ALTERED SERUM LEVELS OF NEURONAL PROTEINS AND ANTIBODIES TO THEM IN OCCUPATIONAL DISEASES OF THE NERVOUS SYSTEM

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A clinical and immunological examination of men with occupational pathology, including vibration disease (VD), occupational sensorineural hearing loss (SHL), and chronic mercury intoxication (CMI), was carried out. The comparison group consisted of men comparable in age and total work experience. Serum concentrations of neurotrophins (S100β, MBP, BDNF) and antibodies (ABs) to S100β and MBP proteins were determined by enzyme-linked immunosorbent assay. An increase in the level of the S100β protein was shown in CMI, VD, and a tendency for its increase was found in SHL. In parallel, an increase in AB to the S100β protein in VD and SHL and a decrease in AB in CMI were noted. A comparative assessment of MBP levels indicated a pronounced increase in its serum concentrations in patients with CMI and VD versus the comparison group. At the same time, an increase in the level of serum ABs to MBP in individuals with VD and SHL, and a decrease in patients with CMI were noted. In patients with CMI, a significant decrease in the BDNF concentration was found, while in SHL and VD, no statistically significant differences were found in comparison with the comparison group. The results obtained confirm importance of assessing serum concentrations of neurotrophic proteins and ABs to them in the case of occupational damage to the nervous system caused by exposure to physical and chemical factors.

Key words: chronic mercury intoxication; professional sensorineural hearing loss; vibration disease; neurotrophic proteins; autoantibodies; diagnostic significance

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INTRODUCTION

Timely diagnostics, prevention, and treatment of occupational diseases of the nervous system still represent an important problem of modern medicine. This is largely due to the similarity of clinical manifestations in the early stages of the disease with other neurological disorders of non-occupational origin. Recently, the exclusive role of neuroproteins in the pathogenesis of various neurological and mental disorders (bipolar affective disorder, depression, schizophrenia, Alzheimer's disease, epilepsy, etc.) has been shown [1, 2]. In addition, neurotrophins are involved in the processes of adaptation to various environmental factors through changes in metabolism, oxidative-antioxidant status, apoptosis processes, stimulation of morphogenetic processes, as well as restructuring the relationship between the nervous system and peripheral tissues [3]. Currently, there is increased interest in a new role of neuroautoantibodies, which have been identified as new generation biomarkers in neuropsychiatric disorders and neurointoxications [4]. Among a significant number of neuroproteins, the most actively studied in recent years are S100β protein, myelin basic protein (MBP), and brain-derived neurotrophic factor (BDNF), influencing a wide range of processes in the nervous system. The S100β protein is the most specific protein for astroglia; it plays an important role for the normal functioning of all brain systems. It can serve as a marker of increased permeability of the blood-brain barrier (BBB) and structural and functional damage of brain glial cells. The serum level of this protein, which correlates with its content in the central nervous system (CNS), can also be considered as an indicator of the effectiveness of treatment [5]. MBP is one of the key structural and functional components of the myelin sheath. It is a marker of damage of oligodendrocytes, which are a group of glial cells localized in the CNS and involved in the myelination of CNS axons. Myelin destruction is a universal mechanism of response of nervous tissue to damage [6].

BDNF also has a wide range of functions; it is involved in the development and maintenance of brain neurons, including sensory neurons, dopaminergic neurons of the substantia nigra, cholinergic neurons of the forebrain, hippocampus, and retinal ganglia. Taking into consideration the ability of neurotrophins to increase neuronal survival, they are often considered as endogenous neuroprotectors [7]. Moreover, they can act both locally, within one cell population, and remotely, circulating in the blood [8]. Despite a significant number of works studying the role of neurotrophins, the full range of their potential in the sanitation and pathogenesis of occupational diseases of the nervous system remains basically unexplored.

The aim of this study was to analyze changes in serum concentrations of neuronal proteins and autoantibodies (ABs) to them (S100β, MBP, BDNF,

AT to S100β, AT to MBP) in patients with occupational sensorineural hearing loss (SHL), vibration disease (VD), and chronic mercury intoxication (CMI).

MATERIALS AND METHODS

The clinical and immunological examination was carried out in three groups of male patients with occupational pathology (Table 1), manifested by predominant damage of the nervous system. The first group included 40 men with VD. The clinical picture of VD patients was characterized by predominant lesions of the peripheral nervous system, peripheral circulation, musculoskeletal system, and the vestibular analyzer [9]. The second group included 20 patients with SHL formed due to exposure to aircraft noise (instructor pilots, aircraft commanders, and flight mechanics). The third group consisted of 22 patients with an established diagnosis of occupational CMI; at the time of examination they were not working under conditions of mercury exposure. In the clinical picture of patients in this group encephalopathy dominated; it was characterized primarily by the manifestation of mental disorders usually in the form of organic asthenic disorder or organic personality disorder with cognitive and emotional-volitional disorders of varying severity. The comparison group consisted of 27 conditionally healthy men, comparable in age, who did not have clinical signs of acute or chronic diseases of any nature during the study period, and lacked occupational exposure to chemical or physical factors. Exclusion criteria were allergic and concomitant somatic diseases. Clinical examination and diagnostics were performed at the Institute Clinic in accordance with the ICD-10 classification criteria for diseases and conditions. The serum concentrations of neuronal proteins were determined by the standard enzyme-linked immunosorbent assay method. Serum concentrations of S100β and MBP proteins were determined using reagents from CanAg (Sweden) and AnshLabs (USA), respectively. The concentration of BDNF was determined using Quantikine Elisa test systems (USA). Serum concentrations of IgG ABs to nervous tissue antigens — protein S100β and MBP were assessed using standard test systems ELI-Neuro-Test (MIC Immunculus, Russia). Blood for the study was taken from patients once in Vacutainer tubes (Improvacuter, China) upon admission to the hospital on an empty stomach before treatment. Blood samples were centrifuged on a laboratory centrifuge TsLMN-R10-01 (Elekon-M, Russia) at 1500 rpm for 15 min to obtain serum, which was collected in separate tubes (Eppendorf, China) and stored in a low-temperature refrigerator (Sanyo, Japan) at -70°C.

The results obtained were processed using the STATISTICA 6.0 package. The normal distribution of variables was checked using the Shapiro-Wilks test. Comparative assessment data are presented as median (Me), lower (Q1) and upper (Q3) quartiles. Statistical significance between independent sets with non-normal distribution was evaluated using the Mann-Whitney test. Differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

It is known that some nervous system diseases are accompanied by destructive, demyelinating processes, with release of neuron-specific proteins from damaged nervous system cells into the interstitial space and further into biological media [10]. A significant part of them leads to disruption of the BBB function. Penetrating from the bloodstream into the brain, these proteins cause destructive processes in neurons, as well as the development of nonspecific acute-phase reactions such as edema or inflammation [11].

A comparative assessment of serum concentrations of neurotrophic proteins in patients with occupational diseases of the nervous system of various etiogenesis revealed differences in their content versus the comparison group and between the groups of patients as well (Table 2). For example, in CMI patients, serum S100β concentrations increased, while in patients with occupational diseases induced by exposure to physical factors (VD and SHL), no statistically significant differences in this parameter were found as compared to the comparison group. However, comparison of the median values of S100β in the groups of patients with VD and SHL revealed statistically significant differences with a more pronounced increase of S100β in the VD patients. It should be noted that the S100β protein is the most studied due to its neurospecificity. In the CNS it is a paracrine neurotrophic factor that influences brain formation, glial cell proliferation, and neuronal maturation. It promotes cell survival under stressful conditions and also counteracts the effects of neurotoxins. At the same time, this protein is widely present in various types of cells; it is considered as a putative marker of the generalized damage of BBB, rather than isolated damage to glia.

Table 1. Some characteristics of groups of patients with occupational pathology and the comparison group

Studied groups	Patients with			Comparison group
	VD	SHL	CMI	
Number of examined persons	40	20	22	27
Age, years	50.28±0.68	52.00±1.36	53.40±0.80	47.20±0.73
Work experience, years	19.20±1.60	22.80±1.14	18.25±1.74	17.20±1.20

Age and work experience data are shown as mean ± SEM.

Table 2. Comparative assessment of neurotrophic proteins and ABs to them in patients with occupational pathology, Me (Q1-Q3)

Parameters, units	Patients with			Comparison group (n=27)	*p*-value
	VD (n=40) 1	SHL (n=20) 2	CMI (n=22) 3		
BDNF, pg/ml	278.02 (128.84–2235.27)	469.70 (169.00–1380.20)	370.51 (59.33–1256.57)*$^{0.009}$	473.80 (262.30–797.00)	p^{1-3}=0.0006
S100β, ng/l	72.01 (59.72–117.59)	52.53 (33.99–80.65)	85.62 (73.83–118.30)*$^{0.03}$	63.46 (43.80–89.34)	p^{1-2}=0.04
MBP, ng/ml	1.27 (0.92–0.20)*$^{0.003}$	1.20 (0.30–2.02)	1.13 (0.45–1.18)*$^{0.04}$	0.49 (0.16–0.81)	—
ABs to S100β, arbitr. units	0.836 (0.585–1.140)*$^{0.000007}$	1.05 (0.930–1.140)*$^{0.000001}$	0.378 (0.202–0.580)*$^{0.03}$	0.285 (0.240–0.410)	p^{1-2}=0.006 p^{1-3}=0.000001 p^{2-3}=0.00000
ABs to MBP, arbitr. units	0.553 (0.436–0.679)*$^{0.00000}$	0.652 (0.525–0.821)*$^{0.00000}$	0.175 (0.144–0.196)*$^{0.000007}$	0.300 (0.270–0.360)	p^{1-2}=0.01 p^{1-3}=0.0000009 p^{2-3}=0.00000

* – Statically significant difference versus comparison group and other groups of patients, $p<0.05$.

MBP is a marker of damage to glial cells localized in the CNS and involved in the myelination of CNS axons [7]. The results of our studies showed a significant (more than 2-fold) increase in the median values of MBP in CMI and VD patients as compared with the comparison group. In SHL patients, there was a pronounced tendency to the increase in the MBP concentration, which, however, did not reach the level of statistical significance. Taking into consideration that the MBP increase reflects the damage of oligodendrocytes, there are reasons to assume that in the examined patients, the myelin sheath is destroyed to a greater or lesser extent and the possibility of disruption of nerve impulse transmission.

The BDNF gene expression is regulated not only by internal factors, but also by environmental factors [12]. Neurotrophins are often considered as endogenous neuroprotectors due to their ability to increase neuronal survival. One of the significant functions of BDNF in the adult brain is considered to be the modulation of synaptic plasticity, which determines its neuroprotective properties. [13]. Analysis of BDNF levels in the study groups revealed a significant decrease in this parameter in CMI patients as compared to the control group. In SHL patients no differences in the BDNF concentrations were detected as compared to the comparison group, while in VD patients a pronounced tendency towards its decrease was noted. A decrease in the concentration of neurotrophic factors may be due to a decrease in their production or intensive degradation by proteolytic enzymes [14]. Due to destruction, individual neurotrophins can acquire antigenic properties stimulating AB production. Some autoantibodies (auto-ABs) exhibit proteolytic activity to some neurotrophins [15]. According to our data, the level of ABs to the S100β protein increased in patients with SHL and VD as compared to the comparison group. This may indicate their protective properties due to the regulation of overexpression of neurotrophins. At the same time, the increased production of auto-ABs is aimed at activating the clearance and utilization of excess of such products and is sanogenic [16]. On the contrary, in CMI patients, a decrease in the levels of ABs to the S100β protein was registered. In highly experienced workers contacting with metallic mercury vapor and persons with early manifestations of neurointoxication with mercury, which we examined earlier, an increase in the above-mentioned ABs was registered [17]. Apparently, serum concentrations of ABs to S100β reflect the stage of development of the pathological process, and their detection in patients with neurological manifestations may be useful for the early diagnosis of diseases.

The results of the analysis of the correlation between the concentration of neurotrophic proteins and the level of ABs to them revealed that in SHL patients, an increase in the S100β protein was accompanied by an increase in the production of S100β ABs (r=0.512, p=0.04). In VD patients, positive correlations were found between BDNF and ABs to S100β proteins and MBP (r=0.463, p=0.005 and r=0.406, p=0.017, respectively), as well as S100β and ABs to MBP (r=0.518, p=0.002). Relationships in CMI were characterized by a positive correlation between the concentration of MBP and ABs to S100β (r=0.433, p=0.04). No correlations were found in the comparison group. This, apparently, may indicate the pathogenetic significance of the established relationships in patients with occupational pathology of the nervous system.

CONCLUSIONS

The results obtained confirm importance of assessing serum concentrations of neurotrophic proteins and ABs to them in the case of occupational damage of the nervous system caused by exposure to physical and chemical factors. Both increased and

decreased values of these markers have diagnostic significance and may indicate the severity of changes in the nervous system. Further research will likely increase our understanding of the role of these proteins in the mechanisms responsible for damage of the nervous system and how to interpret changes in serum concentrations of neurotrophic proteins and antibodies to them in the dynamics of the development of the pathological process.

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COMPLIANCE WITH ETHICAL STANDARDS

The examination of patients complied with ethical standards in accordance with the Declaration of Helsinki of the World Medical Association (2013) and Order No. 200n of the Ministry of Health of the Russian Federation dated April 1, 2016 "On approval of the rules of good clinical practice." The studies were carried out with the informed consent of patients to participate in them and were approved by the Ethics Committee of the Federal State Budgetary Scientific Institution "East Siberian Institute of Medical and Environmental Research" (protocol No. 5 of March 21, 2023).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ИЗМЕНЕНИЕ УРОВНЯ НЕЙРОНАЛЬНЫХ БЕЛКОВ И АНТИТЕЛ К НИМ ПРИ ПРОФЕССИОНАЛЬНЫХ ЗАБОЛЕВАНИЯХ НЕРВНОЙ СИСТЕМЫ

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Проведено клинико-иммунологическое обследование мужчин с профессиональной патологией, включающей вибрационную болезнь (ВБ), профессиональную нейросенсорную тугоухость (НСТ) и хроническую ртутную интоксикацию (ХРИ). Группу сравнения составили мужчины, сопоставимые по возрасту и общему трудовому стажу. Концентрации в сыворотке крови нейротрофинов (S100β, ОБМ, BDNF) и антитела (АТ) к белкам S100β и ОБМ определяли методом твердофазного иммуноферментного анализа. Показано увеличение уровня белка S100β при ХРИ, ВБ и тенденция к его нарастанию при НСТ. Параллельно отмечено увеличение АТ к белку S100β при ВБ и НСТ и снижение АТ при ХРИ. Сравнительная оценка уровней ОБМ свидетельствовала о выраженном нарастании его сывороточных концентраций у пациентов с ХРИ и ВБ относительно группы сравнения. При этом отмечено увеличение уровня сывороточных АТ к ОБМ у лиц с ВБ и НСТ и снижение у пациентов при ХРИ. У пациентов с ХРИ установлено значимое снижение концентрации BDNF, а при НСТ и ВБ по сравнению с группой сравнения статистически значимых различий не выявлено. Полученные результаты подтверждают целесообразность оценки сывороточных концентраций нейротрофических белков и АТ к ним при профессиональных поражениях нервной системы, обусловленных воздействием физических и химических факторов.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: хроническая ртутная интоксикация; профессиональная нейросенсорная тугоухость; вибрационная болезнь; нейротрофические белки; аутоантитела; диагностическая значимость

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