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Review

Diagnosis and treatment of hepatic encephalopathy - review

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ABSTRACT

Hepatic encephalopathy is observed in patients with liver dysfunction. Therefore, chronic liver disease patients are more affected. Due to reduced liver function, neurotoxins generated by damaged intestinal flora reach the brain. Hepatic encephalopathy can be classified according to the degree of symptoms. Ammonia concentration is thought to be important in pathogenesis. Its early phases can be diagnosed with a variety of tests. And it is possible to resolve and eliminate hepatic encephalopathy with imaging and treatment.

Keywords: Ammonia, cirrhosis, hepatic encephalopathy, liver

INTRODUCTION

Liver cirrhosis can be an outcome of variable causes, such as high alcohol consumption, non-alcoholic fatty liver disease, or viral infections. After an inflammation phase, the liver parenchyma transforms into the fibrosis state, which is followed by the compensated state. The symptomatic period of the disease is the decompensated state,[1] which can cause palpable fluid accumulation in the abdomen and bacterial peritonitis.[2] Liver cirrhosis is a pathological result of chronic liver disease, even though primary cause of cirrhosis is hepatocytes' continuous life-and-death cycle.[3] This cirrhotic process causes deceleration of metabolism in which ammonia is converted to urea. As a result, the ammonia increases in circulation.[4] Hepatic encephalopathy is a complication of cirrhosis, which is responsible for the majority of hospitalizations.[5] It is important to make a differential diagnosis from other neurological and psychological situations which may be present in elders with co-morbid diseases in patients with chronic liver dysfunction and is considered a reversible situation. Toxic substances that accumulate in the brain negatively impact on perception and attention. Sleep patterns are also disrupted.[7] Neurotoxins from the intestine reach the brain due to a damaged liver and are demonstrated to be responsible for the symptoms. Although high ammonia levels are expected, it is not thought to be a predictor factor of the severity of the disease.[8] In this review we aimed to highlight the current approaches to hepatic encphalopaty.

MECHANISM OF HEPATIC ENCEPHALOPATHY

In terms of mechanism, when the liver cannot fully perform, ammonia and other substances accumulate in the brain, causing the volume of astrocytes to expand, which increases oxidative stress. These negative changes disrupt the interaction between the astrocyte and other neurons, and the symptoms increase dramatically. The transport of glutamine to the mitochondria also causes an increase in ammonia production.[9] According to the Trojan horse hypothesis, glutamine transported to the mitochondria triggers the formation of reactive oxygen species and ammonia, which causes an increase in glutamate and glutamine. The process results in a decrease in oxidative phosphorylation capacity. Ammonia has an important role in the impairment of mitochondrial functions. Ammonia causes pH alterations, and although this blocks the later stages of the autophagy process, it leads to the breakdown of mitochondria because it is ubiquitous.[9]

STAGING OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is observed at a scale from minimal hepatic encephalopathy to overt encephalopathy depending on the extent of damage caused.[10] This is known as the West Haven Criteria.[11] Minimal hepatic encephalopathy (MHE) is mostly used to describe changes that can be distinguished by tests. Thus, neurophysiological changes may not affect the consciousness. The lack of awareness, decreased attention, decreased ability to perform tasks, sleep disturbance, anxiety and euphoria are among the prominent features of stage one. Along with minimal hepatic encephalopathy, stage one also described as covert hepatic encephalopathy because of lack of overt encephalopathic features. However, this does not mean that it should not be treated. On the contrary, the patient should be intervened at this stage, as it is a precursor to advanced stages.[12]

In stage two, lethargy or apathy, time disorientation, personality changes, inappropriate behavior, dyspraxia-

planning impairment, and flapping tremor may be observed. Stage two has distinguishing features from stage one by confusing at least three of the following: months, day of the month, day of the week, season, and year. Temporary disorientation distinguishes stage two from stage three, which features prominent hepatic encephalopathy symptoms. In stage three, disorientation is expected to be permanent. There are a semi-dazed state and unusual behaviors. Disorientation increased, and disorientation in spatial perception advanced beyond stage two. At this point, it is possible to report at least three of the spatial parameters incorrectly, such as country, state (or region), city or place. In stage four, the stage of coma is reached and there is no response to painful stimuli. Thus, a patient with hepatic encephalopathy is classified and described according to Table.[11]

Table. Hepatic encephalopathy classification - an example: HE, type C, stage 3 classified as recurrent, precipitous

Type	Stage		Progress	Spontaneous or precipitated
A	MHE	Covert	Episodical	Spontaneous
	1		Recurrent	
B	2	Overt		Precipitated
C	3		Persistant	
	4			

Generally, the pathogenesis is based on three types: In type A, an encephalopathy secondary to acute liver failure is expected. Type B is used to describe hepatic encephalopathy secondary to the presence of portosystemic shunts. In type C, there is a hepatic encephalopathy secondary to cirrhosis.[13]

TESTS AND IMAGING

There are some scoring tests, especially for MHE and stage 1 hepatic encephalopathy. The Psychometric Hepatic Encephalopathy Score (PHES) test is considered the gold standard,[14] assessing psychomotor speed and visuospatial coordination, which is thought to detect neuropsychological deficits in latent hepatic encephalopathy.[15] It includes five widely validated tests: Number connection test (NCT)-A, NCT-B, line tracing test, digit symbol test and serial dotting test (SDT).[16,17] The main problem with this test is that it takes 20-30 minutes to complete, which makes it unpractical. The critical flicker frequency (CFF) test is a neurophysiological test that evaluates the patient's ability to discriminate flickering light using a glasses-shaped device and has been widely validated[18,19] and is comparable to the PHES test.A value below 38 Hz is recommended for detecting latent hepatic encephalopathy.[20] The test is easy to accomplish but the device is expensive. Some tests, such as the stroop test, may also be useful. The stroop test reflects frontal region activity. If the color and the color expressed by the word are not the same, measurement is made based on the patient's reaction.[21] In the animal naming test (ANT), fluency in meaning is analyzed by having as many animal names as possible uttered in one minute. An environment isolated from external factors is required. If the patient pauses for 15 seconds before the extinction of one minute, a clue is given with the name of an animal, and the patient is allowed to continue the test.[22]

In hepatic encephalopathy, neuronal loss and manganese accumulation can lead to bilateral, reversibly symmetrical globus pallidus and substantia nigra T1 hyperintensity. An increase in glutamate and glutamine peaks is expected as a result of hyperammonemia. Cerebral edema may also be observed in hepatic encephalopathy. Cytotoxic edema is expected in acute hepatic encephalopathy, and vasogenic edema is expected in chronic hepatic encephalopathy. However, mixed-type edema is expected later. Preservation of perirolandic areas and the occipital cortex is an important finding in differentiating hepatic encephalopathy from hypoxic-ischemic encephalopathy.[23]

DIFFERENTIAL DIAGNOSIS

If overt hepatic encephalopathy and acute confusional state are considered, diabetic symptoms such as hypoglycemia and ketoacidosis, alcohol intoxication, Wernicke's withdrawal symptoms, drugs such as benzodiazepines, opiates, electrolyte disorders, neuroinfections, psychiatric disorders, intracranial hemorrhage, organ failure, dementia and conditions such as brain lesions must be excluded.[11]

TREATMENT

Constipation plays an important role in the development of hepatic encephalopathy. Therefore, as the transition period without digestion is prolonged, toxic metabolites can be reabsorbed and, cause an increase in ammonia. Lactulose and lactitol are considered first-line treatments because they accelerate the passage.[24]

As portal hypertension increases in the liver, spontaneous portosystemic shunts (SPSS) may occur. Splenorenal shunts, especially those located to the left of the spleno-porto-mesenteric junction ("left side") are most associated with recurrent hepatic encephalopathy.[25,26] Shunt obliteration is among the treatment options because it blocks the passage of ammonia.[24] Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure to reduce portal hypertension. For refractory variceal bleeding and refractory ascites, a stent is placed between the portal vein and the hepatic vein. Therefore, the portal venous flow is shunted directly to the systemic circulation. Thus, it reduces bleeding and ascites and indirectly helps to prevent hepatic encephalopathy.[27,24]

Due to the disruption of intestinal flora in liver cirrhosis, probiotics are growing in popularity and significance. In hepatic encephalopathy, probiotics can be used to regulate the disrupted intestinal flora.[28] Also, there are some studies that suggest fecal microbiota transplantation (FMT) is effective in reducing cognitive impairment and the number of hospitalizations in cirrhotic patients. However, it has not been proven yet that further studies should be followed.

L-ornithine L-aspartate (LOLA): L-ornithine and L-aspartate contain amino acids involved in metabolic pathways that produce urea and glutamine.[24] Ornithine is involved as both an activator and substrate in urea production and aspartate stimulates the synthesis of glutamine, which acts as a substrate in urea production. As a result, ammonia levels are reduced through the liver.[29]

Rifaximin is thought to reorganize the intestinal microbiota, as concluded in a recent study. Bacterial composition and diversity are considered beneficial as it prevents impaired bowel regulation, which is an important cause of hepatic encephalopathy.[30]

CONCLUSION

Hepatic encephalopathy should be considered as a preventable symptom. In cases of possible liver failure where hepatic encephalopathy is considered, differential diagnoses should be carefully evaluated with the principle that "non est morbus, ibi est patientes estote": There are no diseases, there are patients. Healthcare providers should be alert for the early stages of hepatic encephalopathy, and awareness of early diagnosis and treatment should be increased.

ETHICAL DECLARATIONS

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REFERENCES

1. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet*. 2021;398(10308):1359-1376. doi:10.1016/S0140-6736(21)01374-X
2. Walter KL. What is cirrhosis? *JAMA*. 2023;330(4):386. doi:10.1001/jama.2023.8935
3. Zhou WC, Zhang QB, Qiao L. Pathogenesis of liver cirrhosis. *World J Gastroenterol*. 2014;20(23):7312-7324. doi:10.3748/wjg.v20.i23.7312
4. Butterworth RF. Hepatic encephalopathy in cirrhosis: pathology and pathophysiology. *Drugs*. 2019;79(Suppl 1):17-21. https://doi.org/10.1007/s40265-018-1017-0
5. Frenette CT, Levy C, Saab S. Hepatic encephalopathy-related hospitalizations in cirrhosis: transition of care and closing the revolving door. *Dig Dis Sci*. 2022;67(6):1994-2004. doi:10.1007/s10620-021-07075-2
6. Bajaj JS, Gentili A, Wade JB, Godschalk M. Specific challenges in geriatric cirrhosis and hepatic encephalopathy. Clin Gastroenterol Hepatol. 2022;20(8):S20-S29. https://doi.org/10.1016/j.cgh.2022.04.035.
7. Mandiga P, Foris LA, Bollu PC. Hepatic encephalopathy. In: StatPearls. Treasure Island (FL): StatPearls Publishing: 2023.
8. R. Bacon B. Chapter 44. Cirrhosis and its complications. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. Harrison's Gastroenterology and Hepatology. 3rd ed. McGraw-Hill Education: 2017:469.
9. Lu K. Cellular pathogenesis of hepatic encephalopathy: an update. *Biomolecules*. 2023;13(2):396. doi:10.3390/biom13020396
10. Nardelli S, Gioia S, Faccioli J, Riggio O, Ridola L. Hepatic encephalopathy - recent advances in treatment and diagnosis. *Expert Rev Gastroenterol Hepatol*. 2023;17(3):225-235. doi: 10.1080/17474124.2023.2183386
11. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the study of liver diseases and the European Association for the study of the liver. *Hepatology*. 2014;60(2):715-735. doi: 10.1002/hep.27210
12. Hızarcıoğlu Gülşen H, Özen H. Hepatik ensefalopati. İçinde: Altunbaşak Ş, editör. Çocuklarda ensefalopati. 1. Baskı. Türkiye Klinikleri: 2021: p.86-94.
13. Thabut D, Bouzbib C, Meunier L, et al. Diagnosis and management of hepatic encephalopathy: the French recommendations. *Liver Int*. 2023;43(4):750-762. doi: 10.1111/liv.15510.
14. Thanapirom K, Wongwandee M, Suksawatamnuay S, et al. Psychometric hepatic encephalopathy score for the diagnosis of minimal hepatic encephalopathy in Thai cirrhotic patients. *J Clin Med*. 2023;12(2):519. doi: 10.3390/jcm12020519
15. Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. *J Hepatol*. 2001;34(5):768-773. doi: 10.1016/s0168-8278(01)00026-5
16. Amodio P, Campagna F, Olianas S, et al. Detection of minimal hepatic encephalopathy: normalization and optimization of the psychometric hepatic encephalopathy score. A neuropsychological and quantified EEG study. *J Hepatol*. 2008;49(3):346-353. doi: 10.1016/j.jhep.2008.04.022
17. Goldbecker A, Weissenborn K, Hamidi Shahrezaei G, et al. Comparison of the most favoured methods for the diagnosis of hepatic encephalopathy in liver transplantation candidates. *Gut*. 2013;62(10):1497-1504. doi: 10.1136/gutjnl-2012-303262
18. Kircheis G, Hilger N, Häussinger D. Value of critical flicker frequency and psychometric hepatic encephalopathy score in diagnosis of low-grade hepatic encephalopathy. *Gastroenterol*. 2014;146(4):961-969. doi: 10.1053/j.gastro.2013.12.026
19. Kircheis G, Nilius R, Held C, 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. *Hepatol*. 1997;25(6):1351-1360. doi: 10.1002/hep.510250609
20. Romero-Gómez M, Córdoba J, Jover R, et al. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. *Hepatol*. 2007;45(4):879-885. doi: 10.1002/hep.21586
21. Karakaş S, Erdoğan E, Sak L, et al. Stroop test TBAG form: standardisation for Turkish culture, reliability and validity. *J Clin Psy*. 1999;2(2):75-88.
22. Agarwal A, Taneja S, Chopra M, Duseja A, Dhiman RK. Animal naming test - a simple and accurate test for diagnosis of minimal hepatic encephalopathy and prediction of overt hepatic encephalopathy. *Clin Exp Hepatol*. 2020;6(2):116-124. doi: 10.5114/ceh.2019.95105
23. Erbay MF. Hepatik ensefalopati. *Trd Sem*. 2023;11(1):1-6. doi: 10.4274/trs.2023.223686
24. Bellafante D, Gioia S, Faccioli J, Riggio O, Ridola L, Nardelli S. Old and new precipitants in hepatic encephalopathy: a new look at a field in continuous evolution. *J Clin Med*. 2023;12(3):1187. doi: 10.3390/jcm12031187
25. Ohnishi K, Sato S, Saito M, et al. Clinical and portal hemodynamic features in cirrhotic patients having a large spontaneous splenorenal and/or gastrorenal shunt. *Am J Gastroenterol*. 1986;81(6):450-455.
26. Nardelli S, Riggio O, Gioia S, Puzzono M, Pelle G, Ridola L. Spontaneous porto-systemic shunts in liver cirrhosis: clinical and therapeutical aspects. *World J Gastroenterol*. 2020;26(15):1726-1732. doi: 10.3748/wjg. v26.i15.1726
27. Amesur NB, Novelli P. Transjugular intrahepatic portosystemic shunt. In: StatPearls. Treasure Island (FL): StatPearls Publishing: 2023.
28. Dazıroğlu MEÇ, Yıldıran H. Intestinal dysbiosis and probiotic use: its place in hepatic encephalopathy in cirrhosis. *Ann Gastroenterol*. 2023;36(2):141-148. doi: 10.20524/aog.2023.0776
29. Kanbakan A. Acilci gözüyle hepatik ensefalopati. Updated January 3, 2019. Available from: https://acilci.net/acilci-gozuyle-hepatik-ensefalopati/.
30. Yu X, Jin Y, Zhou W, et al. Rifaximin modulates the gut microbiota to prevent hepatic encephalopathy in liver cirrhosis without impacting the resistome. *Front Cell Infect Microbiol*. 2022;11:1427. doi: 10.3389/fcimb.2021.761192