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Diagnosis and treatment of hepatic encephalopathy

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Background. Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver cirrhosis which symptoms may vary from imperceptible to severe ones. In recent years, there have been some changes of fundamental hepatic encephalopathy pathogenesis and treatment. The early HE on the stage of minimal hepatic encephalopathy (MHE) is rarely diagnosed and treatable condition worldwide and in Lithuania as well, however, this HE stage is responsible for the cognitive disorders which impair the quality of life of cirrhotic patients. According to resent data, MHE can be diagnosed in up to 70% of cirrhotic patients.

Aim. To evaluate new diagnostic and treatment strategies for HE and especially MHE for further use in clinical practice to cure the quality of life of cirrhotic patients and prevent clinical manifestation of HE.

Methods and materials. This article is based on relevant original publications and reviews in English (1991–2012) that were retrieved by a selective key word based search in the Medline and PubMed databases.

Results. It is recommended not to decrease an amount of proteins in food and consume products containing more branched-chain amino acids. Non-absorbable disaccharides (lactulose) are still the drugs of the first choice, though recent data show significant concerns about their effectiveness. Rifaximin is increasingly used all over the world for hepatic encephalopathy treatment. Other drugs for HE treatment are of secondary importance. Lactulose, probiotics are recommended for minimal hepatic encephalopathy treatment.

Diagnosis, especially of minimal hepatic encephalopathy, remains complicated. There are no reliable and validated blood indicators to establish minimal hepatic encephalopathy diagnosis, and to follow up treatment efficacy. Psychometric and neurophysiologic methods, visualisation methods are used more in scientific researches. Computerized methods, such as inhibitory control and critical flicker frequency tests, are also promising.

Conclusions. Further studies are necessary to design proper algorithms of hepatic encephalopathy diagnostic and treatment.

Key words: hepatic encephalopathy, minimal hepatic encephalopathy, diagnosis, treatment

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INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver cirrhosis which symptoms may vary from imperceptible to severe, invaliding, and even lethal ones. Minimal hepatic encephalopathy (MHE) is also important because it impairs patients' cognitive functions and quality of life (1, 2).

Clinically manifested hepatic encephalopathy (HE) diagnosis is based on the clinical state of the patient. To evaluate its severity, West-Haven's criteria (Table) accepted in 1977 and the Glasgow Coma Scale are most widely used. Diagnostics of 1–2 degree HE according to these criteria is very subjective. West-Haven's criteria may be interpreted differently by different researchers and may have negative influence on the results of multicenter studies.

MHE has no symptoms and may be diagnosed only by using neuropsychometric or neurophysiologic methods.

Despite HE in our country is diagnosed using West-Haven criteria, the initial stage of HE, MHE, is neither diagnosed nor treated worldwide and in Lithuania as well, although it is found in more than 70% of cirrhotic patients and appreciably impairs the quality of life of such subjects. That is why we conducted a review of resent achievements in diagnosis and treatment tools for both HE and MHE with further implication of them in clinical practice for the cure of the quality of life of cirrhotic patients and for prevention of clinical manifestation of HE.

There are a few types of neuropsychometric tests – "paper-pencil" tests, which do not need any special provisions and computerized tests. They help to evaluate patient's concentration, reaction speed, ability to suspend a response to stimulus and visio-spatial functioning.

The "golden standard" for diagnosis of MHE is the PHES (Psychometric Hepatic Encephalopathy Score) battery (3). It is a set of subtests such as the number connection test A, number connection test B, digit symbol test, line tracing test, serial dotting test. MHE is proved if deviation from the normative standard is >2 SD in two or more tests. PHES tests battery is validated for populations in Germany, Italy and Spain. In the USA this battery is not validated, and another set of psychometric tests, namely, RBANS (Repeatable Battery for the Assessment of Neurological Status), is used. It takes as long as PHES – about 20–25 min. The assessment of results is complicated in both sets. Results depend on the education and age of the patient.

One of the most popular computerized psychometric tests is the Inhibition Control Test, where

Table. West Haven's criteria (adapted from Mulen KD. *Aliment Pharmacol Ther.* 2007; 25 Suppl 1: 11–16)

Grade	Criteria
Grade 0	Lack of detectable changes in a personality or behaviour No asterixis
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition Asterixis may be present
Grade 2	Lethargy or apathy Minimal disorientation for time or place Inappropriate behaviour Subtle personality changes Inappropriate behaviour, slurred speech Impaired performance of subtraction
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation Asterixis is usually absent
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

concentration and ability to suppress response to stimulus is assessed (4). The patients follow changing letters on the computer screen and have to react when a certain sequence of letters appears, and ignore the combination of letters which is similar to it. If there are 5 mistakes from 40 attempts, MHE might be diagnosed. The test is sensitive (5, 6) and is commonly used in the USA.

Another computerized test, popular in Great Britain, is the CDR (Cognitive Drug Research) test. It helps to evaluate the ability to keep concentration, quality of short- and long-term memory and speed. CDR test has a high correlation with psychometric tests, though it is appropriate for MHE diagnostic, unfortunately, takes a long time.

Neurophysiologic exploratory methods of HE are also available. One of them is the critical flickering frequency test characterized by high sensitivity, specificity, and high correlation with psychometric tests. It is widely used in clinical trials. This test is based on the fact that retinal glial cells in patients with HE undergo similar changes (swelling, termed hepatic retinopathy) to those seen in cerebral glial cells. Patients watch the decreasing frequency light pulses and fix when they start to see them as discrete ones. MHE is diagnosed if a critical flicker frequency is below 39 Hz. The benefit of this test is that results are not influenced by patient's sex, education, and operating skills. Only age can have a partial influence. A critical flickering frequency test is quick and cost effective, fairly sensitive and specific for MHE diagnostics (7–9).

Electroencephalogram (EEG) is not very specific for HE diagnosis. The most sensitive of all EEG is EEG with computerized data analysis. P300 induced potentials test may be valuable for MHE diagnostics, though both EEG and the latter test require specially prepared personnel and equipment, therefore cannot be used widely in ambulatory environment (10).

Neurovisualization tests are magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). They are not valuable for MHE diagnostics and useful, maybe, only for treatment evaluation (e. g., medical treatment or after liver transplantation) (11–13).

Using MRI, T1 weighted imaging hyperintensive signals because of manganese accumulation in basal ganglions are seen not only for patients with liver cirrhosis, but also for patients with non cirrhotic portal hypertension. This intensity has no correlation with a degree of HE severity.

MRS shows intensification of glutamine and glutamate signals, and decreases intensity of myoinositol and choline signals (because of homeostatic compensative mechanisms) (14). MRS does not help to diagnose MHE.

Other MRI methods, such as magnetization transfer ratio (MTR), fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI), improved diagnostics of cerebral oedema associated with HE. A regression of brain changes after liver transplantation was detected using these methods.

Laboratory tests are not very valuable for HE diagnostics yet. There is no correlation between concentration of ammonia in the blood and severity of C type HE, as against that in case of A type HE (15). Estimation of ammonia in the arterial blood is more precise for HE diagnosis than in venous one, though following of dynamic concentration changes is necessary. There are small studies showing usefulness of laboratory markers such as cGMP (16, 17), IL (IL-6, IL-18) (18) for diagnosis of MHE in cirrhotic patients, though more detailed clinical trials are necessary.

HE TREATMENT

The main aim of HE treatment is to eliminate all factors which had provoked it and to administer a proper empiric therapy. Following these principles, the condition of most patients improves within 24–48 hours of treatment initiation. If HE still persists, it is recommended to re-estimate the diagnosis of HE and to correct missed precipitating factors. If there is ascites, it is necessary to perform diagnostic paracentesis. A short course of antibiotics is recommended for severely affected patients with hepatic coma while waiting for bacterial culture growth results.

It is recommended to avoid sedatives, especially benzodiazepines. If the patient is very agitated, haloperidol might be prescribed.

Diet recommendations for patients with HE

In the twentieth century all patients with cirrhosis and HE were recommended to follow low protein diet. In recent years this point of view has cardinally changed.

For 20–60% of patients with liver diseases nutritional insufficiency was diagnosed (19). Particular attention was paid on protein insufficiency, which can occur in different stages of liver diseases, though more often in later ones. Insufficient nutrition has negative effect on both short- and long-term survival of patients with acute or chronic liver diseases (20), also it is related to higher incidence of bleeding during operation, and higher mortality rate. These patients are treated longer in ICU after operation and their treatment costs are higher (21).

In 2003, Cochrane community published conclusions, which were based on high quality clinical trials that there are no significant evidences about positive effects of branched-chain amino acids on symptoms of HE. However, an assessment of different quality trials showed efficacy of branched-chain amino acids for treatment of HE. It was recommended to continue research in this field with larger groups of patients and extend the duration of trials (22). In 2003 Marchesini and in 2005 Muto had conducted two large randomized controlled clinical trials. The results showed that branched-chain amino acids have a positive influence on patients' condition and survival. Muto et al. ascertained that additional supplementation of diet with preparations of branched-chain amino acids had statistically significant effects on the increase of albumin concentration in the blood, improvement of the quality of life, decrease of the mortality rate, the decreased rate of bleeding from oesophageal varicose veins, and reduction in the development of hepatocellular carcinoma (23). Marchesini et al. also described a positive effect of preparations of branched-chain amino acids on patients' survival rate, nutritional state and biochemical indices, Child-Pugh functional class and shortening of hospitalization rate, though a significant effect on HE was not observed (24). The use of branched-chain amino acids is also limited by an unpleasant taste and high costs of preparation.

According to 2006 guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN), patients with liver cirrhosis have to consume not less than 1.2 g/kg proteins per day. It is also recommended to supply diet of HE patients with preparations of branched-chain amino acids (level of evidence A). In advanced liver cirrhosis such diet improves clinical outcomes (level of evidence B) (25). It is very important to take enough proteins with food and to keep a lean body for effective neutralizing of the increased concentration of ammonia in the blood. A replacement of meat-based proteins with plant-based ones and following of "vegetable diet" (sometimes supplemented with milk and cheese) are recommended. Long-term restriction of protein intake is indefensible both for clinically significant persistent HE and minimal impairment of cognitive functions (26). Short-term protein reduction in food is permissible only in case of episodic severe clinical encephalopathy.

If patients are so constrained that they cannot even safely swallow drugs, both medicines and food may be administered via a nasogastric tube. Varicose nods in oesophagus are not contraindication for nasogastric tube insertion.

PHARMACOLOGICAL THERAPY OF HE

Non-absorbable disaccharides (lactulose)

The main target of HE treatment is the intestine where majority of ammonia is synthesized and absorbed. Non-absorbable disaccharides – lactulose and lactilol – have been widely used for HE treatment since 1970s. Lactic acid (the metabolism product of lactulose) acidifies the content of the intestine, changes a complex of intestinal bacteria, therefore *Lactobacillus* strain becomes predominant and ammonia producing bacteria are inhibited. Non-absorbable disaccharides also accelerate bowel passage.

Lactulose is used depending on the consciousness of patients. If a patient is comatose or unresponsive, lactulose is administered via a nasogastric tube 30 ml/2–4 hours, or rectally through enemas (300 ml lactulose with 700 ml water) every 4 hours depending on response. Doses *per os* are individual. Patients should pass stool 2–3 times per day, otherwise disbalance of electrolytes, dehydration, hypovolemia and worsening of HE symptoms may occur. Some patients do not tolerate this preparation because of meteorism, spastic abdominal pain, and unpleasant taste.

In 2004 Cochrane community conducted a systemic overview of clinical trials where non-absorbable disaccharides were administered for HE treatment. While some small clinical trials approved effectiveness of non-absorbable disaccharides, metaanalysis showed that in high quality clinical

trials lactulose was as effective as placebo. In trials where lactulose was compared with antibiotics (neomycin, rifaximin), clinical effect of antibiotics was preeminent (27). However, there is no better choice, so far, and according to a long lasting clinical experience of lactulose administration worldwide non-absorbable disaccharides remain the first-choice medicines for HE treatment (28). In INASL consensus (2010) on MHE, lactulose is recommended as a medicine which improves psychometric indices and quality of life (evidence level 1b). The recommended dose of lactulose is 30–60 ml 2–3 times per day for 3–6 months (A, 1b) (10).

Antibiotics

For a long time antibiotics (neomycin, metronidazole, quinolones, and oral vancomycin) were considered to be the second-choice medicines for HE treatment when lactulose is not effective or a patient does not tolerate it. However, in recent years this point of view is changing.

Neomycin is one of the first antibiotics administered for treatment of HE. Although FDA approved neomycin only for treatment of acute HE (dose *per os* 1–3 g/6 hours for 6 days), but it is also administered for treatment of chronic HE (0.5–1.0 g/12 hours). Neomycin suppresses glutaminase in the wall of the intestine and synthesis of ammonia is reduced. It also inhibits urea producing bacteria. However, its wider clinical use is limited due to nephrotoxicity and ototoxicity. Long-term use of other antibiotics also has side effects. Metronidazole, which has a similar HE treatment efficacy as neomycin, causes peripheral neuropathies, intestinal disorders and dizziness (29, 30). Vancomycin has better tolerance profile, but resistance of bacteria is of concern. Rifaximin received FDA approval for treatment of HE in March 2010 (at an oral dose of 550 mg twice daily). This antibiotic has a minimal absorption in the intestine, very few side effects, and has no interaction with other medicines.

In 2010 Bass et al. published the results of an international randomized double-blind placebo controlled clinical trial. It was conducted to evaluate the efficacy of rifaximin for prevention of HE recurrences. For one group of patients rifaximin was administered twice daily, and for other group placebo was administered. The patients were followed up for 6 months. Lactulose was given to 91% of patients in both groups. Recurrences were observed more often in the placebo group compared with the rifaximin group (46% and 22%, respectively, $P < 0.001$). The patients treated with the antibiotic were also less often hospitalized because of HE compared with the placebo group (14% and 23%, respectively, $P = 0.01$). However, in the rifaximin group, solitary cases of colitis caused by *Clostridium difficile* were diagnosed (31, 32).

The question of long-term use of antibiotics and related bacteria resistance remains unresolved (33). Some authors recommend taking the medicine continuously with one week break per month. Rifaximin causes peripheral oedemas and nausea. Also it is an expensive preparation (lactulose 30 ml × 4 is 2.2 $ vs rifaximin 400 mg × 3 – 18.42 $). Its cost effectiveness requires more detailed clinical research to evaluate and antibiotics are recommended. According to the results of a retrospective review of Mantry et al., hospitalization rate and duration decrease when rifaximin and lactulose are administered (34). Rifaximin improves psychometric test performance scores, health-related quality of life (35), driving performance in patients with MHE (36).

Results of meta-analysis revealed that rifaximin is as effective as other conventional oral HE treatment with better safety profile (37). It should be administrated for patients, who do not tolerate dissacharides or treatment is unsuccessful.

Probiotics

Using of probiotics changes the composition of intestinal bacteria (the proportion between urease producing and not producing bacteria changes) (38). Results of meta-analysis and systemic review show that administration of probiotics or synbiotics is effective for hepatic encephalopathy treatment (39, 40). MHE regresses, concentration of ammonia in the blood decreases, patients perform psychometric tests better, clinically expressed HE occurs less often as compared with patients who did not get this treatment (41–44). According to the consensus of INASL on MHE, probiotics not only decrease endotoxemia, but also improve the functional indices of the liver, psychometric tests results, and quality of life (1b) (10). Probiotics are well tolerated. The question of probiotics safety remains unresolved. Cirrhotic patients are considered being immunosuppressed therefore the administration of live bacteria preparation for these

patients is negotiable. A dose of probiotics also remains unclear. Prospective randomized controlled dose related clinical trials to evaluate effective doses are required (5, D) (10).

L-ornithine-L-aspartate

Preparations of L-ornithine-L-aspartate (LOLA) promote metabolism of ammonia, decrease its plasma concentration and symptoms of HE.

Ornithine and aspartate are the main substrata for synthesis of urea and glutamine in the liver and muscles (45, 46).

In one smal clinical trial, one group of patients was treated with LOLA 18 g/day 2 weeks, and other group was given placebo. In the first group, concentration of ammonia in the blood significantly decreased and the mental activity, cognitive functions of the patients improved. A good effect of LOLA for both clinically expressed HE and MHE patients was observed (47).

Mittal et al. found that in patients with MHE LOLA, probiotics, and lactulose were equally effective for improvement of psychometric indices and life quality (48). In another study, one group of patients was administered 20 g LOLA intravenously for one week, other group got placebo. The results showed that LOLA decreased concentration of ammonia in the blood, improved the mental activity and cognitive functions in the patients with clinically expressed mild HE. Reliable results about its efficacy for patients with MHE and severe HE were not obtained (49). In recently published meta analysis, LOLA efficacy for patients with MHE was not ascertained, though for I and II grade clinically expressed HE LOLA was effective (50). The preparation is safe. Use of LOLA rarely causes intestinal disorders. For patients with renal insufficiency it should be administered with caution. According to INASL, further prospective randomized controlled clinical trials of LOLA efficacy for treatment of MHE are required (1b, A) (10).

Zinc preparations

Zinc deficiency is frequently found in cirrhotic patients (especially of alcoholic origin). Food supplements with zinc decrease concentration of ammonia in the blood by stimulating urea and glutamine synthesis in the muscles and liver. Zinc sulphate or acetate 600 mg/day were used in research. The results were controversial (51–54).

L-carnitine

In experimental trials on animals L-carnitine decreases concentration of ammonia in serum and cerebrospinal fluid due to stimulating synthesis of urea (55). A randomized placebo controlled clinical trial with 150 patients was conducted. During 90 days one group of patients was treated with L-carnitine 2 g twice per day, other group took placebo. In the first group a significant reduction of ammonia in the blood was observed, also the patients performed psychometric tests better (56). Further studies are necessary to approve the efficacy of L-carnitine (57).

Sodium benzoate, sodium phenyl butyrate and sodium phenyl acetate

Sodium benzoate, sodium phenyl butyrate and sodium phenyl acetate are one more group of medicines which stimulate plasma ammonia reduction. Sodium benzoate connects to glycine and forms hippurates which are eliminated through kidneys. One mole of hippuric acid has one mole of nitrogen.

Symptoms of HE might be effectively controlled with 5 g twice per day of sodium benzoate (58). However, this medicine has an unpleasant taste, patient receives an excessive amount of sodium, which is not desirable for patients with heart, kidneys or liver insufficiency and ascites, and sometimes it causes nausea. The FDA has not approved sodium benzoate for treatment of HE.

Sodium phenyl butyrate in the human body turns into phenyl acetate, it reacts with glutamine forming phenyl acetyl glutamine which is eliminated with urine. In one mole of phenyl acetyl glutamine there are two moles of nitrogen. Sodium phenyl butyrate and intravenous sodium phenyl acetate combined with sodium benzoate are approved by the FDA only for treatment of hyperammonemia when there is a disorder of urea synthesis. Recently, clinical trials were conducted to evaluate the efficacy of these medicines for cirrhotic patients with severe HE.

Alpha-glucosidase inhibitors

Acarbose is an alpha-glucosidase inhibitor which is administered for treatment of diabetes mellitus type 2. This preparation taken before every meal slows down digestion of consumed carbohydrates. Proteins-fragmenting bacteria in the

large intestine are suppressed so less ammonia is produced.

Acarbose is not routinely used for HE treatment. A single study was conducted to evaluate efficacy of acarbose for patients with liver cirrhosis, diabetes mellitus type 2, and with mild HE. In the patient group who was treated with acarbose, concentration of ammonia in the blood significantly decreased, and they performed psychometric tests better than in the placebo group (59). However, this medicine causes diarrhoea, meteorism and tenesmus, increases activity of liver enzymes, and it is not tolerated very well. Furthermore, the manufacturer information leaflet states that one of contraindications for its use is liver cirrhosis.

Benzodiazepine receptor antagonists

For many years, pathogenesis of HE was explained by both ammonia and GABA theories. It was thought that in case of liver cirrhosis, higher than normal amount of endogenous benzodiazepines is circulated in the blood. Also sensitivity of GABA receptors for these substances increases in brain. This theory was the basis for treatment with benzodiazepine receptor antagonist flumazenil. Researches had denied this theory later (60). Recent data show that flumazenil efficacy was seen for a small group of patients and for a short period of time (61).

Dopamine receptor antagonists

Bromocriptine and L-dopa were administered for persistent HE with marked extra pyramidal symptoms. It was assumed that such symptoms develop because of increased dopaminergic activity. Though in recent years, due to advances in neurovisual (MRI) and molecular research, an excessive accumulation of manganese in basal nuclei was proved as a cause of extra pyramidal symptoms (62, 63). Clinical trials with manganese binding preparations are expected to confirm this assumption.

N-methyl-D-aspartate (NMDA) receptor antagonists

In case of liver cirrhosis high levels of glutamate stimulate NMDA receptors and, at the same time, activate many enzymes including nitric oxide synthase. On the other hand, NO activates soluble guanylate cyclase and cGMP concentration increases. These processes are important for circadian rhythms and long-term potentiation, which is important for memory and learning (64).

In animal experiments, memantine, a NMDA receptor antagonist, has a positive effect on all clinical symptoms, EEG data, ammonia concentration in cerebrospinal fluid, but not on blood amonia (65).

NON-PHARMACOLOGICAL THERAPY OF HE

MARS (Molecular Adsorbents Recirculation System)

MARS helps to eliminate small and medium size water soluble molecules, and albumin-binded molecules. Worldwide, it is mostly used in cases of drug poisoning. MARS is not approved by the FDA for HE treatment. During MARS procedure bilirubin binds to albumin, biliary acids and ammonia are eliminated. Results of a multicentre randomized controlled trial with patients who had HE of grade 3–4 showed that after use of MARS for 6 hours per day for 5 days, in addition to standard pharmacological therapy, disappearance of HE symptoms was achieved much faster than with medicinal therapy only (66). The procedure is well tolerated.

TIPS (Transjugular Intrahepatic Portosystemic Shunt)

In 35% of patients after performing TIPS procedure HE develops. Condition of most patients improves when standard therapy is administered, though 3–7% invasive procedures are necessary. For some patients the diameter of a stent has to be minimized, for others a stent has to be even obturated (67).

Liver transplantation

Hepatic encephalopathy after liver transplantation is a reversible condition. Various MRI imaging findings after liver transplantation regress and disappear (68). Incomplete improvement might be in patients with hepatic myelopahty, acquired hepato-cerebral degeneration. Also there is opinion that after an overt HE bout subtle neurological abnormalities remain (69, 70). HE residual changes must be differentiated from intraoperative ischemic brain lesions and persistent portosystemic shunts after liver transplantation, previous stroke, alcohol abuse, trauma, drugs side effects. It is unknown if HE has a significant impact upon the clinical

outcome after liver transplantation. Until now, there is not priority for earlier liver transplantation for HE affected patients (71).

CONCLUSIONS

Hepatic encephalopathy diagnosis is based on patient's clinical condition. HE grading by West-Haven's criteria, especially stages 1 and 2, might be subjective and influence results of clinical trials. MHE is undiagnosed and untreated in most cases due to incompliance of psychometric tests and lack of validated blood tests.

A new approach to the HE pathogenesis allowed to start rifaximin for HE treatment and prophylaxis. Rifaximin has the same clinical effectiveness as disaccharides and oral antibiotics and causes fewer side effects than other oral agents. Rifaximin therapy is more expensive than lactulose. Lactulose is still recommended as the first line therapy.

There are still insufficient research data to design algorithms of hepatic encephalopathy diagnostic and treatment suitable for everyday clinical practice. Further studies are necessary.

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References

1. Hung TH, Lay CJ, Chang CM, Tsai JJ, Tsai CC, Tsai CC. The effect of infections on the mortality of cirrhotic patients with hepatic encephalopathy. Epidemiol Infect. 2013: 1–8.
2. Rahimi RS, Rockey DC. End-stage liver disease complications. Curr Opin Gastroenterol. 2013 Feb 19. Epub ahead of print.
3. Ferenci P. Hepatic Encephalopathy – Definition, Nomenclature, Diagnosis, and Quantification: Final Report of the Working Party at the 11th World Congress of Gastroenterology, Vienna, 1998. Hepatology. 2002; 35: 716–21.
4. Sharma P, Kumar A, Singh S, Tyagi P, Kumar A. Inhibitory control test, critical flicker frequency, and psychometric tests in the diagnosis of minimal hepatic encephalopathy in cirrhosis. Saudi J Gastroenterol. 2013; 19: 40–4.
5. Bajaj JS, Saeian K, Verber MD, Hischke D, Hoffmann RG, Franco J, et al. Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. Am J Gastroenterol. 2007; 102: 754–60.
6. Bajaj J, Hafeezullah M, Franco J, Varma R, Hoffmann R, Knox J, et al. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. Gastroenterology. 2008; 135: 1591–600.
7. Sharma P, Sharma B, Sarin S. Critical flicker frequency for diagnosis and assessment of recovery from minimal hepatic encephalopathy in patients with cirrhosis. Hepatobiliary Pancreat Dis Int. 2010; 9: 27–32.
8. Sharma P, Sharma BC, Puri V, Sarin SK. Critical flicker frequency: diagnostic tool for minimal hepatic encephalopathy. J Hepatol. 2007; 47: 67–73.
9. Romero-Gomez M, Cordoba J, Jover R, del Olmo JA, Ramirez M, Rey R, et al. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatology. 2007; 45: 879–85.
10. Dhiman R, Saraswat V, Sharma B, Sarin S, Chawla Y, Butterworth R, et al. Minimal hepatic encephalopathy: consensus statement of a working party of the Indian National Association for Study of the Liver. J Gastroenterol Hepatol. 2010; 25: 1029–41.
11. Goldbecker A, Weissenborn K, Hamidi SG, Afshar K, Rumke S, Barg-Hock H, et al. Comparison of the most favoured methods for the diagnosis of hepatic encephalopathy in liver transplantation candidates. Gut. 2013 Jan 7. Epub ahead of print.
12. Torlot FJ, McPhail MJ, Taylor-Robinson SD. Meta-analysis: the diagnostic accuracy of critical flicker frequency in minimal hepatic encephalopathy. Aliment Pharmacol Ther. 2013; 37: 527–36.
13. Gundling F, Zelihic E, Seidl H, Haller B, Umgelter A, Schepp W, et al. How to diagnose hepatic encephalopathy in the emergency department. Ann Hepatol. 2013; 12: 108–14.
14. Prakash R, Mullen KD. Mechanisms, diagnosis and management of hepatic encephalopathy. Nat Rev Gastroenterol Hepatol. 2010; 7: 515–25.
15. Kundra A, Jain A, Banga A, Bajaj G, Kar P. Evaluation of plasma ammonia levels in patients with acute liver failure and chronic liver disease and its correlation with the severity of hepatic encephalopathy and clinical features of raised intracranial tension. Clin Biochem. 2005; 38: 696–9.
16. Albrecht J. Cyclic GMP in blood and minimal hepatic encephalopathy: fine-tuning of the diagnosis. J Mol Med. 2007; 85: 203–5.

17. Montoliu C, Piedrafita B, Serra MA, del Olmo JA, Ferrandez A, Rodrigo JM, et al. Activation of soluble guanylate cyclase by nitric oxide in lymphocytes correlates with minimal hepatic encephalopathy in cirrhotic patients. J Mol Med. 2007; 85: 237–45.
18. Montoliu C, Piedrafita B, Serra M, del Olmo J, Urios A, Rodrigo J, et al. IL-6 and IL-18 in blood may discriminate cirrhotic patients with and without minimal hepatic encephalopathy. J Clin Gastroenterol. 2009; 43: 272–9.
19. Cordoba J, Lopez-Hellin J, Planas M, Sabin P, Sanpedro F, Castro F, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol. 2004; 41: 38–43.
20. Chedid A, Mendenhall CL, Gartside P, French SW, Chen T, Rabin L. Prognostic factors in alcoholic liver disease. VA Cooperative Study Group. Am J Gastroenterol. 1991; 86: 210–6.
21. Ricci P, Therneau TM, Malinchoc M, Benson JT, Petz JL, Klintmalm GB, et al. A prognostic model for the outcome of liver transplantation in patients with cholestatic liver disease. Hepatology. 1997; 25: 672–7.
22. Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy. Cochrane Database Syst Rev. 2003; (2): CD001939.
23. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005; 3: 705–13.
24. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003; 124: 1792–801.
25. Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr. 2006; 25: 285–94.
26. Charlton M. Branched-chain amino-acid granules: can they improve survival in patients with liver cirrhosis? Nat Clin Pract Gastroenterol Hepatol. 2006; 3: 72–3.
27. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ. 2004; 328: 1046–51.
28. Sharma P, Sharma BC. Disaccharides in the treatment of hepatic encephalopathy. Metab Brain Dis. 2013 Mar 2. Epub ahead of print.
29. Li YY, Nie YQ, Sha WH, Zeng Z, Yang FY, Ping L, et al. Prevalence of subclinical hepatic encephalopathy in cirrhotic patients in China. World J Gastroenterol. 2004; 10: 2397–401.
30. Romeiro FG, da Silva YF, Americo MF, Cora LA, Silva GF, Miranda JR, et al. Erythromycin versus neomycin in the treatment of hepatic encephalopathy in cirrhosis: a randomized double-blind study. BMC Gastroenterol. 2013; 13: 13.
31. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010; 362: 1071–81.
32. Ridola L, Zullo A, Hassan C. Rifaximin as treatment for hepatic encephalopathy: some considerations. Saudi J Gastroenterol. 2013; 19(1): 56.
33. Patidar KR, Bajaj JS. Antibiotics for the treatment of hepatic encephalopathy. Metab Brain Dis. 2013 Feb 8. Epub ahead of print.
34. Mantry P, Munsaf S. Does the addition of rifaximin to lactulose reduce the severity of hepatic encephalopathy? A single-center experience. Hepatology 2008; 48: 517A.
35. Sidhu SS, Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). Am J Gastroenterol. 2011; 106: 307–16.
36. Bajaj JS, Heuman DM, Wade JB, Gibson DP, Saeian K, Wegelin JA, et al. Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy. Gastroenterology. 2011; 140: 478–87.
37. Eltawil KM, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. World J Gastroenterol. 2012; 18: 767–77.
38. Dhiman RK. Gut microbiota and hepatic encephalopathy. Metab Brain Dis. 2013 Mar 6. Epub ahead of print.
39. Shukla S, Shukla A, Mehboob S, Guha S. Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. Aliment Pharmacol Ther. 2011; 33: 662–71.
40. Holte K, Krag A, Gluud LL. Systematic review and meta-analysis of randomized trials on probiotics

for hepatic encephalopathy. Hepatol Res. 2012; 42(10): 1008–15.
41. Bajaj J, Saeian K, Christensen K, Hafeezullah M, Varma R, Franco J, et al. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. Am J Gastroenterol. 2008; 103: 1707–15.
42. Sharma P, Sharma B, Puri V, Sarin S. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol. 2008; 20: 506–11.
43. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. Hepatology. 2007; 45: 549–59.
44. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology. 2004; 39: 1441–9.
45. Jover-Cobos M, Noiret L, Sharifi Y, Jalan R. Ornithine phenylacetate revisited. Metab Brain Dis. 2013 Mar 2. Epub ahead of print.
46. Bai M, Yang Z, Qi X, Fan D, Han G. L-ornithine-L-aspartate for hepatic encephalopathy in patients with cirrhosis: A meta-analysis of randomized controlled trials. J Gastroenterol Hepatol. 2013 Feb 21. Epub ahead of print.
47. Stauch S, Kircheis G, Adler G, Beckh K, Ditschuneit H, Gortelmeyer R, et al. Oral L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: results of a placebo-controlled double-blind study. J Hepatol. 1998; 28: 856–64.
48. Mittal V. Treatment of minimal hepatic encephalopathy: A randomised controlled trial comparing lactulose, probiotics, and l-ornitine l-aspartate with placebo. Hepatology. 2009; 50(Suppl): 471A.
49. Kircheis G, Nilius R, Held C, Berndt H, Buchner M, Gortelmeyer R, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. Hepatology. 1997; 25: 1351–60.
50. Jiang Q, Jiang XH, Zheng MH, Chen YP. L-Ornithine-l-aspartate in the management of hepatic encephalopathy: a meta-analysis. J Gastroenterol Hepatol. 2009; 24: 9–14.
51. Marchesini G, Fabbri A, Bianchi G, Brizi M, Zoli M. Zinc supplementation and amino acid-nitrogen metabolism in patients with advanced cirrhosis. Hepatology. 1996; 23: 1084–92.
52. Marchesini G, Bugianesi E, Ronchi M, Flamia R, Thomaseth K, Pacini G. Zinc supplementation improves glucose disposal in patients with cirrhosis. Metabolism. 1998; 47: 792–8.
53. Riggio O, Ariosto F, Merli M, Caschera M, Zullo A, Balducci G, et al. Short-term oral zinc supplementation does not improve chronic hepatic encephalopathy. Results of a double-blind crossover trial. Dig Dis Sci. 1991; 36: 1204–8.
54. Bresci G, Parisi G, Banti S. Management of hepatic encephalopathy with oral zinc supplementation: a long-term treatment. Eur J Med. 1993; 2: 414–6.
55. Therrien G, Rose C, Butterworth J, Butterworth RF. Protective effect of L-carnitine in ammonia-precipitated encephalopathy in the portacaval shunted rat. Hepatology. 1997; 25: 551–6.
56. Malaguarnera M, Pistone G, Elvira R, Leotta C, Scarpello L, Liborio R. Effects of L-carnitine in patients with hepatic encephalopathy. World J Gastroenterol. 2005; 11: 7197–202.
57. Malaguarnera M. Acetyl-L-carnitine in hepatic encephalopathy. Metab Brain Dis. 2013 Feb 8. Epub ahead of print.
58. Sushma S, Dasarathy S, Tandon RK, Jain S, Gupta S, Bhist MS. Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial. Hepatology. 1992; 16: 138–44.
59. Gentile S, Guarino G, Romano M, Alagia IA, Fierro M, Annunziata S, et al. A randomized controlled trial of acarbose in hepatic encephalopathy. Clin Gastroenterol Hepatol. 2005; 3: 184–91.
60. Ahboucha S, Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at GABA from the molecular standpoint. Metab Brain Dis. 2004; 19: 331–43.
61. Lock BG, Pandit K. Evidence-based emergency medicine / systematic review abstract. Is flumazenil an effective treatment for hepatic encephalopathy? Ann Emerg Med. 2006; 47: 286–8.
62. Solomou E, Velissaris D, Polychronopoulos P, Kalogeropoulos A, Kiriakopoulou M, Mpadra F, et al. Quantitative evaluation of magnetic resonance imaging (MRI) abnormalities in subclinical hepatic encephalopathy. Hepatogastroenterology. 2005; 52: 203–7.
63. Reza ZM, Eslimi ED, Oryan S, Nasehi M, Torabi NM. Effects of dopamine receptor agonist and

antagonists on cholestasis-induced anxiolytic-like behaviors in rats. Eur J Pharmacol. 2013; 702: 25–31.
64. Monfort P, Munoz MD, Felipo V. Molecular mechanisms of the alterations in NMDA receptor-dependent long-term potentiation in hyperammonemia. Metab Brain Dis. 2005; 20: 265–74.
65. Vogels BA, Maas MA, Daalhuisen J, Quack G, Chamuleau RA. Memantine, a noncompetitive NMDA receptor antagonist improves hyperammonemia-induced encephalopathy and acute hepatic encephalopathy in rats. Hepatology. 1997; 25: 820–7.
66. Hassanein T, Tofteng F, Brown RS Jr, McGuire BM, Lynch P, Mehta R, et al. Efficacy of albumin dialysis (MARS) in patients with cirrhosis and advanced grades of hepatic encephalopathy: a prospective, controlled, randomized multicenter trial. Hepatology. 2004; 4 Suppl 1: 726A.
67. Madoff DC, Wallace MJ, Ahrar K, Saxon RR. TIPS-related hepatic encephalopathy: management options with novel endovascular techniques. Radiographics. 2004; 24: 21–36.
68. Rovira A, Minguez B, Aymerich FX, Jacas C, Huerga E, Cordoba J, et al. Decreased white matter lesion volume and improved cognitive function after liver transplantation. Hepatology. 2007; 46: 1485–90.
69. Krieger S, Jauss M, Jansen O, Theilmann L, Geissler M, Krieger D. Neuropsychiatric profile and hyperintense globus pallidus on T1-weighted magnetic resonance images in liver cirrhosis. Gastroenterology. 1996; 111: 147–55.
70. Mullen KD, Cole M, Foley JM. Neurological deficits in "awake" cirrhotic patients on hepatic encephalopathy treatment: missed metabolic or metal disorder? Gastroenterology. 1996; 111: 256–7.
71. Arab JP, Meneses L, Perez RM, Arrese M, Benitez C. Hepatic encephalopathy in a liver transplant recipient with stable liver function. Hepatology. 2013 Feb 6. Epub ahead of print.

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HEPATINĖS ENCEFALOPATIJOS DIAGNOSTIKA IR GYDYMAS

Santrauka

Įžanga. Hepatinė encefalopatija (HE) yra neuropsichinis sutrikimas, nustatomas sergantiesiems kepenų ciroze, jo simptomai varijuoja nuo nepastebimų iki sunkių. Pastaraisiais metais pasikeitė požiūris į hepatinės encefalopatijos gydymą. Ankstyva hepatinės encefalopatijos stadija – minimali hepatinė encefalopatija (MHE) – pasaulyje, taip pat ir Lietuvoje, retai diagnozuojama ir gydoma, nors ši pradinė HE stadija yra atsakinga už kognityvinius sutrikimus ir ženkliai blogina ciroze sergančių pacientų gyvenimo kokybę. Naujausių tyrimų duomenimis, ši neurologinė komplikacija pasitaiko apie 70 % ciroze sergančių pacientų.

Tikslas. Apžvelgti hepatinės encefalopatijos diagnostikos ir gydymo naujoves bei jų pritaikymo klinikinėje praktikoje galimybes siekiant pagerinti ciroze sergančių pacientų gyvenimo kokybę bei atitolinti klinikinių HE simptomų atsiradimą.

Metodai ir medžiaga. Šis straipsnis parašytas remiantis originaliais straipsniais ir apžvalgomis anglų kalba (1991–2012), kurie rasti Medline ir Pubmed duomenų bazėse naudojant raktažodžius.

Rezultatai. Pastaraisiais metais pasikeitė požiūris į hepatinės encefalopatijos (HE) gydymą. Rekomenduojama nemažinti baltymų pacientų racione, vartoti daugiau šakotųjų amino rūgščių turinčius produktus. Neabsorbuojami disacharidai (laktuliozė) vis dar yra pirmo pasirinkimo vaistai, nors jų efektyvumu, remiantis paskutiniais tyrimais, suabejota. Gydant HE plačiai pradėta taikyti rifaksiminą, o kiti vaistai laikomi antraeiliais.

Minimaliai hepatinei encefalopatijai (MHE) gydyti rekomenduojama laktuliozė ir probiotikai. MHE diagnostika išlieka sudėtinga – nėra patvirtintų kraujo tyrimų, kurie padėtų ją diagnozuoti bei stebėti gydymo efektyvumą. Psichometriniai ir neurofiziologiniai, taip pat vizualizacijos metodai daugiau taikytini moksliniuose tyrimuose, kasdienėje praktikoje gali būti naudingi kompiuterizuoti metodai (psichometrinis inhibicinis kontrolės testas, kritinio mirgėjimo dažnio testas).

Išvados. Reikalingi tolesni klinikiniai tyrimai, kurie leistų sukurti klinikiniam pritaikymui tinkamą HE diagnostikos ir gydymo algoritmą

Raktažodžiai: hepatinė encefalopatija, minimali hepatinė encefalopatija, diagnostika, gydymas