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MYELIN BASIC PROTEIN AND ITS DIAGNOSTIC VALUE IN HIV-INFECTED INDIVIDUALS WITH 4th CLINICAL STAGE AND NEUROINFECTIONS

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It was shown that in HIV-infected patients, pathomorphological changes in the white matter in the form of demyelinization are already observed in the early stages of the disease. The most studied marker of this process is myelin basic protein that can be detected in cerebrospinal fluid or serum immediately after acute myelin breakdown.
The aim. *To assess the diagnostic value of myelin basic protein content in serum and cerebrospinal fluid of HIV-infected individuals with 4th clinical stage and central nervous system opportunistic infections.*
Materials and methods*. Using ELISA with diagnostic kit "MBP ELISA" (Ansh Labs, USA), we studied the myelin basic protein content in serum and cerebrospinal fluid of 53 HIV-infected patients with 4th clinical stage and central nervous system opportunistic infections depending on its etiology, the outcome of the diseases and according to Glasgow coma scale score. As well correlation analysis with some laboratory and clinical indicators was performed.*
Results. *We found significantly increased myelin basic protein content in both cerebrospinal fluid and serum of HIV-infected patients 4th clinical stage with central nervous system opportunistic infections compared to control ($p<0.01$), which indicate the presence of active demyelinization in central nervous system. The highest cerebrospinal fluid myelin basic protein was registered in patients with an unfavourable outcome of the disease, as death or residual neurologic deficit, and patients with cerebral toxoplasmosis. The cerebrospinal fluid myelin basic protein had an association with the size of white matter lesions on magnetic resonance imaging and serum myelin basic protein content.*
Conclusions. *Myelin basic protein detection in cerebrospinal fluid as well as in serum can serve as an additional quantitative marker of myelin disruption, which can be used along with magnetic resonance imaging for the diagnosis improvement and prognosis of central nervous system opportunistic infections in HIV-infected individuals with 4th clinical stage*
Keywords: *HIV-infection, myelin basic protein, opportunistic infections, central nervous system*

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1. Introduction

The central nervous system (CNS) is second affected after the immune system during the course of HIV-infection. Up to 70 % of HIV-infected people have clinically different neurologic manifestations and this indicator reaches 90 % in autopsy data [1]. CNS impairment can be primary, caused by HIV-1 itself, and secondary, caused by reactivated opportunistic infections (OIs) on the background of the severe immunodeficiency [2]. Due to the direct cytopathic action of both HIV-1 and OIs and subsequent activation of the inflammatory response, which leads to dysregulation of cytokines, oxidative stress, as well as secretion of soluble factors including the viral proteins (gp120, tat, etc), that are found to be a potent neurotoxin, the destruction of the myelin sheath of neurons and their death occur [3]. Pathologic changes of the white matter during the course of HIV-infection may manifest as small perivascular foci of demyelinization or, in case of severe myelin loss, as a diffuse leukoencephalopathy and can be found in 75 % of the HIV-infected patients even in the early stages of the disease [4].

Myelin is a special type of membrane cell, consisting of a bimolecular lipid layer located between monomolecular layers of proteins, spirally twisted around the nerve cell axons forming white matter. In the CNS it is synthesized by oligodendrocytes with one cell taking part in myelinization of several axons. The main functions of myelin are: isolation and acceleration of the nerve impulse, axon nutrition, as well as supporting and barrier function. The damage to the myelin membrane causes a wide range of motor, sensory and cognitive symptoms [5].

Additionally, myelin shivers may trigger or enhance neuroinflammation through stimulation microglial activation [6]. Among the 29 myelin proteins described, the most important is myelin basic protein (MBP). Elevated MBP level within the cerebrospinal fluid (CSF) provides a marker for CNS demyelinization, as has been shown in patients with relapsing-remitting multiple sclerosis. The MBP content in the CSF mainly increases with acute demyelinization [7]. Through interaction with various molecules and activation of the immune response in

the CNS, released MBP causes a wide range of negative effects on the nerve cells, thereby causing even greater damage to them [8]. Currently, for the diagnosis of CNS impairment in HIV-infected patients successfully used magnetic resonance imaging (MRI) methods. However, it does not provide quantitative characteristics of myelin damage. Development of new methods for quantifying myelin might help to improve the diagnosis of neurologic complications in the early stages of the disease, especially, in the absence of the possibility to provide MRI.

Therefore, the **aim** of our study was to assess the diagnostic value of MBP content in serum and CSF of HIV-infected individuals with 4th and CNS OIs.

2. Materials and methods

The study was conducted according to the Helsinki Declaration based on Municipal Non-commercial Enterprise of Kharkiv Regional Council «Regional Clinical Infectious Hospital» in 2016–2020. The study was approved by the Bioethics Committee of Kharkiv National Medical University, Ukraine (protocol No. 8 from 05.10.2016).

Main group I – 53 HIV-infected patients with 4th clinical stage with neurologic disorders caused by different OIs. The age in this group was ranged from 23 to 61 with mean of 38.7±1.1 years. There were 27 males and 26 females. These patients were divided into 3 subgroups depending on the outcome of the disease, which was assessed following Glasgow Outcome Scale with modifications: 1) patients with 5 points (*n*=6), 2) patients with 3 and 4 points (*n*=26) and 3) patients with 1 point (*n*=21). Where: 1 point – the death of the patient, 2 points – vegetative status (absent), 3 points – severe cognitive or motor deficiency, the patient who is unable to provide self-service during the day, 4 points – mild cognitive or motor deficiency, the patient can provide daily activities without help and 5 points – patient discharged from hospital without any neurological deficit. As well the main group was divided into subgroups depending on the etiology: *C.neoformans* (*n*=7), *T.gondii* (*n*=7) and Ebstain-Barr virus (*n*=10), given their numbers.

Group II – 19 HIV-infected individuals with 4th clinical stage without CNS OIs or other complaints (mean age 39.3±1.9 years) were enrolled as a comparison. They were outpatients in Kharkiv Regional Center of HIV/AIDS. The control group consists of 20 particularly healthy individuals with mean age 37.3±2.2 years. Additionally, in spite we had no right to take CSF from healthy individuals and those HIV-infected patients without CNS OIs, to compare results in CSF were taken 15 patients with acute respiratory infections and meningismus, who underwent lumbar puncture with the subsequent exclusion of neuroinfectious and other non-infectious neurologic pathology (mean age 33.6± ±3.04 years). All groups were matched by sex and age.

Patients included in the study were chosen by selection criteria. Inclusion criteria were: written consent to voluntary participation in the study, age range from 18 up to 61 years, 4th clinical stage of HIV-infection, clinically and laboratory confirmed neurologic disorders due to OIs. Exclusion criteria were: pregnancy, non-infectious neurologic disease (malignancy, acute disorders of cerebral circulation, traumatic brain injury, multiple sclerosis, etc) and severe systemic disorders (coagulopathy, diabetes, etc).

For HIV diagnosis in all examined patients were provided an ELISA test with subsequent confirmation by Western blot and detection of HIV viral load in the blood by polymerase chain reaction (PCR), as well as CD4, CD3 cell count. Clinical and biochemical studies of CSF were performed to reveal neurologic abnormalities as well as a brain MRI. The etiologic agent was detected with CSF culture studies for fungi and bacteria and PCR for herpes viruses and *T. gondii*. The etiology of CNS impairment was found in 44 (83 %) of examined patients. The most frequent were: *Epstein-Barr virus* which was detected in 10 (18,9 %) patients, *T. gondii* – in 7 (13,2 %) patients and *C. neoformans* – in 7 (13,2 %) patients. CSF and serum samples were collected from patients, immediately frozen and stored at -20 °C until analysis.

The MBP content in CSF and serum which were taken in the first days of admission was determined using a commercial diagnostic kit "MBP ELISA" (Ansh Labs, USA) by the three-step ELISA type Sandwich in the Central scientific research laboratory of Kharkiv National Medical University. Statistical processing of the obtained results was performed using a statistical calculator (https://www.socscistatistics.com/tutorials/). Shapiro-Wilk test was used to determine the distribution normality of variables. To compare quantitative indicators in comparison groups was used Mann-Whitney test (*U*). Correlation analysis was performed using the Spearman test (ρ). *P* value <0.05 was considered to be significant.

3. Research results

The obtained data (Table 1) showed that CSF MBP level in HIV-infected patients with CNS OIs manifested as encephalitis or meningoencephalitis was significantly higher than in the comparison group ($p<0.01$). Thus, in patients with CNS impairment CSF MBP level was 13.5±1.7 ng/ml, while in the comparison group it was 1.9±0.2 ng/ml. No differences in level of this indicator between male (13.6±2.4 ng/ml) and female (12.9±2.8 ng/ml) were found ($p>0.05$) (Table 1).

Table 1

Distribution of MBP levels among the HIV-infected patients with 4th clinical stage (Mean±SE)

Parameters	Control (*n*=15)	I HIV-infected patients with CNS OIs (*n*=53)	II HIV-infected patients without CNS OIs (*n*=19)
CSF MBP (ng/ml)	1.9±0.2*	13.5±1.7*	ND
Serum MBP (ng/ml)	0.08±0.01 [1]	0.9±0.3 [1.2]	0.2±0.02 [2]

*Note: * – differences between control and I group $p<0.01$; [1] – differences between control and I groups $p<0.01$; [2] – differences between I and II group $p<0.05$; ND-not done*

27 patients were included in the group of meningoencephalitis as they had increased CSF cell counts >6 /mm^3 either due to neutrophils or lymphocytes, other 26 – had no inflammatory changes of the CSF and were considered as a group of encephalitis. The CSF MBP level in patients with meningoencephalitis was 14.8±2.4 ng/ml and was not different from those patients with encephalitis, where its level was 12.2±2.6 ng/ml (p>0.05).

Analysis of the CSF MBP content in examined patients, depending on the etiology of the CNS impairment, revealed significant differences between the group of *C.neoformans* and *T.gondii* (p<0.01), as well as *C.neoformans* and EBV (p<0.05), but it did not differ from control (p>0.05). There was no differences between groups of *T.gondii* and EBV (p>0.05). The MBP level was significantly higher in the group of *T.gondii* (p<0.01) and EBV (p<0,05) than in the control group. The highest rates of CSF MBP were observed in a group of HIV-infected patients with *T.gondii* with median of 24.5 ng/ml, and the lowest in the group of *C.neoformans* – 0.6 ng/ml. The median of the CSF MBP level in the EBV group has amounted to 15.9 ng/ml.

Assessment of the CSF MBP content was made depending on the consciousness level according to the Glasgow Coma Scale score. We revealed a tendency to the positive relation between these indicators, the more severe disturbances of consciousness the higher CSF MBP content, which did not reach statistical significance (p=0.05368). Thus, in patients with the normal level of consciousness equal 15 points (n=30), the CSF MBP content has amounted to 10.8±2.2 ng/ml, and in patients with its disturbances (14 points or less) (n=23) – 17.1±2.5ng/ml.

As shown in Table 2, there are significant differences between the groups of patients depending on the disease outcome. The highest CSF MBP level in the first 24 hrs of admission – 18.6±2.6 ng/ml was registered in patients, who had been discharged with a different neurologic deficiency, from mild cranial nerves disorders to severe disability with tetraplegia. It was significantly higher compared to the group without neurologic deficit (p<0.01) and the group of patients who died (p<0.05), as well as the control (p<0.001). Contrary, favourable outcome of the disease, in examined patients, was associated with the lowest value of the CSF MBP – 4.2±2.4 ng/ml and did not differ from the control group (p>0.05). In patients with fatal outcome of the disease CSF MBP content was significantly increased 9.9±2.3 ng/ml in comparison with control (p<0.05) and significantly lower than those in patients with a neurological deficiency, but higher than those without it (p>0.05) (Table 2).

The performed correlation analysis in the group I showed a positive relation between the CSF MBP content and size of white matter lesions detected by MRI (r=0.46, p<0.05). Correlation analysis did not show any relation between CSF MBP and age of patients (r=0.16, p>0.05), CSF MBP and CSF protein (r=0.10, p>0.05), as well as pleocytosis (r=0.02, p>0.05).

There was only a tendency between this indicator and duration of neurologic symptoms (r=0.26, p=0.063953).

Table 2

Distribution of CSF MBP levels in the group I depending on Glasgow Outcome Scale score (Mean±SE)

Group	Glasgow Outcome Scale score	CSF MBP, ng/ml
1 (n=6)	5 points (11.3 %)	4.2±2.4 *
2 (n=26)	4+3 points (49.1 %)	18.6±2.6 *,[1,2]
3 (n=21)	1 point (39.6 %)	9.9±2.3 [1,3]
Control	(n=15)	1.9±0.2[2,3]

*Note: *– differences between 1 and 2 groups p<0,01; [1] – differences between 2 and 3 groups p<0,05; [2] – differences between control and 2 group p<0,001; [3] – differences between control and 3 group p<0,05*

The serum MBP level in examined patients was also studied. As shown in Tab. 1, a significant increase of serum MBP level is observed in HIV-infected patients with CNS impairment in comparison with this indicator in HIV-infected patients without it and in the control group (p<0.05) and (p<0.01) retrospectively. Serum MBP content in HIV-infected patients with encephalitis/meningoencephalitis was 0.9±0.3 ng/ml and significantly higher compared to HIV-infected patients without signs of CNS impairment, where it was 0.16±0.02 ng/ml (p<0.05). There was no differences in serum MBP content between encephalitis – 0.9±0.4 ng/ml and meningoencephalitis – 0.90±0.4 ng/ml, as well as depending on sex, thus its level in female was 0.8±0.3 ng/ml and male – 1.1±0.5 ng/ml (p>0.05). We revealed a positive correlation between levels of CSF MBP and serum MBP in HIV-infected patients with CNS impairment manifested as meningoencephalitis (r=0.50, p<0.05). In HIV-infected patients with encephalitis it was absent (r=0.09, p>0.05). No correlation was found between serum MBP level and CD4 cell count (r=-0.15, p>0.05), CD3 cell count (r=-0.10, p>0.05), as well as a viral load of HIV-1 RNA in serum (r=0.16, p>0.05).

4. Discussion of research results

The myelin degradation is a universal mechanism of the nervous tissue reaction for its damage. It was found that MBP is appeared in the CSF and subsequently in the blood after the acute neurologic accident and remains elevated up to 3-6 weeks with gradual decline [9]. Thus, increased CSF MBP has been shown as a nonspecific marker of active myelin destruction in various CNS pathologies, such as multiple sclerosis, acute cerebrovascular accident, transverse myelitis, traumatic brain injury, bacterial meningitis, brain tumours, etc. [9, 10].

Our study also showed the significant changes of MBP content in CSF and serum of HIV-infected patients depending on the presence or absence of CNS impairment. We found only two reports about measurements of MBP in HIV-infected individuals. Pfister et al. investigated CSF MBP content in 40 HIV-infected individuals and found its increase only in two patients as they had severe encephalopathy. Such results can be due to only 13 of these patients had HIV-encephalopathy and only four of them had clinically pronounced neurologic symptoms. Later in G. M. Liuzzi et al. research, it was estab-

lished an increased CSF MBP level in HIV-infected patients depending on the severity of AIDS dementia complex compared to HIV-infected patients without neurologic disorders, as well as seronegative control, where CSF MBP did not exceed reference values [11]. In the present study, all examined patients had a late stage of HIV-infection with severe CNS involvement due to OIs presented as encephalitis or meningoencephalitis with different focal neurologic symptoms.

It is known, that HIV and OIs enhance the pathological properties of each other, thereby causing even more pronounced cerebral damage [12] and, probably, active myelin breakdown which is reflected in the increasing of CSF MBP in our patients. However, we found a wide range in this indicator, which proves the presence of many factors influencing it, such as time from the onset of neurologic symptoms, localization of lesions, its activity, etc. Besides, we revealed the differences in CSF MBP content depending on etiology of CNS lesions. The lowest level of CSF MBP was observed in HIV-infected patients with CNS cryptococcosis and the highest in CNS toxoplasmosis. Presumably, such results can be explained by various pathogenic properties of microorganisms, since *Cryptococcus* is more likely to cause damage to the brain membranes and less the brain tissue, in contrast to *Toxoplasma*, which is an intracellular parasite is causing multiple brain lesions [13]. Contrary to our findings, another study in HIV-infected patients with CNS involvement showed the highest rates of CSF MBP in the group with CNS cryptococcosis, and lower – with CNS toxoplasmosis [14].

J. de Vries et al. as well as H. Nakagawa et al. at their studies demonstrated a strong association between CSF MBP concentrations and brain edema [15, 16] which corresponds to our results. 22 examined patients with impaired consciousness of different levels caused by cerebral edema had a more pronounced increase MBP level than those 29 – with normal mental status. Apparently, brain edema both general and perilesional plays an important role in its release.

Different levels in this indicator depending on its outcome were observed and considered serving as a predictive marker. In recent studies was found a higher CSF MBP level in non-survivors compared to survivors in HIV-infected patients with neurologic disorders and patients with bacterial meningitis [14, 17]. Furthermore, we revealed a higher CSF MBP level in survivors with residual neurologic deficiency compared to those who died. This can be explained by the fact that not all of those who died had pronounced neurologic deficit or the reason for their death was due to respiratory failure or other comorbidities. So it was suggested that CSF MBP content may be a predictive marker exactly for irreversible motor and cognitive deficiency.

A significant relation between MBP content and mass lesions was established. In patients with the cerebrovascular accidents had been shown that serum MBP content was higher in those patients with more extensive lesions of acute ischemia [18]. Thus, K. Borg found that serum MBP level was higher in CT-positive patients with traumatic brain injury compared to those CT-negative [10]. In our study, we found a positive correlation between this indicator in CSF and the size of white matter lesions on MRI that can be useful for quantification of its damage.

Pathological processes such as immune activation, brain edema with elevated intracranial pressure, and altered cerebral blood flow lead to increase blood brain permeability and penetration of NSPs into the bloodstream [19]. Thus, it was suggested that changes in its level in CSF can be reflected in serum. We found an increased in serum MBP levels in both HIV-infected individuals with meningoencephalitis and encephalitis, but only in patients with meningoencephalitis it directly correlated with CSF MBP. These findings can be explained by more pronounced blood brain barrier permeability in this group of patients. Additionally, in earlier studies van Engelen et al investigated 937 samples of CSF from people who underwent diagnostic lumbar puncture and determined an age-dependent increase of CSF MBP [20]. The absence of this dependency in our study may be due to the small number of patients or due to having them of severe brain lesion which may contribute to its levelling.

Study limitations. The impossibility of performing lumbar puncture and determination of MBP levels in the CSF in a group of HIV-infected patients with 4th clinical stage without CNS impairment, therefore, blood serum in both groups were also studied considering the revealed positive correlation between the MBP levels in serum and CSF in HIV-patients with CNS OIs. Small numbers of the patient in the etiological subgroups.

Prospects for further research. Further research will be aimed to investigate MBP level in blood serum and brain tissue in HIV-infected patients with cerebral toxoplasmosis.

5. Conclusions

1. A significant increase in the MBP level in both CSF and serum indicates active destruction of myelin structures in the brain tissue in HIV-infected patients 4th clinical stage with CNS OIs.

2. Given the significant differences in its level in CSF among etiological groups can be assumed that various pathogenetic properties of microorganism and the course of the disease that they cause influence the degree of demyelinization in CNS.

3. Changes of its indicator in CSF depending on the outcome of the disease probably, have its prognostic value especially for predicting residual neurologic deficit in these patients.

4. The relationship between the CSF MBP level and the size of brain lesions on MRI can be used as an additional criterion for assessing the severity of brain damage as well, as monitor the state of CNS in dynamics or therapy effectiveness.

5. MBP detection in CSF and serum blood can be used along with *magnetic resonance imaging* and other tests for the diagnosis and prognosis improvement in HIV-infected patients 4th clinical stage with CNS OIs.

Conflict of interests

The authors declare that they have no conflicts of interest.

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