

THE LEVEL OF SYSTEMIC INFLAMMATION AND CHANGES IN ADAPTIVE IMMUNITY IN ALCOHOLIC PSYCHOSES

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УРОВЕНЬ СИСТЕМНОГО ВОСПАЛЕНИЯ И ИЗМЕНЕНИЯ АДАПТИВНОГО ИММУНИТЕТА ПРИ АЛКОГОЛЬНЫХ ПСИХОЗАХ

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The aim of the work is to study the level of systemic inflammation and changes in adaptive immunity in the early period after acute psychosis to assess their participation in the pathogenesis of alcoholic mental and cognitive disorders. We examined 28 patients with alcoholic psychosis (AP) and a control group of 17 healthy volunteers. Indicators of systemic inflammation and immunity, including key cytokines and lymphocyte subpopulations, were investigated. After acute psychosis of patients with alcoholism, pronounced activation of humoral immunity with impaired clearance of immune complexes, increased content and activity of Th2 with signs of insufficiency and dysfunction of Th1, reduced content and activity of cytotoxicity system cells and signs of systemic inflammation (increased CRP, cortisol, cytokines). Activation of Th2 response and an excess of proinflammatory mediators in patients with AP through various ways of interaction with the Central nervous system (*n. vagus*, choroidal plexus of the ventricles, and others) can participate in the disorders of metabolism of neurotransmitters in the Central nervous system involved in the pathogenesis of alcoholism, and in the maintenance of neuroinflammation. A high level of systemic inflammation can be both a trigger of psychosis and a manifestation of violations of neuroimmune interactions, as well as the development of excitotoxicity and damage to neurons in acute psychosis.

Keywords: alcohol dependence; alcohol psychosis; immunity; cytokines; systemic inflammation.

Цель работы — исследование уровня системного воспаления и изменений адаптивного иммунитета в ранний период после острого психоза для оценки их участия в патогенезе алкогольных ментальных и когнитивных расстройств. Обследованы 28 больных с алкогольным психозом (АП). Группа сравнения 17 здоровых добровольцев. Исследовали показатели системного воспаления и иммунитета, включая ключевые цитокины и субпопуляции лимфоцитов. После острого психоза у больных алкоголизмом обнаружены выраженная активация гуморального звена иммунитета, повышение содержания и активности Тх 2-го типа с признаками недостаточности Тх 1-го типа, снижение содержания и активности клеток систем цитотоксичности, а также маркеры системного воспаления. Активация ответа Th2 и избыток провоспалительных медиаторов у пациентов с АП через различные пути взаимодействия с ЦНС (*n. vagus*, хореоидные сплетения желудочков мозга, и другие) могут участвовать в нарушениях обмена нейротрансмиттеров в ЦНС, вовлеченных в патогенез алкоголизма, и в поддержании нейровоспаления. Высокий уровень системного воспаления может быть как триггером психоза, так и проявлением нарушений нейроиммунных взаимодействий, а также развития эксайтотоксичности и повреждения нейронов при остром психозе.

Ключевые слова: алкогольная зависимость; алкогольный психоз; иммунитет; цитокины; системное воспаление.

Introduction. Alcohol abuse is more than 80% of cases of drug addiction in Russia, with 90% of alcoholics in working age — from 20 to 59 years. Alcohol dependence (AZ) is more often diagnosed in young patients under 30 years of age and leads to premature death of about half a million people annually. AZ leads to changes in systemic immunity and increased risk of infectious complications and severe organ damage. According to

data of experimental and postmortem studies of AZ leads to neuroinflammation and disruption of the architectonics of the Central nervous system. Neuroimmune signal transmission is known to be critical for neuroplasticity regulation and is necessary for learning and memory [1, 2]. Excessive production of inflammatory mediators in the brain leads to damage to neurons. Chronic exposure to ethanol in mice increases levels of immune proteins

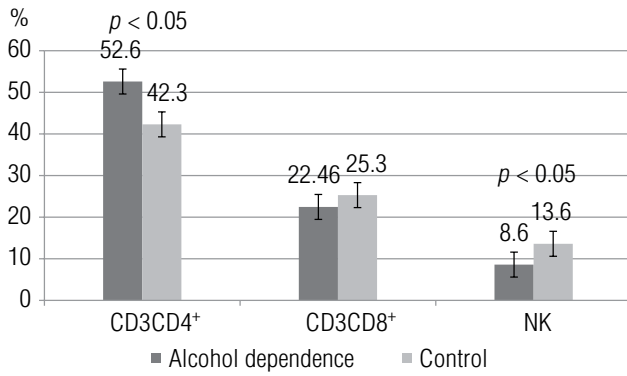


Fig. 1. Lymphocyte subpopulations [%] in patients with alcohol dependence ($n = 28$) and in the control group ($n = 17$)

CD14, TNF- α (tumor necrosis factor α), IL-1 β (interleukin-1 beta), NF- κ B p65, iNOS (inducible nitric oxide synthase), and COX-2 in the cortex, but these changes are not observed in mice knocked out by TLR4 [3]. It is suggested that immune signaling regulates alcohol consumption and that excessive alcohol consumption alters neuroimmune signaling by allowing positive feedback to increase consumption, cravings, and dependence [4, 5].

Objective: to study the level of systemic inflammation and changes in adaptive immunity in the early period after acute psychosis to assess their participation in the pathogenesis of alcoholic mental and cognitive disorders.

Materials. The study included patients with stage 2 alcoholism with alcoholic psychosis (AP) — 28 people, 21 men and 7 women, mean age — 44.6 ± 4.1 years. The duration of AZ — 23.2 ± 6.3 years. Diagnosis (organic personality disorder And 07.8) installed in the hospitalization to the PCB 1. N. Alekseeva of Moscow. The exclusion criteria were acute infections, exacerbation of chronic infections, severe somatic pathology, viral hepatitis. The comparison group included 17 healthy volunteers 12 men, 5 wives, mean age 41.2 ± 6.5 .

Methods. Serum levels of IgA, IgM, IgG, CC (IL-1, IL-1RA, IL-2, IL-4, IL-8, IL-10, IFN γ ,

TNF α), CRP and CIC were studied by ELISA. Phenotyping of the main lymphocyte subpopulations (CD3, CD4, CD8, CD16, CD19, CD45, CD56, CD38, HLA-DR, Treg) by flow cytometry (monoclonal at BD) was also performed.

Results. The assessment of humoral immunity parameters revealed a significant increase in IgG levels in patients with alcohol dependence compared to the norm (1565 ± 114.32 and 1215 ± 95.12 , respectively, $p < 0.05$). The content of IgA and IgM did not change in comparison with the norm and indicators of the control group. There was also a significant increase in CEC to 128 ± 13.40 at a rate of 79 ± 8.63 ($p < 0.05$). In the group of patients with alcohol dependence there was an increase in the main markers of systemic inflammatory response: the level of circulating immune complexes, C-reactive protein, cortisol, and proinflammatory cytokines IL-1 β , IL-8 and TNF α (Table 1) compared with the control group and with normal values. In particular, the level of CRP was increased to 20.63 ± 7.3 mg/l, which was more than 10 times higher than the control values.

Thus, in patients with CA after acute psychosis (delirium) activation of humoral immunity with impaired clearance of immune complexes was found. In addition, there was an increase in the content and activity of T-helpers, mainly of type 2 (with signs of insufficiency and dysfunction of Th1), a decrease in the content and activity of cytotoxicity system cells (EC, TNC and CTL) (figure 1). Signs of systemic inflammation (increased CRP, cortisol, IL) were found.

Conclusion. Activation of Th2 response and an excess of proinflammatory mediators in patients with AP through various ways of interaction with the Central nervous system (*n. vagus*, Horodnya plexus of the ventricles of the brain, and others) can participate in the disorders of metabolism of neurotransmitters in the Central nervous system involved in the pathogenesis of alcoholism, and in

Table 1

Cytokine concentrations (pg/ml) in patients with alcohol dependence ($n = 28$), in the control group of healthy volunteers ($n = 17$) and in the normal range

	Alcohol dependence $n = 28$	Controls $n = 17$	Normal range $n = 40$
IL-1 β , pg/ml	$19.57 \pm 3.5^*$	3.66 ± 2.74	6.0 ± 1.2
IL-2, pg/ml	16.61 ± 1.59	13.75 ± 2.08	10.1 ± 2.0
IL-4, pg/ml	$5.53 \pm 1.41^*$	1.42 ± 0.53	1.27 ± 1.09
IL-8, pg/ml	$28.27 \pm 15.88^*$	9.41 ± 1.83	8.5 ± 0.7
IL-10, pg/ml	5.41 ± 3.46	5.27 ± 3.14	3.42 ± 1.0
IFN γ , pg/ml	207.5 ± 200.19	34.37 ± 8.97	37.61 ± 7.39
TNF α , pg/ml	$5.03 \pm 0.49^*$	2.3 ± 0.65	1.88 ± 0.3
IL-1RA, pg/ml	787.76 ± 603.21	116.94 ± 91.34	369.06 ± 179.92

Note. *significant differences with control and norm ($p < 0.05$).

the maintenance of neuroinflammation. A high level of systemic inflammation can be both a trigger of psychosis and a manifestation of violations of neuroimmune interactions, as well as the development of excitotoxicity and damage to neurons in acute psychosis.

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