МЕДИЦИНСКИЕ НАУКИ

THE LEVEL of BRAIN-DERIVED NEUROTROPHIC FACTOR IN CEREBROSPINAL FLUID in ADULT PATIENTS WITH ACUTE BACTERIAL AND VIRAL MENINGITIS AND MENINGOENCEPHALITIS.

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Abstract

The aim of the work is to determine the level of brain-derived neurotrophic factor (BDNF) in the CSF in adult patients with bacterial viral meningitis and meningoencephalitis. **Patients and Methods**. 168 cases of acute bacterial and viral neuroinfections were analyzed. The level of BDNF in CSF was determined at admission and on 10-12 day of treatment using the ELISA method. **Results.** The level of BDNF in CSF in the control group was 75,43±1,32 pg/ml. The highest BDNF level was obtained in patients with meningococcal (91,12±3,85 pg/ml) and pneumococcal (83,46±3,83 pg/ml) meningitis at the time of admission. In the groups of bacterial meningoencephalitis, the level of BDNF during the admission was significantly lower compared with the bacterial meningitis but was not significantly differ from the control group indicators. In patients with viral neuroinfection, the level of BDNF was significantly lower than in the control group, both with meningitis and meningoencephalitis. The BDNF level was particularly low in groups of HSV 1,2, EBV and HHV-6 meningoencephalitis ($P<0,05$). The level of BDNF in CSF in non survivors was 70,30±4,85 pg/ml – significantly lower than in the control group, but not differ from the levels of survivors. **Conclusions.** Obviously, determining the diagnostic and predictive roles of BDNF level in the CSF in patients with acute neuroinfection needs further research. However, the data obtained indicate the diagnostic value of BDNF in adult patients with acute neuroinfection.

Keywords: brain-derived neurotrophic factor, CSF, meningitis, meningoencephalitis.

BACKGROUND

Neuroinfections are a worldwide problem and an important cause of morbidity and mortality [1].

Infections of the central nervous system (CNS) pose an unique challenge to physicians, due to both the potential morbidity and mortality that they cause as well as the inherent difficulties involved in their treatment. These infections mainly involve meningitis, encephalitis, and brain abscesses, and tend to cause more morbidity and mortality on average than infections involving other organ systems. [2-4]. In the United States, more than 20,000 cases of encephalitis in adults are registered annually, about $ 2 billion spent on treatment [5]. Currently, in developed countries and Europe, acute neuroinfection in immunocompetent adults is most often caused by viruses - enteroviruses, herpesviruses, arboviruses, which cause 70-90% of all cases of infectious diseases of the CNS [6-9]. In European countries, among the factors of acute bacterial neuroinfections in adults, is the most common Streptococcus Pneumoniae (53%), Neisseria meningitidis (27%), Haemophilus influenzae (3%) and Listeria monocytogenes (4%). Despite the relative rarity of bacterial neuroinfections, they have a severe course with a mortality of up to 50% and the development of prolonged residual effects in 39-70% of patients [10]. At present, the determination of the importance of neurotrophic factors is an actual direction in the study of pathogenesis and diagnosis of neuroinfection.

One of the most studied neurotrophin is the brain-derived neurotrophic factor (BDNF), which plays a major role in the growth and survival of neurons, is a modulator of neurotransmitters and promotes neuronal plasticity. BDNF stimulates and controls the growth of new neurons from nerve stem cells (neurogenesis), while protein and matrix ribonucleic acids (mRNAs) of BDNF are found in most areas of the brain and spinal cord [11]. The ability of BDNF to enhance neurogenesis [12-15] and synaptic plasticity [16, 17] has been proved. It is believed that BDNF can play a role in some neurological conditions, such as Alzheimer's Disease, dementia and autism. The level of BDNF in blood decreased in patients with type 2 diabetes mellitus with cognitive deficits [18]. The level of BDNF was significantly lower in patients with schizophrenia who had lower cognitive performance than in the control group, suggesting that BDNF may be involved in the patho-

physiology of schizophrenia and related cognitive impairment, especially short-term memory [19]. Low level of BDNF in patients with depression and type 2 diabetes has also been identified. [20]. In this context, it is interesting to note that chronic alcohol intake can exacerbate Type 2 diabetes and reduce BDNF level, which means that alcohol induced peripheral neuropathy, dementia and cognitive decline may also be associated with low level of BDNF [21]. Experimental studies have found that exogenously administered BDNF can prevent neuronal loss and reduce the susceptibility of neurons to glutamate injections [22, 23], and may thus be useful in Huntington and Parkinson's diseases. Studies of BDNF level in patients with brain injuries showed contradictory results - on the one hand, there was no relationship between the state of the patient with brain trauma and the level of BDNF in serum [24] or CSF [25]. On the other hand, a link was found between the adverse course of traumatic brain damage and the low level of serum BDNF [26], as well as high levels of BDNF in the CSF [27].

At present, research on the clinical significance of BDNF in various pathologies is at an early stage. Data on the level of BDNF in the CSF and the blood of patients with acute neuroinfection are not enough to determine the diagnostic role of this marker.

METHODS

Potential study participants were treated at the Kharkiv Regional Clinical Infectious Diseases Hospital (Kharkiv, Ukraine). The work was carried out in accordance with the Helsinki Declaration. The study period (2012 – 2017) was approved by the local Ethics Committee of Kharkiv National Medical University, Kharkiv, Ukraine.

Informed consent was obtained from patients to use their biological samples and clinical data for research purposes. The selection criteria were not applied, i.e. all available patients with suspected bacterial and virus meningitis that underwent lumbar puncture were included in the study. Inclusion of patients in the research program was carried out using selection criteria. Inclusion criteria: clinical symptoms typical for acute meningitis, etiological confirmation etiology of disease by bacteriological methods or CSF PCR, age of patients from 18 to 65 years, voluntary consent of the patient to participate in the study. Patients were excluded in the following cases: presence of CNS diseases in the anamnesis, HIV, cancer. Demographic data were obtained from patients, clinical indicators were evaluated, and studies were conducted upon admission to the hospital. An anamnesis of the disease, complaints and neurological status was recorded. All significant events were recorded until discharge from the hospital or death.

Patients were divided into groups depending on the etiology and severity of the disease. 186 cases of acute bacterial and virus meningitis/meningoencephalitis were analyzed. In the control group, we selected 15 patients with acute respiratory diseases and meningizmus. Lumbar puncture was performed as a routine diagnostic test to exclude the presence of neuroinfection. Neuroinfection was excluded in all patients in the control group.

CSF was aspirated by lumbar puncture. Performing of lumbar puncture was conducted according to standard protocols of diagnostics and treatment of patients with signs of meningitis. Patients involved in the study were not been exposed to additional invasive procedures. The CSF samples were immediately refrigerated at −70°C until analysis conducting. Levels of BDNF in CSF were identified on admission and after 10-12 days of treatment. Commercially available enzyme–linked immunoassays were used to analyze neuromarker BDNF (Merck Millipore, Germany) according to manufacturer instructions, in Central scientific–research laboratory of Kharkiv National Medical University. All data were analyzed using «BioStat Pro» and «Microsoft Excel» programs. Differences in the values of BDNF in the CSF and clinical variables were estimated using the Mann Whitney U test. The value of $P<0,05$ was used for significance.

RESULTS AND DISCUSSION

346 patients with acute infectious diseases of the CNS were registered during the research. 186 patients with confirmed etiology of the disease were selected. There were 36 patients with meningococcal infection, 43 patients with pneumococcal infection, 20 patients with HSV 1,2 infection type, 19 with EBV, 15 with VZV, 14 with HHV–6 type and 39 patients with enteroviral meningitis. The average age of patients with bacterial neuroinfections was significantly higher than in groups with viral neuroinfections ($P<0,01$). The highest age was observed in patients with pneumococcal meningitis – 47,82 ± 14,15 years, the youngest – in patients with enteroviral meningitis – 24,05 ± 5,72 ($P<0,001$).

The quantity of women and men was the same almost in all groups, however, among patients with HSV 1,2 neuroinfection, women significantly predominated – 16 (80%) of 20 cases. The most severe was bacterial meningitis, a severe course of the disease was observed in almost 76% of patients.

Meningitis was observed in 11 (30,56%) patients with meningococcal infection, 10 (23,26%) with pneumococcal, 15 (75%) with HSV 1,2, 10 (52,63%) with EBV, 8 (72,73%) with HZV, 9 (64,29%) with HHV–6 and 39 (100%) with enteroviral etiology of the disease. The highest mortality was observed in patients with pneumococcal (17,78%) and meningococcal (8,33%) neuroinfection (Table 1). The lethal outcome in patients with bacterial disease occurred within 1 to 8 days of hospital treatment, with viral – on 5–14 days of treatment.

Table 1. Baseline characteristics of groups.

	Meningococcal (n=36)	Pneumococcal (n=45)	HSV 1,2 (n=20)	EBV (n=19)	VZV (n=15)	HHV–6 (n=14)	Enterovirus (n=39)
Age (Mean±SD)	40,28± 14,78	47,82± 14,15	35,47± 14,71	36,43± 16,09	38,27± 18,24	31,69± 13,03	24,05± 5,72
Male, n/%	19/52,78	21/46,67	4/20,00	7/36,84	9/60,00	8/57,14	20/51,28
Female, n/%	17/47,22	24/53,23	16/80,00	12/63,16	6/40,00	6/42,86	19/48,72
meningitis, n/%	11/30,56	10/22,22	15/75,00	10/52,63	11/73,33	9/64,29	39/100
meningoencephalitis, n/%	25/69,44	35/77,78	5/25,00	9/47,37	4/26,67	5/35,71	0/
Non survivors, n/%	3/8,33	8/17,78	1/5,00	2/10,53	1/6,67	1/7,14	0/

The level of BDNF in the CSF of patients at admission and on 10-12 day of treatment are summarized in Table 2. The BDNF level in CSF in the control group was 75,43±1,32 pg/ml. The highest BDNF level was obtained in patients with meningococcal (91,12±3,85 pg/ml) and pneumococcal (83,46±3,83 pg/ml) meningitis at the time of admission. In the groups of bacterial meningoencephalitis, the level of BDNF during the admission was significantly lower compared with the bacterial meningitis but was not significantly differ from the control group indicators.

In patients with viral neuroinfection, the level of BDNF was significantly lower than in the control group, both with meningitis and meningoencephalitis. Particularly low were the BDNF level in groups of HSV 1, 2, EBV and HHV-6 meningoencephalitis (P<0,05). Level of BDNF in CSF at non survivors was 70,30±4,85 pg/ml – significantly lower than in the control group, but not differ from the level of survivors (table 2).

Table 2. The level of BDNF in the CSF in patients at admission and on 10-12 day of treatment.

Etiology on neuroinfection	BDNF, pg/ml	
	At admission	On 10-12 day of treatment
Meningococcal meningitis, (n=11)	91,12±3,85 [2, 3]	77,93±1,25
Meningococcal meningoencephalitis, (n=25)	71,62±1,12 [1, 2, 3]	76,57±2,68
Pneumococcal meningitis, (n=10)	83,46±3,83 [2, 3]	77,08±1,74
Pneumococcal meningoencephalitis, (n=35)	72,21±1,01 [1]	75,69±1,92
HSV 1,2 meningitis, (n=15)	72,98±2,03	74,05±2,56
HSV 1,2 meningoencephalitis, (n=5)	66,88±2,77 [1, 3]	65,99±2,62
EBV meningitis, (n=10)	71,57±2,65	72,29±2,23
EBV meningoencephalitis, (n=9)	66,41±2,16 [1, 3]	64,91±3,07
VZV meningitis, (n=11)	70,12±3,23 [3]	71,89±3,09
HHV–6 meningitis, (n=9)	73,21±2,87 [2]	78,21±2,34
HHV–6 meningoencephalitis, (n=5)	65,11±2,83 [1, 3]	66,09±3,45
Enterovirus meningitis, (n=39)	70,53±2,96 [2, 3]	74,24±2,67
Non survivors, (n=16)	70,30±4,85 [3]	
Control group, (n=15)	75,43±1,32	

[1] : statistically significant difference between patients with meningitis and meningoencephalitis accordingly of the etiology of the disease (p <0,05);

[2] : statistically significant difference between BDNF levels on admission and on 10-12 day of treatment accordingly of the etiology of the disease (p <0,05);

[3] : statistically significant difference between BDNF levels in group of patients and control group (p <0,05);

Thus, the level of BDNF in the CSR of patients with bacterial meningitis was significantly higher than that of the control group. At the same time, in patients with bacterial meningoencephalitis, the level of BDNF did not differ from those of the control group. Thus, we can assume that in patients with bacterial meningitis, increased expression of BDNF protects the neurons from the lesion and reduces the number of affected neurons. Such an effect may reduce the severity of neurological manifestations of neuroinfection. In patients with viral meningitis, the level of BDNF did not differ from that of the control group. In meningoencephalitis, especially herpesvirus, BDNF level has been reduced (P<0,05). Such changes can be a confirmation that during acute neuroinfections the development of lesions of the CNS is associated not only with the direct action of the microorganism, but also with the decompensation of neuroprotective mechanisms.

Obviously, determining the diagnostic and predictive role of BDNF levels in the CSF in patients with acute neuroinfection needs further research. However, the data obtained indicate the diagnostic value of this marker in adult patients with acute neuroinfection.

COMPETING INTEREST

The authors declare that they have no competing interests

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