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Hepatic encephalopathy. Clinical case

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Abstract

Hepatic encephalopathy is a neuropsychiatric syndrome associated with abnormal liver function and portosystemic venous shunting. According to the West-Haven classification, depending on the degree of neurological disorders, there are minimal, I - IV stages of HE, which are characterized by a gradual progression of the disease. To date, the pathogenesis of HE is controversial.

Key words: hepatic encephalopathy; West Haven classification; liver cirrhosis; pathogenesis; neurotransmitters; ammonia; asterixis; clinical case.

Hepatic encephalopathy (HE) is a spectrum of potentially reversible neuropsychiatric disorders resulting from metabolic dysfunction caused by liver damage after excluding other causes of their occurrence [1, 2].

There are three types of hepatic encephalopathy: type A, associated with acute liver failure; type B, associated with the formation of a portosystemic shunt in absence of liver disease; and type C, associated with scarring and liver dysfunction due to chronic disease (cirrhosis) [3]. Hepatic encephalopathy develops most often in patients with liver cirrhosis (in 70% of cases).

In general, clinical symptoms for these different subtypes of hepatic encephalopathy are similar. However, acute liver failure is more associated with cerebral edema and increased intracranial pressure, which can potentially cause life-threatening complications.

The West Haven classification system is used in assessing HE severity [1]. As a rule, HE starts with mild symptoms in the form of minimal changes in memory, attention, intellectual function, mild coordination disorders, and sleep disturbances (the minimal grade of hepatic encephalopathy according to West Haven **[**1]). It progresses accompanied naturally by increasing severity of symptoms. In case of HE grade I according to West Haven **[**1**],**impairment of the ability to retain attention and a decrease in the volume of memorization, hypersomnia or insomnia, asthenia objectively reveals against the background of simple unawareness of the patient's condition. Grade II HE is characterized by gross cognitive deficits, apathy or lethargy, inappropriate behavior, personality changes, and often, unconnected speech [1]. At this stage of the disease, a characteristic tremor appears in the upper limbs in the form of slow flapping of the arms up and down when trying to stretch the arms forward, known as asterixis. In the most severe forms of HE, patients develop clearly marked confusion or disorientation, amnesia, occasional bouts of anger, incomprehensible speech (grade III HE according to the West Haven), or loss of consciousness (coma) with or without reaction to painful stimuli (grade IV HE). **[**1**].**

Exact mechanisms, underlying the development of hepatic encephalopathy in people with liver disease, are not fully understood. It is believed that high levels of substances produced during the breakdown of proteins, such as ammonia, when reaching the brain, damage the blood-brain barrier, astrocytes and neurons **[**5**].**

Dysfunction of the blood-brain barrier, which prevents negative substances from entering the brain, as well as dysfunction of astrocytes, regulating the blood-brain barrier and helping detoxify ammonia, play a certain role in the development of hepatic encephalopathy. Another

factor in HE development is a high level of aromatic amino acids (phenylalanine, tyrosine and tryptophan) in the plasma. With an increased permeability of the blood-brain barrier, they intensify influx into the brain; there is an imbalance in the synthesis of neurotransmitters. False neurotransmitters accumulate as well as short chain fatty acids. Inflammation; increased activity of GABA, an inhibitory neurotransmitter in the central nervous system add to HE development [6, 7**].**

At present, hepatic encephalopathy of minimal and I grades is considered "covert forms", while hepatic encephalopathy of II - IV grade - an "overt" form. **[**1, 4**].** In recent years, the researchers have been attracted by "covert forms" of HE, which respond most effectively to therapy and, if diagnosed in a timely manner, can prevent further progression of the disease. Prevalence of the minimal grade of HE is quite high (in 20–80% of patients). However, already at this stage, the patients' performance disrupts and their quality of life deteriorates **[**8-10**].** Moreover, in 5% - 25% of patients with a minimal grade of HE, an overt form develops within 5 years after the diagnosis of liver cirrhosis **[**11**].**

Next, we describe a clinical case of a patient whose hepatic encephalopathy developed against the background of chronic hepatitis C, and HE was not timely diagnosed. Patient K., 48 years old, was admitted to the neurological department of the Educational and Scientific Medical Center "University Clinic" KNMU on 04/09/2019 with complaints of head tremor, tremor of upper and lower extremities, increasing with physical, psycho-emotional stress, constant diffuse headache, unsteadiness when walking, loss of memory, attention and vision, general weakness, fatigue.

Medical history. According to the patient, she was diagnosed with hepatitis C virusin 2015. She underwent a course of treatment once, and did not go to the doctor again. In June 2018, the family began to notice that the patient became absent-minded, with frequent mood swings from apathy to irritability. A family doctor examined her and prescribed sedatives. In December 2018, complaints of persistent headache appeared, which periodically worsened. She treated herself, took ibuprofen, often without effect. In February 2019, she developed a finely sweeping tremor in the hands, unsteadiness when walking, and impaired attention. The patient consulted the family doctor and was diagnosed with chronic cerebral ischemia. From March 2019, the patient began to notice a decrease in vision, increased lethargy, difficulty remembering, slowness of thinking, disturbed sleep, she had difficulty falling asleep, frequently awakening at night. The

patient turned to the Educational and Scientific Medical Complex "University Clinic" KNMU where she was hospitalized for further examination and treatment.

Life history: the patient developed without any peculiarities in childhood. Physical and intellectual development was age appropriate. In 2015, she suffered from viral hepatitis C.

Somatic status: general condition is relatively satisfactory, the physique is correct, the skin is of normal color, clean, heart rate 68 beats / min, blood pressure 100/70 mm. Hg, muffled heart sounds, rhythmic, vesicular breathing over the lungs, the abdomen on palpation is soft, slightly painful in the right hypochondrium. There are no peripheral edema, stool and urination are unchanged, Pasternatsky's symptom is negative on both sides.

Neurological status: The patient is inhibited, answers the questions correctly but with a time delay. Oriented in space and personality. Emotionally labile, fixed. The face is hypomimic. Eye slits D=S. Pupils D=S. The movement of the eyeballs is limited to the sides, painful. Convergence is weak. Asymmetry of the facial muscles. Tongue in the midline. Muscle tone in the limbs is high according to the plastic type. Muscle strength is 5 points in all muscle groups. Tendon reflexes D≥S, increased. There are no sensitive violations. Ataxia in the Romberg position. Performs coordination tests with an overshoot on both sides. There is a finely sweeping tremor of the head and limbs, aggravated by static stress.

The patient underwent neuropsychological testing: a test onmemorizing 10 words according to Luria (result - direct reproduction of 5 words, delayed reproduction of 2 words).The number connection test was fully completed, without errors, execution time 80 sec, norm - <30 sec; attention test, using Schulte tables (execution time 74 sec, norm - <30 sec)); SDMT – Symbol-digital modalities test (30 symbols in 90 seconds, no errors); MoCA scale - 22 points out of 30 points (moderate cognitive impairment). Hospital Anxiety and Depression Scale (HADS) is 15 points (clinically significant anxiety / depression).

Laboratory screening revealed an increase in blood levels of total bilirubin - 29.1 μmol / L (N = 0 - 8.5 - 20.5 μmol / L), direct fraction of bilirubin - 8.9 μmol / L (N = 0.9 - 4.3 μmol / L), indirect bilirubin - 20.2 μmol / L (N = 6.4 - 17.1 μmol / L),ALT - 0.96 mmol / L (N = 0.1 - 0.66 mmol / L). AsAT - 0.59 mmol / L (N = 0.1 - 0.48 mmol / L), α-amylazi - 6.23 (1-5), ammonia - 35.34 μmol / L (N = 11.0-32.0 μmol / L), blood glucose - 6.6 mmol / L (N = 4.4 - 6.0 mmol / L). A blood test for viral hepatitis revealed an increase in the level of total antibodies to HCV hepatitis C (total antibodies) - 2.59 - positive (N = negative, control - 0.251) and normal values

for other types of hepatitis: HAV, Hepatitis A IgM - antibodies - 0.044 - negative (N = negative, control - 0.237); HBsAg Antigen, Hepatitis B - 0.072 - negative (N = negative, control - 0.161); HDV, Hepatitis D (total antibodies) - 2.3 - negative (N = negative, control - 1.08); HEV, hepatitis E, IgG - antibodies - 0.069 - negative (N = negative, control - 0.242).The indices of the blood coagulation system, INR, lipid metabolism, and thyroid status were within the reference values. Screening for Wilson's disease was also performed. Ceruloplasmin levels - 270 mg / l (N = 180-450 mg / l), copper in the blood were within the reference values. There was a slight increase in the 24-hour urinary copper excretion - 15.7 mmol / day (N = 2.36 - 10.99). Blood test result onpresence of antibodies in her blood to the human immunodeficiency virus and result of the test was NEGATIVE.

USG MAG and TKD - all vessels are passable, the direction of blood flow is physiological, velocity characteristics along the main arteries of the head and neck, as well as intracranial arteries are within the age norm.

The electroencephalogram showed slowdown of the alpha rhythm to 8.17 oscillations per minute in the occipital leads, an increase in the power of slow wave activity in the θ-range, appearance of single bilaterally synchronous flashes of "three-phase waves", mainly in the frontal-temporal leads in response to functional tests (hyperventilation). Paroxysmal activity is in the form of flashes of theta waves and alpha waves.

MRI of the brain revealed multiple foci, which produce hyperintense MR - a signal on T2 - and Flair, measuring up to 0.2 - 1.1 cm on a series of tomograms obtained subcortically and in the deep sections of the white matter of the frontal, temporal and parietal lobes. There was no limited diffusion detected. We determined a moderate expansion of the Virchow-Robin perivascular spaces. The median structures are not displaced. There are relatively symmetrical areas of increased MR - signal on T2 and Flair with fuzzy, uneven contours, spread along the pathways from the level of the hind thighs of the inner capsules, cerebral peduncles to the ventro-lateral parts of the brain pons with damage to the upper and partially middle pedicles (fig. 1, 2). The lateral ventricles are symmetrical, somewhat dilated. An additional cerebrospinal fluid cavity is between the lateral ventricles, up to 5.8 x 0.9 cm in size, without mass effect. The fourth ventricle is not changed. The subarachnoid space of the convexital surface of both hemispheres is not expanded, in the basal regions it is without features. The pontine-cerebellar angles are free. *Conclusion:*damage of internal capsules, peduncles, probably of a neurodegenerative nature.

Multiple foci of white matter gliosis of the brain according to the visual scale for assessing micro-angiopathy Fazekas I. Dysontogenetic Verga's cavity. Mild non-occlusive hydrocephalus.

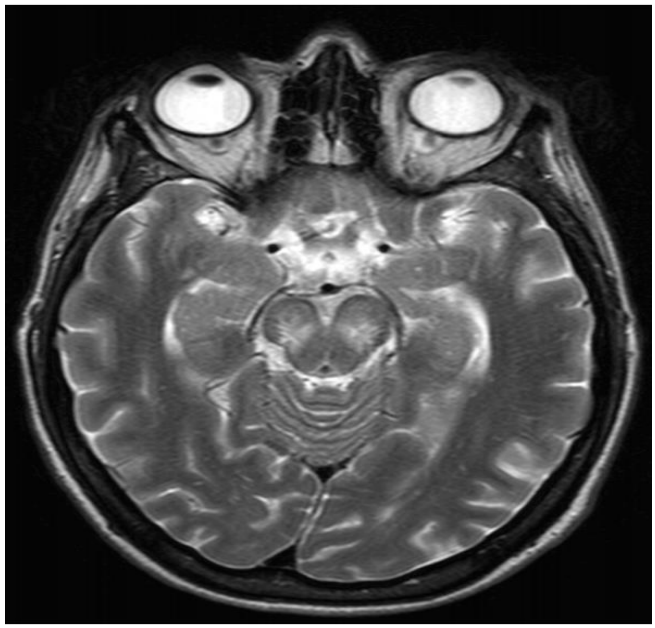

Fig. 1 – Axial view at the level of the midbrain. Hyperintensity on T2 FSE (a) and weak diffusion limitation (b - diffusion-weighted image and c - image of the measured diffusion coefficient) from the substantia nigra are determined.

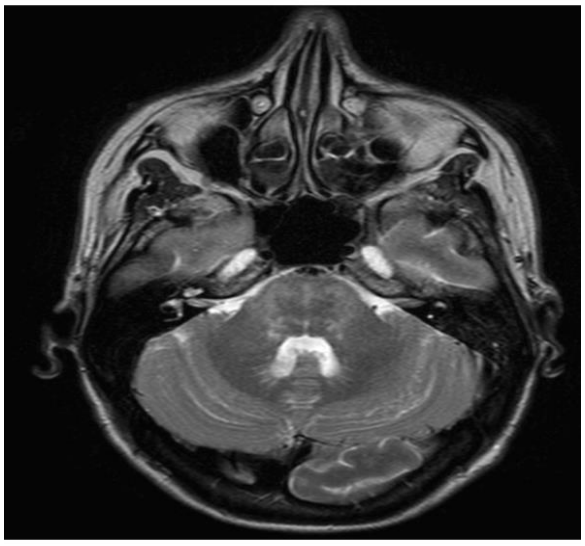

Fig. 2 – Axial view at the level of the pons. Hyperintensity on T2 FSE (a) and weak diffusion limitation (b - diffusion-weighted image and c - image of the measured diffusion coefficient) of the base with involvement of the corticospinal tracts and lateral parts of the pons was determined.

Ultrasound diagnostics of the abdominal cavity - *Conclusion*: ultrasound signs of chronic hepatitis, biliary dyskinesia. Pancreas, spleen, kidneys without pathology.

The patient was examined by a gastroenterologist with a diagnosis: Chronic viral hepatitis C, stage of moderate activity. By an ophthalmologist - signs of local intra-retinal edema in both eyes (OD> OS), neuro-dystrophic changes in the retina of both eyes with a dry type. No Kayser – Fleischer rings were found in the Descemet membrane of the cornea of both eyes. Psychiatric diagnosis: recurrent depression F 32.1.

Based on the presence of objective cognitive, motor, behavioral disorders, the results of neuropsychological testing, anamnesis data (viral hepatitis C since 2015), laboratory and instrumental examination, the patient was diagnosed with chronic viral hepatitis C, stage of moderate activity. Grade I hepatic encephalopathy with cognitive, motor impairments and depressive syndrome. The patient received the following treatment in the hospital: Glutargin (ARGININUM) 10 ml (2 g) intravenous drip 1 time a day for 150-250 ml of isotonic sodium chloride solution for 10 days, then 0.75 mg 3 times a day for 8 days, lactulose in syrup, 25 ml every 12 hours for 4 days, later - 20 ml every 12 hours for 4 days. Then 15 ml every 12 hours for 10 days under the control of the frequency of bowel movements (2-3 bowel movements per day) **[**1**]** , Alpha normix (rifaximin) 200 mg every 8 hours for 18 days [1, 12**].**

After the treatment, tremors of the head, arms and trunk reduced. The results of neuropsychological testing: test for memorizing 10 words according to Luria (result - direct reproduction of 8 words, delayed reproduction of 5 words). Communication test numbers (the test was completed completely, without errors, execution time 51 sec, norm - <30 sec); SDMT (47 symbols in 90 seconds, no errors); MoCA scale - 25 points out of 30 points (moderate cognitive impairment); Hospital Anxiety and Depression Scale (HADS) - 9 points (clinically significant anxiety / depression). The patient was discharged from the hospital with the following recommendations: supervision by a neuropathologist, gastroenterologist, therapist, ophthalmologist; continue the course of treatment with Glutargin (ARGININUM) 0.75 mg 3 times a day and lactulose 15 ml every 12 under the control of the frequency of bowel movements (2-3 bowel movements per day).

Discussion. The patient's complaints, data from neurological examination and neuropsychological testing indicated the presence of cognitive, psycho-emotional, and motor disorders. The data of neuroimaging examination confirmed multiple focal lesions of the

subcortical-brainstem structures in the brain of a neurodegenerative nature, which coincided with clinical data. Localization of lesions (internal capsules, peduncles) and the lack of data on cerebral hemodynamic disturbances according to the data of ultrasound diagnostics of cerebral vessels made it possible to doubt the diagnosis of chronic cerebral ischemia as the cause of the disease. At the same time, the data in the anamnesis on chronic hepatitis C, confirmed by the laboratory examination, gave reason to think about the damage to the nervous system associated with liver pathology.

Taking into account the probable relationship between hepatic and neurological pathology, we made a differential diagnosis with Wilson's disease (WD), according to Modern Guidelines AASLD, EASL and ESPGHAN **[**13-16**].** An algorithmic approach to the diagnosis of WD is based on the presence or absence of Kaiser-Fleischer KF rings, hepato-splenomegaly, neurological symptoms, serum ceruloplasmin level, presence or absence of Coombs negative hemolytic anemia. It also considers quantitative determination of copper in the liver, urinary copper excretion within 24 hours (spontaneous or after provocation with penicillamine), liver biopsy for quantitative determination of copper and analysis of ATP7B mutations. **[**13-16**].** Taking into account the fact that no specific clinical and laboratory marker of WD was identified in the patient, we excluded WD and considered it inappropriate to conduct further biopsy and genetic testing.

The next step was to assess the likelihood of the patient having HE, given that she was not diagnosed with liver cirrhosis or portosystemic shunting.

The following evidenced in favor of HE: anamnesis (the patient has been suffering from chronic viral hepatitis C for 4 years and practically did not receive treatment during this period. Present clinical symptoms (impaired sleep, intellectual status (impaired executive function, attention, visual-spatial abilities, memory function and a decrease in the speed of cognitive processing according to test results) supported the evidence. The patient's motor function was disturbed (impaired fine motor skills, tremors), she had behavioral disorders (recurrent depression F 32.1). Laboratory screening data (hyperammonemia, hyperenzymemia, hyperbilirubinemia (impaired liver function with accumulation of ammonia), the presence in the blood of an increased amount of total antibodies to the hepatitis C virus, impaired liver parenchyma structure according to ultrasound data)confirmed HE. The diagnosis was also confirmed by electroencephalography and magnetic resonance imaging **[**2, 8, 17**].**

It is a known fact that an increase in the level of ammonia with the realization of its toxic effect on brain cells can be found in other diseases, such as the Reye's syndrome and some metabolic disorders.

The Reye's syndrome (acute non-inflammatory encephalopathy) is a dangerous disease that in most cases affects children and adolescents under 14 years of age. A syndrome occurs after taking antipyretic drugs based on acetylsalicylic acid. It develops, as a rule, against the background of viral and other diseases (measles, chickenpox, hepatitis, influenza and others) **[**18]**,** and is accompanied by three or more times an increase in the levels of serum glutamine oxaloacetic transaminase (SGOT), serum ammonia, hyperenzymemia, hyperbilirubinemia, impaired coagulation system, increased amylase and lipase levels, and decreased serum bicarbonate **[**18-20**].** Despite similar changes in laboratory data (increased levels of total bilirubin - 29.1 μmol / L, direct fraction of bilirubin - 8.9 μmol / L, indirect bilirubin - 20.2 μmol / L, ALT - 0.96 mmol / L, AsAT - 0.59 mmol / L, α-amylazi - 6.23, ammonia - 35.34 μmol / L), we excluded the Reye's syndrome in the patient due to inconsistency of the clinical picture. It included acute onset, persistent vomiting, seizures, delirium, impaired consciousness, irritability, instability of the emotional state **[**18, 21**].** There wasno connection with a viral infection or reception of salicylates.

We also considered metabolic and toxic variants of encephalopathies, such as diabetic, uremic, alcoholic.

Liver diseases (cirrhosis of the liver) can often be associated with the development of diabetes (hepatogenic diabetes). It can aggravate brain damage and lead to the development of metabolic encephalopathy [22, 23]. Although these two diseases (cirrhosis and diabetes) generally have different initiating factors, they can exhibit synergism, negatively affecting the structural and functional state of brain cells **[**24**].** Several studies have shown that an increased risk of diabetes in patients with liver disease is associated with a genetic predisposition to elevated levels of circulating aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are markers of liver dysfunction [25, 26]. On the other hand, diabetes mellitus due to insulin resistance and obesity is closely associated with fatty liver disease, which can progress to the development of cirrhosis **[**27].

In the given clinical case, the patient had mild hyperglecaemia. For differential diagnosis, we assessed the glycemic profile (fasting glycemia - 6.0 mmol / L, after meals - 4.8 mmol / L),

glycated hemoglobin level (Hbs1c) - 5.6%, (N - <6.0%), the level of C-peptide - 2.7 ng / ml (N - 0.5 - 3.2 ng / ml). This made it possible to exclude disruption of carbohydrate metabolism, the diagnosis of diabetes and development of metabolic (diabetic) encephalopathy.

Hyperammonemia can also occur with alcohol-induced toxic encephalopathy. The Gaie-Wernicke encephalopathy (acute form) is manifested by muscle hypertonia, multiple neuropathies of different localization, oculomotor disorders, autonomic disorders **[**28**].** The Korsakovsky's psychosis is characterized by memory impairment with retrograde and fixation amnesia, speech retardation, and motor reactions **[**29**].** Alcohol pseudoparalysismanifests itself with the development of dementia, euphoria, adequate perception of reality, loss of knowledge and skills. We did not confirm these clinical signs, nor anamnestic data on alcohol abuse in the patient. Consequently, we excluded alcoholic encephalopathy.

Thus, the final diagnosis should be chronic viral hepatitis C, at the stage of moderate activity. Grade I hepatic encephalopathy with cognitive, motor impairment and depressive syndrome. It should be notedthat there is a clinical and neuropsychological discrepancy in the degree of HE in this clinical case.According to the West Haven classification **[**1, 4**],** the patient's clinical picture corresponds to grade I HE. However, the results of neuropsychometric testing confirm presence of HE grade II. In our opinion, this may indicate that cognitive deficit in HE is not only an obligate part of the clinical picture of the disease, but also its early component. This can be explained by a network of synaptic connections in the structures of cognitive support (prefrontal cortex, hippocampus, mediobasal parts of the temporal lobes, thalamus, reticular formation, etc.) with other parts of the brain, as well as multi-focal lesions of the brain matter in HE. On the other hand, our data confirm the importance of neuropsychometric testing, especially at the minimal grade of HE, for early diagnosis of the disease and timely prescription of specific therapy.

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