2	6.7	1	2.9	1	2.9

Table 2
CK levels in patients with PS (M±m)

CK	Normal values	F 20.00 (n=30)	F 20.01 (n=34)	F 20.02 (n=34)
IL-1β, pg/ml	19.3±1.0	71.2±1.6***	55.4±1.5***	48.9±1.4***
TNFα, pg/ml	56.4±1.8	169.2±2.9***	141.6±2.4***	127.2±2.6***
IL-4, pg/ml	45.4±1.4	69.0±1.8***	62.8±1.6**	54.1±1.4*
IL-10, pg/ml	1.3±0.05	1.91±0.05**	1.74±0.04*	1.51±0.03*

Notation:
Significantly * p<0.05; ** p<0.01; *** p<0.001 higher than normal values.

progressive type of PS course (F20.00), which was 3.0 times higher than the norm (P<0.001). In the group of patients with episodic course of PS with an increasing defect (F20.01), the mean concentration of TNFα was 141.6±2.4 pg/ml, which exceeded the norm in 2.5 times (P<0.001). In patients with PS with episodic course with a stable defect (F20.02) the TNFα mean concentration was 127.2±2.6 pg/ml, which was 2.3 times higher than the norm (P<0.001).

The concentration of anti-inflammatory CKs in the serum did not change significantly, but the maximum shifts were observed with PS F20.00. The concentration of IL-4 (Table 2) in the group of patients with continuous-progressive type of PScourse increased averagely in 1.5 times comparing to the normal values (45.4±1.4) pg/ml, and equaled 69.0±1.8 pg/ml (P<0.001). In the group with an episodic course ofPS and increasing defect (F20.01), there was 1.4 times normal values exceeding (P<0.01) and mean values equaled 62.8±1.6 pg/ml, in the group of patients with an episodic course of PS and stable defect (F20.02), values of CK werein 1.2 times higher than normal (P<0.05), and reached mean values 54.1±1.4 pg/ml. The concentration of IL-10 in patients with the continuously progressive type of PS (F20.00) was also increased averagelyin 1.46 times and equaled 1.91±0.05 pg/ml (P<0.01). In episodic course with an increasing defect (F20.01) concentration of IL-10 was increased in 1.3 times and averaged 1.74±0.04 pg/ml (P<0.05). In patients with episodic course of a PS and a stable defect (F20.02) the mean levels of IL-10 was equaled 1.51±0.03 pg/ml, that was 1.2 times higher than the norm (P<0.05).

Thus, positive syndromes are typical for PS, and the combination of these two types of disorders manifested via negative and positive syndromes creates a polymorphic and various picture of the disease, which determines the clear patterns of the development of the psychopathological process and determines the forms or variants of PScourse.

Analyzingthe obtained data it was found that the maximum shifts of the studied proinflammatory and anti-inflammatory CKs were observed in patients with continuously-progredientcourse of the paranoid process (F20.00), and the minimal changes occurred in patients with episodic course with a stable defect (F20.02), which makes further development of new methods of immunotherapy in the complex treatment of PS pathogenetically grounded and expedient.

Authors declare no conflict of interest.

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