DOI: 10.23934/2223-9022-2019-8-1-18-29

Cerebrospinal Fluid Presepsin as a Marker of Nosocomial Infections of Central Nervous System

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ABSTRACT Introduction Nosocomial infection of the central nervous system (NI-CNS) is a serious complication in neurocritical patients that leads to deterioration of patient's condition, worsening of outcomes and increased cost of treatment. The timely diagnosis of NI-CNS is a relevant problem and the search for new reliable markers of NI-CNS is an important issue.

MATERIAL AND METHODS The prospective observational study consisted of two parts. The aim of the first part was to define normal ranges of cerebral spinal presepsin (CSF PSP). The aim of the second part was investigation of CSF PSP in neurocritical patients. We studied CSF sampling obtained during spinal anesthesia for elective urologic surgery in order to define the normal CSF PSP. The following data was collected in neurocritical patients: CSF cell count, glucose, lactate, PSP, microbiological tests, polymerase chain reaction (PCR), when it was possible. Blood tests included complete blood count, C-reactive protein (CRP), procalcitonin (PCT), PSP. IBM SPSS Statistics (version 23.0) was used for statistical analysis.

RESULTS Fifteen CSF samplings were obtained for investigation of normal CSF PSP ranges, which was 50–100 pg/ml. Nineteen neurocritical patients were included. Sixty-three pairs of CSF and blood samplings were obtained. All pairs were divided into the 4 groups in accordance with presence/absence of NI-CNS or systemic infection. In cases without both NI-CNS and systemic infection (group 4) CSF PSP was 406±203.1 pg/ml. In cases without NI-CNS and with systemic infection (group 2) CSF PSP was 614.9±315 pg/ml. In cases with NI-CNS and without systemic infection (group 3) CSF PSP was 547.8±264.3 pg/ml. In cases with both NI-CNS and systemic infection (group 1) CSF PSP was 731.1±389.7 pg/ml. The ROC analysis showed that in neurocritical patients without systemic infection CSF PSP 537 pg/ml meant NI-CNS with sensitivity 68.8% and specificity 85.7%.

CONCLUSION The normal value of the CSF PSP is 50-100 pg/ml. CSF PSP more than 537 pg/ml in neurocritical patients without systemic infection meant NI-CNS with 688% sensitivity and 857% specificity. CSF PSP may be used for diagnosing NI-CNS in neurocritical patients as an additional marker only. CSF may be used as an additional diagnostic criterion, but further research is needed.

Keywords: nosocomial infection of central nervous system, meningitis, ventriculitis, presepsin, markers of inflammation

For citation Abudeyev S.A., Kiselyov K.V., Parinov O.V., et al. Cerebrospinal fluid presepsin as a marker of nosocomial infections of central nervous system. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2019; 8(1): 18–29. DOI: 10.23934/2223-9022-2019-8-1-18-29 (In Russian)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments The study had no sponsorship

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ALV — artificial lung ventilation
CNS — central nervous system
CSF — cerebrospinal fluid
CT — computed tomography
EEG — electroencephalography
ELD — external lumbar drain
EVD — external ventricular drain
FOUR — Full Outline of UnResponsiveness Score
GCS — Glasgow Coma Scale
ICP — intracranial prssure
MRI — magnetic resonance imaging
NI — nosocomial infection
PCR — polymerase chain reaction
RICU — resuscitation and intensive care unit
SAH — subarachnoid hemmorhage
SOFA — sequential organ failure assessment

INTRODUCTION

Nosocomial infection of the central nervous system (NI CNS) is a serious complication in neurological critical patients, which worsens their condition, disease outcomes and results in longer duration of treatment [1-3]. Risk factors for NI CNS development are the installation of intracranial devices, especially external ones, their prolonged use, decompression of the cerebrospinal fluid system, skull base fractures, duration of neurosurgical surgery, intraventricular hemorrhage, and the use of antibiotics [4-6]. Liquorrhea, external ventricular drainage (EVD) and open head injury are the most significant predictors of the development of NI CNS. The incidence of NI CNS in patients with EVD varies from 10 to 27% [7–11]. Timely and adequate administration of antibiotic therapy in neurologic critical patients with suspected NI CNS is an actual problem. Early antibiotic therapy of NI CNS improves the results, reduces the patient's stay in the intensive care unit and the cost of treatment [12]. At the same time, unsubstantiated antibiotic therapy in patients without CNS infections leads to the growth of the resident flora, colonization of nosocomial bacterial strains on the skin and mucous membranes, infection with multi-resistant strains of microorganisms and worsening of outcomes [13, 14]. An adequate antibiotic therapy cannot be achieved without correct diagnosis of the NI CNS and rapid pathogen verification. The timely diagnosis of CNS NI improves the results of treatment and reduces the cost of medical care [15].

Traditional clinical and diagnostic criteria of CNS NI: changes in the level of consciousness, meningism, fever, increased cytosis and liquor lactate, glucose consumption of cerebrospinal fluid (CSF), and increased levels of systemic inflammation markers in the blood. These criteria often prove to be false positive or false negative in many clinical situations. Changes in consciousness and fever develop in 50–90% of neurocritical patients as a result of brain damage of non-infectious genesis [16–19]. Meningeal symptoms are characteristic of both the CNS and patients with subarachnoid hemorrhage (SAH) [20, 21]. Leukocytosis, increased levels of *C*-reactive protein, procalcitonin and presepsin are characteristic of the early postoperative period and the development of systemic infection [22, 23]. An increase in CSF cytosis is characteristic of subarachnoid (SAH) and intraventricular hemorrhage [24]. The presence of blood in the cerebrospinal fluid makes it difficult to interpret its analysis, since this increases the level of protein, and red blood cells are able to consume glucose and synthesize lactate [25]. As a result, the ratio of cerebrospinal glucose to blood glucose decreases, the level of lactate and protein in cerebrospinal fluid increases [26], which is identical to changes in cerebrospinal fluid during bacterial inflammation. Microbiological examination by the method of polymerase chain reaction (PCR) or mass spectrometry requires that the pathogen be verified to differentiate a CNS infection from microbial contamination and colonization [27–31].

In this regard, the search for new specific and sensitive biomarkers of NI CNS is an important scientific task. Recently, presepsin has been used as a marker of systemic infection and sepsis in the routine practice of intensive care [32-35]. Presepsin has shown good diagnostic capabilities in patients with sepsis, pneumonia, and intra-abdominal infection [36, 37]. Today, very few studies have been published on the study of the diagnostic capabilities of presepsin in neurologic critical patients [38, 39]. There is almost no data on the dynamics of presepsin content in the CSF. The presented study is devoted to the study of presepsin as a biomarker of the NI CNS.

MATERIAL AND METHODS

at the Anesthesiology, Resuscitation and Intensive Therapy Center of A.I. Burnazyan FMBC and consisted of two parts.

Part I. Aim: to determine the range of normal values of presepsin in the CSF.

Objectives:

- to study the level of presepsin in cerebrospinal fluid in patients who do not have CNS infections

Inclusion Criteria:

- age over 18 years;
- urological, general surgical pathology;
- elective surgery performed under spinal anesthesia.

Exclusion Criteria:

- age under 18 years;
- concomitant neurosurgical and neurological pathology;
- signs of systemic infection and inflammation.

The first part of the study included patients with urological and general surgical pathology, without CNS disorders or infectious complications. All patients were hospitalized to the clinic for routine surgical interventions, CSF was taken during spinal anesthesia under aseptic conditions, prior to introduction of a local anesthetic drug into the intraspinal space. In patients of this group, inflammatory markers were not analyzed. Only presepsin in the CSF was assessed. All patients gave written consent for surgery under spinal anesthesia, and were also informed that during spinal puncture, 1.0 ml of cerebrospinal fluid would be collected for examination.

Part II. Aim: to study the diagnostic value of presepsin in the CSF as a biomarker of CNS infection.

Objectives:

- to study the effect of NI CNS on the concentration of presepsin in the cerebrospinal fluid and in plasma in neurological critical patients;
- to study the effect of systemic nosocomial infectious complications on the dynamics of the presepsin level in the cerebrospinal fluid in neurocritical patients;
- to compare the diagnostic capabilities of presepsin as a biomarker of the NI CNS and common markers of CNS infection in neurocritical patients.

Inclusion Criteria:

- neuro-critical patient with suspected NI CNS;
- age over 18 years;
- stay in the resuscitation and intensive care unit (ICU) for more than 48 hours;
- the possibility of collecting cerebrospinal fluid.

Exclusion Criteria:

- the impossibility of collecting cerebrospinal fluid;
- contraindications to lumbar puncture;
- diagnosed brain death.

The patient's neurological status was assessed daily; it included assessment according to the Glasgow coma scale (GCS), *FOUR* scale, study of segmental-stem reflexes, muscle strength and tone, as well as tendon and other reflexes. A patient was assessed daily according to the *SOFA* scale.

Instrumental methods. Computed tomography (CT) of the brain was routinely performed, at least once per week and each time when cerebral or focal neurological symptoms appeared. If necessary, magnetic resonance imaging (MRI) of the brain was performed. X-ray examination of the chest was performed upon admission of patients to the RICU or when pneumonia or pneumo-hydrothorax were suspected. If necessary, spiral CT examination of the chest was performed. Electroencephalography of the brain (EEG) was performed to exclude an epileptic seizure or status, and monitor the efficacy of anticonvulsant therapy as well. Intracranial pressure (ICP) monitoring was performed in patients with depression of consciousness or, if sedation was necessary in a patient with cerebral edema, focal damage or an increase in ventricular size. In a normal CT scan of the brain, the sensor is installed when coma develops and there are two of the following symptoms for age over 40 years: the presence of unilateral or bilateral decerebration; systolic blood pressure lower than 90 mmHg. A combined sensor of intracranial pressure, oxygen partial pressure and temperature in the brain parenchyma (*Licox*, *Integra*, USA) was installed in patients with cerebral vasospasm.

Methods of laboratory diagnosis. A clinical analysis of the blood was performed daily in patients with suspected NI CNS and the following biochemical parameters were examined: urea, creatinine, albumin, total protein and *C*-reactive protein. If proteins of the acute phase and leukocytes grew with a shift of the leukocyte formula to the left, procalcitonin and plasma presepsin were examined. The acid-base state of arterial blood, electrolytes and plasma glucose were examined every 6–8 hours. In the cerebrospinal fluid, cytosis, glucose, lactate and presepsin levels were assessed, and a microbiological study of CSF was performed as well. PCR was performed whenever possible. Clinical analysis of urine was performed upon admission of the patient to the RICU and urinary infection was suspected. Microbiological studies included culture of sputum, blood, urine, cerebrospinal fluid, sinuses, and pleural cavity.

Diagnosis of infectious complications and systemic inflammatory response syndrome (SIRS). The diagnosis of a systemic infection was established on the basis of the *CDC* criteria [40–42]: body temperature above 38° C or below 36° C; heart rate more than 90 beats/min; respiratory rate more than 20 breaths/min with pCO_2 less than 32 mm Hg; leukocytosis more than 12 x 10^9/l, leukopenia less than 4 x 10^9/l.

NI CNS criteria: increased cytosis in the cerebrospinal fluid more than 300 in 1 μl, the ratio of plasma glucose to cerebral glucose less than 0.4, the level of lactate in the cerebrospinal fluid more than 2.1 mmol/l in the presence or absence of positive results of microbiological cultures of cerebrospinal fluid. Bacterial colonization of intracranial devices was diagnosed in the absence of clinical manifestations of NI CNS, changes in the cerebrospinal fluid and repeated positive results of microbiological studies of the cerebrospinal fluid with the definition of the same pathogen. The contamination of samples of cerebrospinal fluid was diagnosed in the absence of clinical manifestations of NI CNS, with changes in cerebrospinal fluid and the presence of positive results of microbiological studies with the release of various pathogens during repeated stutdies of CSF.

The nosocomial systemic infection such as sinusitis, pneumonia, urinary system infection, surgical wound infection, sepsis is the most common complication in neurologic critical patients. The listed complications in neurocritical patients were diagnosed according to the following criteria:

- sinusitis: fever, leukocytosis with a shift of the leukocyte formula to the left in combination with the darkening of the paranasal sinuses on CT images.
- pneumonia: fever, leukocytosis with a shift of the leukocyte formula to the left in combination with the darkening of the lung tissue on X-ray images and the presence of purulent sputum or positive microbiological examination of sputum.
- urinary system infection: fever, leukocytosis with a shift of the leukocyte formula to the left left; leukocyturia (more than

30 leukocytes in sight) or positive results of microbiological examination of urine.

- infection of the surgical wound: fever, leukocytosis with a shift of the leukocyte formula to the left in combination with purulent discharge from the wound or spontaneous breakdown of the wound edges, or combination with a verified microorganism during microbiological examination of the wound contents.

- sepsis: verified focus of infection and the development of organ dysfunction (*SOFA* growth by 2 or more scores). With the development of arterial hypotension with a decrease in systolic pressure of less than 100 mmHg septic shock was diagnosed [43].

Intensive therapy. All neurocritical patients received therapy according to international guidelines. The sedation has been used for intracranial hypertension; refractory epileptic status, desynchronization of the patient with a ventilator; psychomotor agitation. Depending on the clinical situation, propofol was used at a dose of 1-2 mg/kg/h, fentanyl, muscle relaxants, dexamedetomidine, and neuroleptic drugs. When consciousness was depressed and/or respiratory failure occurred, tracheal intubation and mechanical ventilation *(Maquet, Puritan Bennet) were* performed in the normal ventilation rate. Percutaneous dilational tracheostomy was performed if a patient was critically ill, had dysphagic disorders, and/or the predicted duration of mechanical ventilation was more than 5 days. In all cases, arterial hypotension was managed immediately, if necessary, arterial pressure control was initiated, depending on the intracranial pressure, oxygen partial pressure in the brain parenchyma, and linear blood flow velocity in the cerebral arteries. All patients received proton pump blockers and balanced enteral nutrition with target values: 25–30 kcal/day, protein 1.2–1.5 g/kg/day. In patients with the gastrointestinal tract paresis, parenteral or combined nutrition was performed with three-component nutrient mixtures.

Perioperative antibiotic prophylaxis for planned neurosurgical interventions included the prescription of cefazolin 30 minutes before the skin incision and then every 6 hours on the first day after the operation. Empirical antibiotic therapy for the NI CNS included carbapenems in combination with vancomycin. For nosocomial sinusitis, pneumonia, urinary tract infection, depending on the clinical situation, empirical antibacterial therapy involved the use of protected III–IV generation penicillins or cephalosporins in the form of monotherapy or in combination with vancomycin, linezolid or aminoglycosides. The correction of antibiotic therapy was carried out after verification of the pathogen. When the pathogen was verified, intrathecal administration of colistin, amikacin, or vancomycin was initiated in accordance with the results obtained. The duration of antibacterial therapy was 21 days for NI CNS, 10-14 days sepsis, and 7-14 days for nosocomial pneumonia, urinary system infections.

Statistical analysis was performed using *IBM SPSS* version 23.0. The *Shapiro-Wilk* method was used to check the localization of the normal state. All comparisons between groups were made using nonparametric tests (*Mann-Whitney U-rank test* or *Willcoxon W-test*, as appropriate) with a statistical significance set at $p \leq 0.05$. The specificity and sensitivity of the determination of presepsin in the cerebrospinal fluid in different groups of patients was evaluated using *ROC* analysis in *SPSS* .

Study design. If NI CNS was suspected, they took blood and CSF. Then, the clinical situation, results of blood and cerebrospinal fluid tests, as well as data of additional instrumental methods of examination (CT, MRI, X-ray, ultrasound) were analyzed. Each pair of blood/cerebrospinal fluid, together with the interpretation of the data obtained during the examination, was a single variant of the clinical situation. Each time all data were analyzed and a judgment was made about the presence or absence of the patient's CNS and systemic infection. The design of the presented research is shown in Fig. 1.

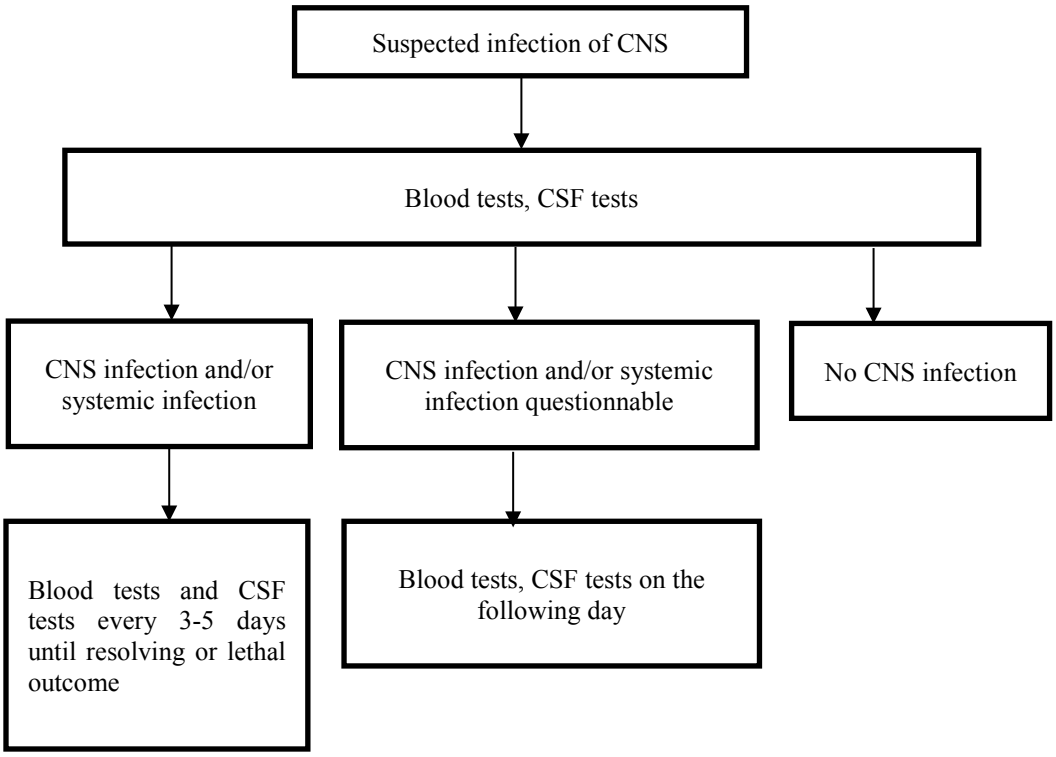

Fig. 1. The study design
Notes: CNS — central nervous system

RESULTS

The study was conducted from September 2015 to June 2017.

Part I. We examined 15 patients with urological and general surgical pathologies. The average age of the patients was 59.3±14.1 years, all patients were men. The first part of the study included patients with the diagnoses: “Bladder tumor” (*n*=6), “Bladder cancer” (*n*=3), “Male infertility” (*n*=2), “Prostate neoplasm” (*n*=2), “Chronic pyelonephritis in remission” (*n*=1), “Unspecified inguinal hernia” (*n*=1). The postoperative period was uneventful. Infectious complications were not observed in any of the clinical observations. The duration of hospital stay after surgery was 5.2±2.3 days. All patients were discharged in satisfactory condition. The presepsin level in the CSF was 74.32±25.32 pg/ml. Thus, the value of 50–100 pg/ml should be considered as a normal level of presepsin in CSF .

Part II. This part of the study included 19 neuro intensive care patients with suspected NI CNS. The average age was 51.5±15.5 years; there were 11 men and 8 women in the group. Diagnoses: “Brain tumor” (*n*=6), “Intracerebral hemorrhage” (*n*=5), “Traumatic brain injury” (*n*=3), “Ischemic stroke” (*n*=4), “SAH” (*n*=1).

ALV was performed in 17 patients. Percutaneous dilational tracheostomy was performed in 14 patients. The duration of mechanical ventilation was 12±9.7 days, the duration of stay in intensive care was 16.4±9.6 days and 40.1±38.7 days at rhe hospital. NI CNS was diagnosed in 9 patients. The manifestation of the NI CNS was 5.9±3.5 days after surgery. According to microbiological studies and PCR diagnostics of cerebrospinal fluid, pathogens were verified in 3 cases: *Proteus mirabilis was* isolated from cerebrospinal fluid in one clinical observation of a patient with EVD on the 5th day after installing drainage, *Streptococcus pneumoniae* was verified in the patient's CSF also in one observation on the 7th day after the neurosurgical operation. *Enterococcus faecium was* verified in the cerebrospinal fluid in another clinical case also on the 7th day after neurosurgical operation and on the 6th day after the repeated emergency removal of the intracerebral hematoma and EVD. The most significant risk factors for the development of NI CNS and the outcome of the disease are presented in Table 1. The results of the study of cytosis, glucose and lactate levels in the CSF and system markers are presented in Table 2.

Table 1. **Risk factors and outcomes in patients with NI-CNS and without infection**

	EVD Number/duration	ELD Number/duration	Without drains	Liquorrhea	Basal skull fracture	Intraventricular bleeding	SAH	Neurosurgery	GOS		
									3-5	1-2	1
NI-CNS+	5 (8.6±3.1)*	2 (3.5±0.7)	4	2	-	5	1	15*	9	-	2
NI-CNS-	1 (12)*	-	7	1	1	1	-	4*	3	-	5

Notes: * — significant differences (p<0.05). CNS — central nervous system; EVD — external ventricular drain; ELD — external lumbar drain; GOS — Glasgow Outcome Scale; NI — nosocomial infection; SAH — subarachnoid hemorrhage

Table 2. **The results of cerebrospinal fluid and inflammatory markers tests**

	CSF cytosis /3 mcl	CSF Glucose, Mmol/l	CSF Lactate, Mmol/l	C-reactive protein, mg/ml		PCT, ng/ml	Leukocytosis, mcl
NI-CNS+	1523.1±2122*	3.87±1.82*	5.47±3.01	84.0±64.9		0.66±0.96	11.7±3.7
NI-CNS-	130.8 ±268.2*	5.14±1.5*	3.78±1.14	87.4±70.3		3.7±4.7	14.4±6.7

Notes: * — significant differences (p<0.05). CNS — central nervous system; CRP — C-reactive protein; CSF — cerebrospinal fluid; NI — nosocomial infection; PCT — procalcitonin

When conducting a statistical analysis, the statistically significant risk factors for the development of NI CNS were the installed EVD and the fact of a neurosurgical operation (Table 1). According to the statistical analysis, statistically significant markers for the diagnosis of NI CNS were the level of cytosis and glucose of the cerebrospinal fluid (Table 2).

We obtained and analyzed 63 pairs of CSF/blood samples. As mentioned above, when describing the design of a study, a pair of blood/cerebrospinal fluid in combination with the clinical picture and data from additional studies was a separate variant of the clinical situation. Thus, there were a total of 63 variants, which were divided into 4 groups depending on the presence of NI CNS and systemic infection (Fig. 2, Table 3).

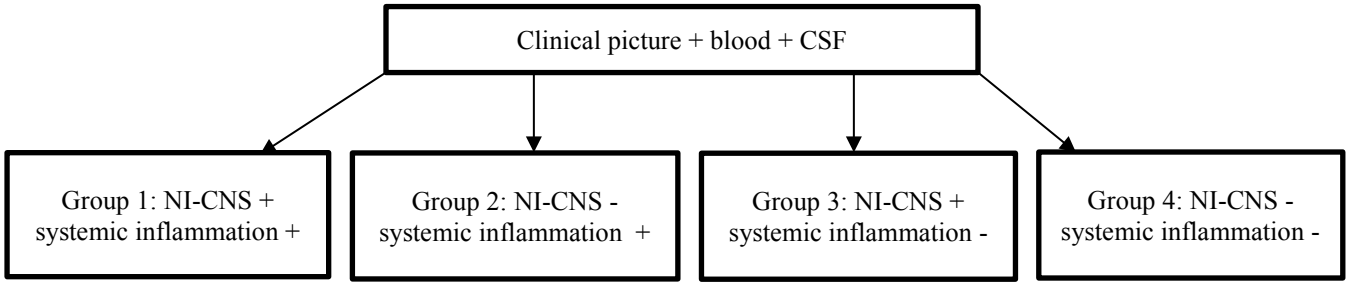

Fig. 2. The distribution of clinical situations

Notes: CNS — central nervous system; NI — nosocomial infection

Table 3. **The distribution of clinical situation according to presence or abscence of NI-CNS and sytemic infection.**

Systemic infection \ NI-CNS	Yes	No
Yes	36 (group 1)	14 (group 2)
No	33 (group 3)	3 (group 4)

Notes: CNS — central nervous system; NI — nosocomial infection

In the absence of NI CNS and systemic infection (group 4) in neuro intensive care patients, the presepsin level in the CSF was 406±203.1 pg/ml, which is statistically significantly higher (p<0.05) compared to the normal values (50–100 pg/ml) (Fig. 3). With the presence of NI CNS and the absence of a systemic infection (group 3), presepsin concentration in the CSF was 547.8±264.3 pg/ml. In the absence of NI CNS and the presence of systemic infection (group 2), the presepsin

level in the CSF was 614.9±315 pg/ml. With the presence of the CNS and systemic infection (group 1), the presepsin level in the CSF was 731.1±389.7 pg/ml. With the presence of NI CNS and the absence of a systemic infection, the presepsin level in the CSF was 2 times higher than in patients without NI CNS and systemic infection. Thus, the growth of presepsin in the CSF above 537 pg/ml in a neuro critical patients without a systemic infection meant the presence of NI CNS with sensitivity and specificity of 68.8% and 85.7%, respectively (Fig. 3).

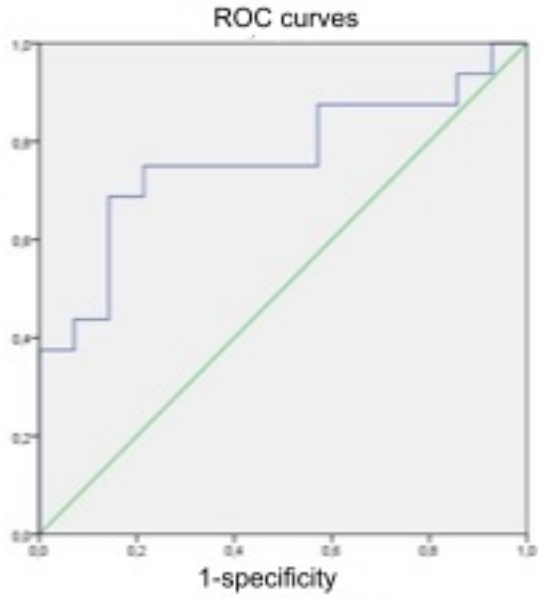

Fig. 3. Specificity and sensitivity of elevated PSP CSF in Group 3 and Group 4 (ROC analysis)

Based on the data obtained, CSF cytosis of 440/3 and higher with sensitivity and specificity of at least 95% and 90%, respectively, meant the presence of NI CNS (Fig. 4). The glucose content in the cerebrospinal fluid of 3.75 mmol/l and less meant the presence of NI CNS with a sensitivity and specificity of 35.3% and 17%, respectively (Fig. 5). The level of lactate in CSF 4.15 mmol/l and higher also meant the presence of NI CNS with a sensitivity and specificity of 70% and 67%, respectively (Fig. 6).

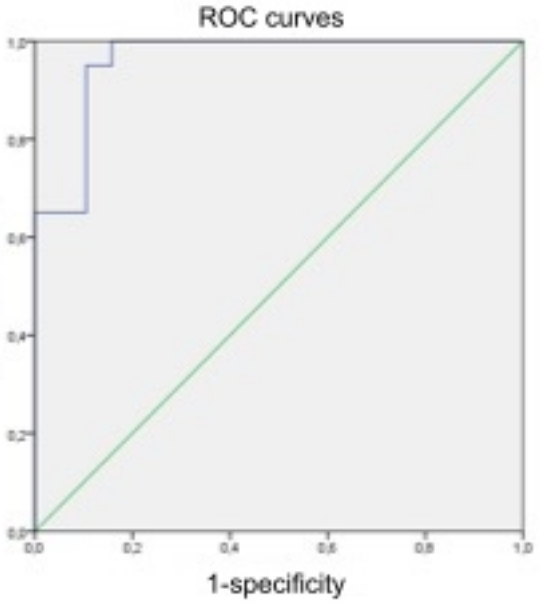

Fig. 4. Specificity and sensitivity of the cytosis level in Group 1 and Group 3 (ROC analysis)

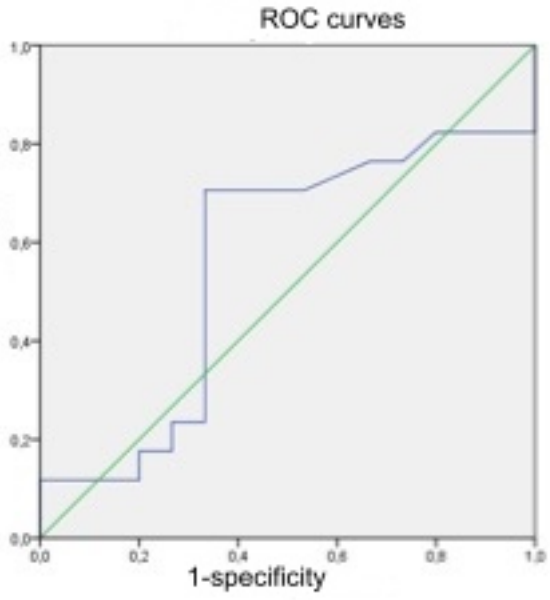

Fig. 5. Specificity and sensitivity of the CSF glucose level in Goup 1 and Group 3 (ROC-analysis)

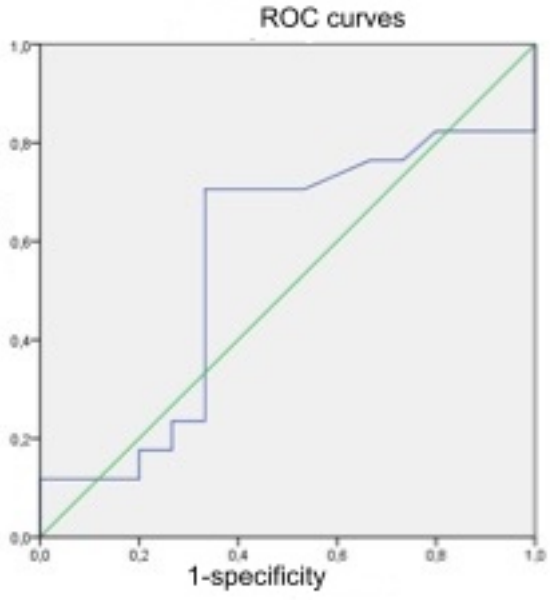

Fig. 6. Specificity and sensitivity of the CSF lactate level in Goup 1 and Group 3 (ROC-analysis)

The effect of blood in the cerebrospinal fluid on the level of presepsin was studied in group 2 and 3 (the absence of the NI CNS with the presence of systemic infection and the presence of NI CNS with the absence of systemic infection, respectively). A statistical analysis showed that the presence of blood in the cerebrospinal fluid didn't affect the level of presepsin in the CSF. For group 3, *Mann – Whitney U-test* was 0.776, and for group 2 , it was 0.699 (Fig. 7).

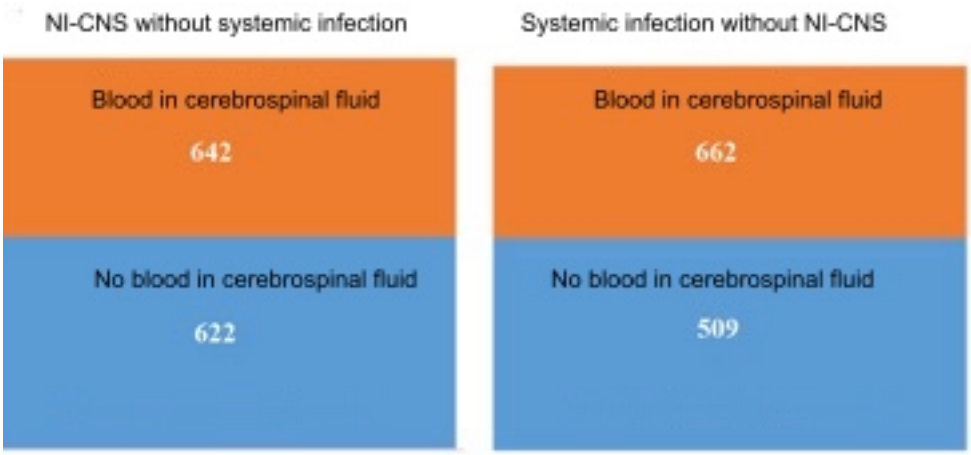

Fig. 7. The influence of CSF in blood on PSP in CSF in Group 3 (left) and Group 2 (right)

Notes: CNS — central nervous system; NI — nosocomial infection

DISCUSSION

In the available literature there are only isolated reports on the role of presepsin in the CSF for the diagnosis of CNS infection in newborns [38–39]. We did not manage to find studies that would study the level of presepsin in the cerebrospinal fluid in adults, both in normal conditions and in neurocritical pathology. At the same time, presepsin, which is the *CD* 14 macrophage receptor peptide, was successfully introduced into the routine practice of intensive therapy as a sufficiently sensitive and specific systemic marker of bacterial inflammation [32–37]. Presepsin plasma levels of less than 200 pg/ml indicate that the patient has no infectious complications. Presepsin secretion occurs by macrophages during phagocytosis. The function of macrophages in the central nervous system is performed by microbial cells, which activation occurs during infection of the central nervous system [44, 45]. This should probably increase the concentration of presepsin in the CSF, which can be used as a diagnostic marker.

It is first necessary to know the reference values to determine the diagnostic capabilities of any marker. In order to determine the normal values of presepsin in CSF, we investigated the cerebrospinal fluid in patients without neurological and neurosurgical pathology, which was taken during spinal anesthesia. We found that 50–100 pg/mg should be considered normal values for presepsin level in the CSF. The activation of microglial cells occurs not only with bacterial inflammation, but also with non-infectious damage to the CNS [46]. In this regard, we faced the problem of assessing how presepsin changes in CSF of neurocritical patients who had neither the NI CNS nor systemic infectious complications. It was found that presepsin in CSF in such situations was 406±203.1 pg/ml, which is statistically significantly higher compared with the normal level of presepsin in CSF in patients who do not have neurological and neurosurgical pathology. Thus, the non-infectious brain damage itself actually occurs to the growth of presepsin in the CSF also likely due to activation of the micro cells of glia. This should be taken into account when interpreting the level of presepsin in CSF in patients with suspected NI CNS.

With systemic infection, it is theoretically possible that the concentration of presepsin in the CSF will grow. We can assume two mechanisms for that. First, this increase occurs against the background of an increase in the concentration of presepsin in the blood. The second possible mechanism is the activation of microglia. It is known that in case of severe systemic infection, the involvement of the central nervous system occurs and the formation of so-called septic encephalopathy (SE) is possible [47–49]. The pathophysiological mechanisms of SE are leukoencephalopathy and periventricular leukomalacia [50, 51]. Obviously, this is accompanied by the activation of microglia and the synthesis of presepsin [52, 53]. Our data confirm this point of view. In the absence of NI CNS and presence of systemic infection (group 2), the presepsin level in CSF was 614.9±315 pg/ml, which was slightly higher than in the absence of NI CNS and systemic infection in neurocritical patients and statistically significantly higher than normal values.

The activation of microglia during infection of the central nervous system always occurs, and this response should hypothetically be more significant than in non-infectious lesions of the central nervous system or in neurocritical patients with systemic infection [54, 55]. Consequently, the level of presepsin of the cerebrospinal fluid in NI CNS should be hypothetically higher than with noninfectious CNS damage or systemic infection. However, according to our data, in patients with no NI CNS and no systemic infection (group 3), the concentration of presepsin in the CSF was 547.8±264.3 pg/ml. This level was statistically significantly lower than in the group of neurocritical patients without NI CNS, but with confirmed systemic infection. Thus, it is extremely important to analyze the clinical picture thoroughly while assessing presepsin and procalcitonin in plasma to exclude systemic infectious complications. An increase in the presepsin level in the CSF and the normal presepsin and procaltitonin in the plasma will definetely indicate the presence of NI CNS, while the situation where presepsin in the CSF and plasma and procalcitonin in plasma are increased will remain complex and require additional diagnostic markers for its verification. Indeed, according to our data, the highest level of presepsin in CSF was observed in patients with NI CNS and systemic infection (group 1), amounting to 731.1±389.7 pg/ml.

The diagnosis of CNS is an extremely relevant clinical task in neurologic intensive therapy, and the search for new sensitive and specific markers of CNS infection is an extremely relevant scientific goal. The classical clinical and diagnostic criteria of CNS are the presence of relevant clinical symptoms (cephalalgia, meningism, impaired consciousness, fever);

“Inflammatory” changes in cerebrospinal fluid (“three-digit” or more cytosis of CSF, consumption of CSF glucose less than 2.5 mmol/l or blood glucose/CSF ratio less than 0.4; lactate in CSF more than 2.1 mmol/l), increased values of systemic inflammation markers (leukocytosis, increased levels of C-reactive protein, procalcitonin, presepsin in the plasma) and/or detection of microorganisms by cytological tests, bacteriological tests, PCR or mass spectrometry. Most of the diagnostic criteria for CNS infection are not specific, especially in neuro-critical patients.

The values of systemic markers of inflammation in neurocritical patients increase both in systemic infections and in NI CNS. According to our data, C-reactive protein in the groups with the presence and absence of NI CNS were 84.0±64.9 mg/ml and 87.4±70.3 mg/ml, respectively, and were not statistically significantly different in both groups (p>0.05). The levels of procalcitonin in the groups with the presence or absence of NI CNI were 0.66±0.96 ng/ml and 3.7±4.7 ng/ml, respectively, and according to statistical analysis, they also did not statistically differ in both groups (p>0.05). The level of leukocytosis in the presence of NI CNS was 11.7±3.7x10^9/l, and 14.4±6.7x10^9/l in the absence of the NI CNS, the data did not differ statistically significantly in both groups (p>0.05).

The cytosis, glucose and lactate in the cerebrospinal fluid are the "golden standard" in the diagnosis of NI CNS despite the rather low sensitivity and specificity. According to our data, CSF cytosis in the NI CNS was 1,523±2,122 in 3 μl, which is statistically significantly higher (p <0.05) than in the group without NI CNS - 131±268 in 3 μl. Normally, CSF cytosis is only 3–15 per 3 μL, so it is extremely difficult to exclude NI CNS with “three-digit” CSF cytosis, which is often normal for neuro-critical patients due to the presence of blood in the CSF [56]. A *ROC* analysis showed that cytosis 440 in 3 μl and more indicates the presence of NI CNS in a neurocritical patient with a sensitivity of 95% and a specificity of 90%. According to our data, the level of glucose in cerebrospinal fluid in NI CNI was 3.87±1.82 mmol/l, which is statistically significantly lower (p <0.05) than in the group without NI CNS — 5.14±1.5 mmol/l. The *ROC*-analysis showed that the level of glucose of cerebrospinal fluid of 3.75 mmol/l and less means the presence of NI CNS in a neurocritical patient with a sensitivity of 35.3% and specificity of 17%. The level of lactate in the cerebrospinal fluid with the presence of NI CNS, according to our data, was 5.47±3.01 mmol/l and 3.78±1.14 mmol/l in the group without NI CNS. The differences were not statistically significant (p>0.05). A *ROC*- analysis showed that the level of lactate in the cerebrospinal fluid of 4.15 mmol/l and higher means the presence of NI CNS in a neurocritical patient with a sensitivity of 70% and a specificity of 67%.

The data obtained demonstrate a low sensitivity and specificity of standard diagnostic criteria for CNS infection. In this regar, the information obtained regarding the sensitivity and specificity of presepsin in CSF is of particular interest. The *ROC*-analysis showed that presepsin in the CSF 537 pg/ml and more in a neurocritical patient without a systemic infection means the presence of NI CNS with a sensitivity of 68.8% and a specificity of 85.7%. Thus, according to our data, CSF cytosis has the highest sensitivity and specificity for diagnosis of CNI, then the content of presepsin in the CSF, and glucose and lactate in the CSF.

The effect of blood in the cerebrospinal fluid on the indicators of markers used to diagnose the NI CNS is an extremely important issue. It has been repeatedly emphasized above that the presence of blood in the cerebrospinal fluid leads to the growth of cytosis and lactate in the cerebrospinal fluid, consumption of glucose in the cerebrospinal fluid, as well as to the appearance of fever and leukocytosis [57-60]. It was extremely important to study the effect of blood on the level of presepsin in CSF. Our data suggest that the presence of blood in the cerebrospinal fluid does not affect the level of presepsin in CSF.

When analyzing the data obtained, we studied the risk factors of NI CNS development. It was found that the risk of NI CNS after neurosurgical surgery was significantly higher (p<0.05) than in the group without surgical intervention. The risk of NI CNS development was statistically significantly higher (p<0.05) in patients with EVD. The duration of EVD presence was 8.6±3.1 days in the group with NI CNS, and 3.5±0.7 days in the group without NI CNS, which may indicate the importance intracranial devices in the development of NI CNS. With external lumbar drainage, the risk of NI CNS development in groups was not statistically significantly different. According to our data, the most significant risk factors for NI CNS development are the facts of surgical intervention and the presence of EVD.

The presented study has a number of advantages and limitations that need to be discussed. First, the work performed is the first in the world literature, which is studying the diagnostic possibilities of determining presepsin in CSF for verification of NI CNS in neurocritical patients of adult age. Second, the study included a relatively small absolute number of patients with suspected NI CNS, 19 observations in total. However, not every patient was analyzed individually, but a variant of the clinical situation, when every time a decision was made: is there a nosocomial infection of the central nervous system and a systemic infection in each specific period of time and with each collection of cerebrospinal fluid and blood. There were 63 such variants, which were subsequently divided into groups and analyzed. We used modern and adequate statistical methods, which made it possible to draw correct conclusions. Third, the study was single-center, but its design was prospective. We also consider it necessary to conduct further researches.

FINDINGS

1. The normal level of presepsin in spinal fluid is 50–100 pg/ml. Its increase to 537 pg/ml and higher in neurocritical patients without a systemic infection means the presence of a nosocomial infection of the central nervous system with a sensitivity of 68.8% and a specificity of 85.7%.

2. The presence of blood in the cerebrospinal fluid does not statistically significantly affect the concentration of presepsin in the cerebrospinal fluid.

3. When diagnosing nosocomial infections of the central nervous system presepsin cerebrospinal fluid should be additionally analyzed together with conventional markers of the central nervous system infections.

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Received on 02.10.2018

Accepted on 27.11.2018