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Abstract**A. V. Sokhan,***Kharkiv National Medical University, 4 Nauky ave., Kharkiv, 61000, Ukraine***CLINICAL AND LABORATORY CHARACTERISTICS OF ENTEROVIRAL MENINGITIS IN ADULTS**

The aim is to detect and characterize clinical symptoms and laboratory abnormalities in adult patients with enteroviral meningitis.

Materials and methods. 39 cases of enteroviral meningitis in adults were analyzed. The average age of the patients was 24.05 ± 0.91 years. Among them were 20 men and 19 women. The comparison group consisted of 12 patients without diseases of the central nervous system. We analyzed the clinical symptoms, indicators of complete blood count, clinical analysis of cerebrospinal fluid (CSF), as well as the level of neuron-specific enolase (NSE), lactate, LDG, cortisol, creatine kinase and cholinesterase in the CSF of patients at the time of admission and on 10–12 day of treatment.

Results. The disease is characterized by acute onset with fever, headache, photophobia, sore throat, cough, dyspeptic symptoms. Patients hospitalized at 3.33 ± 0.27 day of illness. Noteworthy is the absence or weak expression of meningeal signs in more than 76 % of cases. In the clinical analysis of the CSF we discovered two types of change – in 24 (61.54 %) cases dominated lymphocytes, while in 15 (38.46 %) predominated neutrophils. In the first day after admission CSF levels of creatinine kinase and lactate was significantly higher and levels of cortisol, cholinesterase and lactate dehydrogenase was significantly lower compared with the control group ($P < 0.05$).

Conclusions. Enteroviral meningitis is found mostly in young people. It is characterized by acute onset with typical symptoms of meningeal syndrome, but meningeal signs in most patients are mild (61.54 %) or negative (15.39 %). Clinical analysis of CSF is characterized by typical for aseptic meningitis changes, but in 38.46 % cases neutrophil level was above 50 %. In the acute phase there is a significant increased CSF level of cortisol, lactate, NSE, CK and decrease of LDH and cholinesterase, which can be used in differential diagnosis and evaluation of pathogenic disorders.

Keywords: enteroviral meningitis, clinical symptoms, cerebrospinal fluid analysis.

Corresponding author: antonsokhan@gmail.com**Резюме****А. В. Сохань,***Харківський національний медичний університет, проспект Науки 4, м. Харків, Україна, 61022***КЛІНІЧНІ ТА ЛАБОРАТОРНІ ОСОБЛИВОСТІ ЕНТЕРОВІРУСНИХ МЕНІНГІТІВ У ДОРОСЛИХ**

Мета роботи – оцінка особливостей клінічного перебігу та лабораторних змін у дорослих пацієнтів з ентеровірусним менінгітом.

Матеріали та методи. Були проаналізовані 39 випадків менінгіту ентеровірусної етіології у дорослих. Середній вік хворих склав $24,05 \pm 0,91$ років. Серед них 20 чоловіків і 19 жінок. У групу порівняння увійшли 12 пацієнтів без захворювань ЦНС. Проаналізовано клінічні симптоми захворювання, показники клінічного

аналізу крові, клінічний аналіз цереброспінальної рідини (ЦСР), а також рівні нейрон специфічної енолази, лактату, лактатдегідрогенази, кортизолу, креатинінкінази і холінестерази у ЦСР хворих на момент надходження до стаціонару та на 10–12 добу лікування.

Результати. Захворювання характеризувалося гострим початком з підвищення температури тіла, головного болю, фотофобії, болю у горлі, кашлю, диспепсичних симптомів. Пацієнти госпіталізувалися на $3,33 \pm 0,27$ день хвороби. Звертає на себе увагу відсутність або слабка вираженість менингеальних знаків в більш ніж 76 % випадків. У клінічному аналізі ЦСР, спостерігалися два види змін – у 24 (61,54 %) пацієнтів переважали лімфоцити, в той час як у 15 (38,46 %) переважали нейтрофіли. В гострому періоді у ЦСР визначені достеменно вищий у порівнянні з контрольною групою рівень лактату та креатинінкінази, та нижчі рівні кортизолу, холінестерази та лактатдегідрогенази ($P < 0,05$).

Висновки. Ентеровірусні менингіти зустрічаються в основному у молодих людей. Вони характеризується гострим початком з типовими для менингеального синдрому симптомів, однак менингеальні знаки у більшості пацієнтів негативні (15,39 %) або слабка виражені (61,54 %). Клінічний аналіз ЦСР характеризується типовим для асептичних менингітів змін, але в 38,46 % випадків рівень нейтрофілів був вищий 50 %. В гострому періоді спостерігається значне підвищення рівня кортизолу, лактату, NSE, креатинінкінази, і зниження активності ЛДГ та холінестерази, що може бути використано в диференційній діагностиці та оцінці патогенетичних порушень.

Ключові слова: ентеровірусний менингіт, клінічні симптоми, аналіз цереброспінальної рідини.

Резюме

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КЛИНИЧЕСКИЕ И ЛАБОРАТОРНЫЕ ОСОБЕННОСТИ ЭНТЕРОВИРУСНЫХ МЕНИНГИТОВ У ВЗРОСЛЫХ

Цель работы – оценка особенностей клинического течения и лабораторных изменений у взрослых пациентов с энтеровирусным менингитом.

Материалы и методы. Были проанализированы 39 случаев острого менингита энтеровирусной этиологии у взрослых. Средний возраст больных составил $24,05 \pm 0,91$ лет. Среди них 20 мужчин и 19 женщин. В группу сравнения вошли 12 пациентов без заболевания ЦНС. Проанализированы клинические симптомы заболевания, показатели клинического анализа крови, клинический анализ цереброспинальной жидкости (ЦСЖ), а также уровень нейтронов специфической енолазы (NSE), лактата, лактатдегидрогеназы, кортизола, креатининкиназы и холинэстеразы в ЦСЖ больных на момент поступления в стационар и на 10–12 сутки лечения.

Результаты. Заболевание характеризовалось острым началом с повышения температуры тела, головной боли, фотофобии, боли в горле, кашля, диспепсических симптомов. Пациенты госпитализировались на $3,33 \pm 0,27$ день болезни. Обращает на себя внимание отсутствие или слабая выраженность менингеальных знаков в более чем 76 % случаев. В клиническом анализе ЦСЖ, мы обнаружили два вида изменений: у 24 (61,54 %) пациентов преобладали лимфоциты, в то время как у 15 (38,46 %) преобладали нейтрофилы. В остром пе-



риоде в ЦСЖ определены достоверно высокие, по сравнению с контрольной группой, уровень лактата и креатининкиназы, и низкие уровни кортизола, холинэстеразы и лактатдегидрогеназы ($P < 0,05$).

Выводы. Энцефалиты встречаются в основном у молодых людей. Они характеризуются острым началом, с типичными для менингеального синдрома симптомами, однако менингеальные признаки у большинства пациентов отрицательные (15,39 %) или слабо выражены (61,54 %). Клинический анализ ЦСЖ характеризуется типичными для асептических менингитов изменениями, но в 38,46 % случаев уровень нейтрофилов был выше 50 %. В остром периоде наблюдается значительное повышение уровня кортизола, лактата, NSE, креатининкиназы, и снижение активности ЛДГ и холинэстеразы, что может быть использовано в дифференциальной диагностике и оценке патогенетических процессов.

Ключевые слова: энцефалит, клинические симптомы, анализ цереброспинальной жидкости.

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Introduction

Enteroviruses are the leading cause of aseptic meningitis, which is the most frequent central nervous system infection worldwide. Aseptic meningitis in children is the most commonly encountered serious illness associated with enteroviral infections, often appearing in the form of an outbreak [1–3]. In adults, enterovirus neuroinfections also expired, since they are most common. Enteroviruses are the most common cause of viral meningitis in Kharkiv region, accounting for 43.9 % of aseptic meningitis cases in which a causative agent has been identified [4]. In Ukraine, despite the high prevalence of enteroviral neuroinfections, research aimed at the description of the features of the clinical course and laboratory changes in these patients is not enough.

The present study **aimed** to detect and characterize clinical symptoms and laboratory abnormalities in adult patients with enteroviral meningitis.

Methods. Potential study participants were admitted in Kharkiv Regional Clinical Infectious Diseases Hospital (Kharkiv, Ukraine). The inclusion of patients in the research program conducted with the selection criteria. Inclusion criteria: clinical symptoms typical for acute meningitis, etiological confirmation of enteroviral etiology of disease by CSF PCR, age of patients 18 to 65 years, voluntary consent of the patient to participate in the study. Patients were excluded in the following cases: the presence of comorbidities, which can influence the clinical course and laboratory changes – HIV, Alzheimer's disease,

multiple sclerosis, hematological diseases, malignant neoplasms, etc.

At hospital admission, demographic data were obtained from study patients along with a number of clinical indices. Briefly, anamnesis of the disease complains and neurological status were recorded. Past medical history was obtained along with routine laboratory exams. All significant events up to hospital discharge or death were recorded. Detection of enteroviral RNA (Human enterovirus) in CSF performed by polymerase chain reaction (PCR), with hybridization-fluorescence detection method («AmpliSens® Enterovirus-FL», Russian Federation).

39 cases of enteroviral meningitis were analyzed. We have been analyzed clinical symptoms of the disease, indicators of complete blood count (CBC) test, clinical analysis of CSF, as well as the CSF levels of neuron specific enolase (NSE), lactate, lactate dehydrogenase (LDG), cortisol, creatine kinase (CK) and cholinesterase. The laboratory parameters of CSF that were used in this study are used to determine the severity of metabolic disorders and the degree of neuronal damage in bacterial neuroinfections and strokes [5, 6]. However, the diagnostic significance of these indicators for enteroviral neuroinfections is not clear.

As a comparison group 12 patients with acute respiratory infection and meningism were selected. Cerebrospinal fluid of patients was sampled only with diagnostic purposes, and the presence of CNS inflammatory processes has been excluded. Performing a lumbar puncture was in line with the



usual protocols of diagnostics and treatment of patients with meningeal signs. Patients involved in the study were not subjected to additional invasive procedures. The CSF samples were immediately frozen at -20°C until subsequent analysis. To determine level of metabolic, neurodegenerative and other pathogenic changes was identified level of CSF NSE, lactate, LDG, cortisol, CK and cholinesterase level on admission and after 10–12 days of treatment. Analysis of CSF NSE and cortisol level, was performed using an enzyme immunoassay based on the sandwich technique («Xema–Medica» Kit, Russian Federation); the level of LDG, total cholinesterase, CK, determined by the kinetic photometric method using a diagnostic kit «DAC–SpectroMed» company, Moldova; lactate was determined by an enzymatic calorimetric method («Olvex Diagnosticum», Russian Federation), in Central scientific research laboratory of Kharkov National Medical University. Work conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Kharkiv National Medical University, Kharkiv, Ukraine. All data were analyzed using «BioStat» and «Microsoft Excel» programs. Descriptive statistics, including mean, standard error of the mean were computed for all continuous variables. Frequencies and percentages

were determined for categorical variables. Normality was assessed for all continuous variables using the Kolmogorov–Smirnov test. An independent samples *t*-test was used when no violations of the normality assumption were observed. Otherwise, a Mann–Whitney test was used, as appropriate. P- value of < 0.05 was used for significance.

Results and discussion

39 cases of enteroviral meningitis were analyzed; the median age was 24.05 ± 0.91 years old. Among them – 20 men and 19 women. The results of the analysis of the clinical picture of enteroviral meningitis have shown that they are characterized by acute onset, with the increase body temperature to $37\text{--}38^{\circ}\text{C}$ (58.97 % of patients) or to $38\text{--}40^{\circ}\text{C}$ (41.02 % of patients), headache (100 %), sore throat (23.07 %), cough (17.95 %), dyspeptic symptoms are suddenly rare – diarrhea at 20.51 % and abdominal discomfort only in 23.07 % cases (Table 1). At 2–3 day of illness the patient's condition getting worse by increasing headache, photophobia, vomiting, due to which patients asked for medical help. On average, patients hospitalized at 3.33 ± 0.27 day of illness. On examination, attention is drawn to the absence or weak expression of meningeal signs in more than 76 % of such patients (Table 1).

Table 1 – Clinical symptoms and their frequency in patients with enteroviral meningitis at admission in hospital

<i>Symptoms</i>	<i>Enteroviral meningitis (n = 39)</i>
headache (n, %)	39 (100 %)
<i>increased body temperature</i>	
37–38°C (n, %)	23 (58.97 %)
38–39°C (n, %)	13 (33.33 %)
39–40°C (n, %)	3 (7.69 %)
<i>meningeal signs</i>	
negative (n, %)	6 (15.39 %)
mild severity (n, %)	24 (61.54 %)
moderate severity (n, %)	9 (23.07 %)
photophobia (n, %)	7 (17.95 %)
dizziness (n, %)	9 (23.08 %)
nausea (n, %)	29 (74.36 %)
vomiting (n, %)	27 (69.23 %)
diarrhea (n, %)	8 (20.51 %)
abdominal discomfort (n, %)	9 (23.07 %)
sore throat (n, %)	9 (23.07 %)
cough (n, %)	7 (17.95 %)
enlarged submandibular, neck lymph nodes (n, %)	3 (7.69 %)



After the start of the standard treatment, in accordance with the Ukrainian standards for the treatment of serous meningitis with sorbents, rheosorbilact, L-lysine, furosemide, ceftriaxone, magnesium sulfate, metoclopramidum, piracetam, vitamins B1 and B6, paracetamol – status of patients improved rapidly. The main symptoms like headache – disappeared after 3.95 ± 0.35 days of treatment, the body temperature returned to normal on 4.00 ± 0.58 day, meningeal symptoms disappeared after 2.67 ± 0.27 days. Complications were not observed, including the appearance of focal neurological symptoms. The duration of treatment in the hospital was 15.10 ± 0.45 days.

Only two patients had prolonged duration of the disease – the symptoms were observed for 5–7 days longer than usual.

Analyzing data of CBC test, it is clear that even in the first days of treatment in patients with enteroviral meningitis results of CBC are no different from the normal rate.

In the clinical analysis of the CSF, we have found two kinds of changes – some patients with predominated number of CSF lymphocytes ($n = 24$, 61.54 %), while others – neutrophils ($n = 15$, 38.46 %). For this indicator, the patients were divided into two groups (Table 2).

Table 2 – Clinical analysis of CSF parameters in patients with enteroviral meningitis depending on the level of lymphocytes in the course of the disease

CSF parameters	Enteroviral meningitis with CSF lymphocytes level higher than 50 % (n = 24)		Enteroviral meningitis with CSF lymphocytes level lower than 50 % (n = 15)	
	The first 24 hours after admission ($M \pm SE$)	On 10–12 day of treatment ($M \pm SE$)	The first 24 hours after admission ($M \pm SE$)	On 10–12 day of treatment ($M \pm SE$)
WBCs, $10^6 \cdot 1 \mu\text{L}$	187.70 ± 37.00^1	51.35 ± 13.47	309.53 ± 70.85^1	41.08 ± 7.92
Protein, g/l	0.51 ± 0.05	0.33 ± 0.06	0.54 ± 0.08	0.29 ± 0.03
Neutrophil, %	19.26 ± 2.43^1	4.53 ± 1.07	73.87 ± 3.11^1	5.63 ± 1.80
Lymphocyte, %	81.58 ± 2.50^1	96.00 ± 1.15	25.2 ± 3.2^1	90.08 ± 6.55
Glucose, mmol/l	3.10 ± 0.13^1	2.58 ± 0.12	2.77 ± 0.27^1	2.81 ± 0.15
Chloride, mmol/l	116.40 ± 1.98	114.23 ± 2.37	118.70 ± 2.77	111.46 ± 2.50

Remark: ¹ – a statistically significant difference between the results on groups of patients ($p < 0.05$); M – mean levels; SE – standard error.

In patients with a predominance of neutrophils was found significantly higher levels of CSF WBCs ($p < 0.05$). CSF analysis characterized by increased levels of WBCs up to $500 \cdot 10^6 \cdot 1 \mu\text{L}$, and increased level of protein to 0.5 g/l. Other parameters of the clinical analysis of the CSF remained within normal limits. At 10–12 days of treatment clinical indicators CSF analysis were normalized, but WBCs level was still elevated a little (Table 2). Comparing the clinical, laboratory, and other indicators we do not detect significant differences among patients with a predominance of CSF lymphocytes or neutrophils.

To determine the severity of metabolic disturbances and compensatory reactions in brain tissue and the diagnostic significance of some CSF parameters we determined the CSF levels of cortisol, lactate, LDH, CK, cholinesterase and NSE in the course of the disease.

In patients with enteroviral meningitis CSF cortisol level in the first 24 hours after admission was 46.23 ± 4.17 nmol/L, which was significantly lower than in control group – 69.26 ± 3.68 ($p < 0.05$). After 10–12 days of treatment CSF cortisol levels decrease to 30.26 ± 0.82 nmol/L ($p < 0.05$) (Table 3). The level of CSF lactate – 2.74 ± 0.70 mmol/L was significantly raised than in the control group 1.65 ± 0.29 mmol/L ($p < 0.05$), which together with a significantly low rate of LDH activity ($p < 0.05$) reflects the presence of a significant hypoxic disorders of brain tissue in patients with enteroviral meningitis in comparison with control group ($p < 0.05$). Even at 10–12 day of treatment in CSF of patients with meningitis saved a significant increased lactate levels ($p < 0.05$) (Table 3). Such changes show that, despite the improvement in the patient's condition and the disappearance of clinical symptoms, hypoxic changes persist, which subsequently causes the



formation of residual phenomena such as chronic headaches, asthenic syndrome, memory loss, etc.

It is proved that CK activity is increased in patients with meningitis [7, 8] our results show

significantly high levels of activity of CK in the first 24 hours of treatment in patients with enteroviral meningitis in comparison with the control group (Table 3).

Table 3 – The level of cortisol, lactate, LDG, CK, cholinesterase and NSE in CSF of patients with enteroviral meningitis in the first 24 hours after admission and on 10–12 day of treatment

CSF parameters	Enteroviral meningitis (n = 39)		Control group (n = 12)
	the first 24 hours after admission (M ± SE)	on 10–12 day of treatment (M ± SE)	the first 24 hours after admission (M ± SE)
Cortisol, nmol/L	46.23 ± 4.17 ^{1,2}	30.26 ± 0.82	69.26 ± 3.68
Lactate, mmol/L	2.74 ± 0.70 ²	2.20 ± 0.12 ²	1.65 ± 0.29
LDG, U/L	15.02 ± 3.6 ^{1,2}	23.79 ± 1.07	25.04 ± 2.32
CK, U/L	3.24 ± 0.52 ^{1,2}	4.45 ± 0.72	2.43 ± 0.61
cholinesterase, U/L	94.31 ± 8.77 ²	82.74 ± 7.32	147.16 ± 11.43
NSE, mcg/L	16.32 ± 0.36 ¹	11.65 ± 0.21 ¹	15.71 ± 0.47

Remark: ¹ – a statistically significant difference between the results on the first 24 hours after admission and on 10 – 12 day of treatment ($p < 0.05$); ² – a statistically significant difference with the control group ($p < 0.05$); M – mean levels; SE – standard error.

Cholinesterase involved in the transmission of nerve impulses. Suggest that the cholinesterase hydrolyzes acetylcholine at neuromuscular junctions and thereby protects them from excess of acetylcholine [9, 10]. In addition, the cholinesterase is able to carry out the hydrolysis of many toxic organophosphorus compounds [9, 10]. It is found that the introduction of animal recombinant human cholinesterase 100 % protects against lethal doses of organophosphorus compounds organophosphorus compound [10]. In our study we found a significant decrease in cholinesterase activity in patients with enteroviral meningitis when compared with the control group ($p < 0.001$) (Table 3). However, on the 10-th–12-th day of treatment, the level of cholinesterase also remained low, which, together with lactate, indicates longer – lasting metabolic changes and the violation of compensatory functions of CNS tissues compared

with the clinical symptoms of the disease (Table 3). The level of NSE in the first 24 hours of treatment was significantly increased in patients with meningitis – 16.32 ± 0.36 mcg/L and at 10–12 day of treatment the level of NSE significantly decrease – 11.65 ± 0.21 mcg/L ($p < 0.001$) (Table 3). A significant increase level of NSE in the acute period of the disease was unexpected for us, as it is proved that the level of NSE increases with neurons damage [11]. However, the patients we observed had no symptoms typical for encephalitis, such as focal neurological deficits or mental disorders. Such NSE indications confirm neuronal damage even in patients with mild meningitis. It can help to understand the mechanisms of formation of residual symptoms in survivors after meningitis, and to improve diagnostic and therapeutic methods including during the recovery period.

Conclusions

1. The results showed that enterovirus meningitis occurs mainly in young adults. It is characterized by acute onset with fever, severe headache, since 2–3 day of the disease photophobia, nausea and vomiting start. However meningeal symptoms in most patients, negative (15.39 %) or mild (61.54 %). Symptoms of dyspeptic syndrome found only in 23.07 % of cases.

2. Even in the first day of treatment in patients with enteroviral meningitis results of CBC are no different from the normal rate.

3. The clinical analysis of CSF characterized by typical for aseptic meningitis changes, but in 38.46 % neutrophil level was higher than 50 %.

4. In the first 24 hours after hospitalization identified a significant increase in levels of cortisol, lactate, NSE, CK, and decreased activity of LDH,



cholinesterase. That reflects the pathogenic disorders and CNS cell damage that develop in patients with enteroviral meningitis. These markers can be used in differential diagnosis and evaluation of pathogenic disorders.

5. On the 10–12th day of treatment, despite the

disappearance of clinical symptoms of the disease, CSF of patients with enterovirus meningitis retained an increased level of lactate and a decrease in cholinesterase activity, which indicates a prolonged metabolic disorders and damage to CNS cells, longer than clinical manifestations of the disease.

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