UGC Approved Journal
© UNIVERSAL RESEARCH REPORTS | REFEREED | PEER REVIEWED
ISSN : 2348 - 5612 | Volume : 05 , Issue : 04 | January - March 2018

Minimal Hepatic Encephalopathy (MHE), A burden or an opportunity to ease one: A review

Kirti Arora
arorakirti815@gmail.com

Abstract

A brain dysfunction caused by liver insufficiency is Hepatic Encephalopathy (HE). It has a spectrum of progression with varying and wide clinical and subclinical abnormalities. This review article will particularly focus on covert stages of HE i.e. A mildest and reversible neuropsychological complication with wide ranging manifestations throughout the spectrum of disease progression**.** By forming a correlation between varying clinical and sub-clinical symptoms with an awareness towards pathophysiological factors involved, a potent future approach could be established. However, lack of studies to establish such relationships makes it a laborious task keeping the non-specific symptoms of HE in site. But, with present severity and number progression, it is established by the use varying diagnostic tools, up to 80% of persons suffering through liver disease developed Minimal Hepatic Encephalopathy (MHE) as a further complication, making further research even crucial as so in order to avail better QoL (Quality of Life), socioeconomic status to subjects. The heterogeneous nature requires the testing of different diagnostic tools with a personalized analysis in order to form an effective treatment protocol. This article will focus on critical evaluation of different diagnostic techniques and treatments available with a view to cure MHE and keeping an open end point as to favour varying case by case basis approach and to prevent the further progression into its overt stages.

Keywords: Minimal hepatic encephalopathy, Diagnostic tools/Principles, Treatment course.

Introduction

One of the most prevalent and devastating complications of liver illness is hepatic encephalopathy (HE). It's a reversible **(**Cao et al., 2018) neurologic disorder that occurs when the liver fails to detoxify blood in the portal circulation, either due to hepatic insufficiency or shunting between the portal and systemic vasculature. Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting [1] , which manifests as a wide spectrum of neurological or psychiatric abnormalities, ranging from subclinical alterations to coma (Hepatol 2014,
p. 642-659). Because of wide range of clinical manifestations, Hepatic encephalopathy is graded on recommendation into covert and overt type. Covert being the hidden and is commonly mistaken as debilitating but, involves a myriad of symptoms that usually go undetected as, this condition is often not considered clinically relevant. The initial stage of HE is called minimal hepatic encephalopathy (MHE). In fact, the term MHE refers to modest alterations in cognitive function, electrophysiological parameters, cerebral neurochemical/ neurotransmitter homeostasis, cerebral blood flow, fluid homeostasis, and metabolism that

can be detected in patients with liver disease, with or without portosystemic shunt (PSS), or in patients with PSS but no liver disease, and clinical evidence.

Diagnosing MHE holds the most significant place in limiting the progression to severe stages of HE that could be done by Electroencephalograph, performing various Neuropsychological testings, checks performed by certain neuroimaging techniques (Nardone, 2016, p. 7), performing neuropsychometric assessments such as Pyschometric Hepatic Encephalopathy Score (PHES), Critical Flicker Frequency (CFF), Inhibitory Control Test (ICT), and others **(**Hadjihambi, 2017, p. S137). Diagnosis must be in done in consideration with various upstream factors leading to it as to have an efficient treatment. Currently, MHE is treated in combination with various probiotics (Cao, 2018, P. 15-16) (Sharma, 2008, p. 510), lactulose with or without using non absorbable antibiotics like rifaximin (Hudson, 2018, p. 436), L-Ornithine and L-aspartate (LOLA) (Bai et al., 2013, p. 783-792) treatments are some early treatments in prevalence. However, there is currently no comprehensive evaluation of current evidence supporting the effectiveness and safety/tolerability of HE treatment in the long-term environment. This article will focus on critical theoretical evaluation of various diagnostic tools and treatment procedures in order to formulate a better strategy to target MHE clinically.

Pathophysiology

The complicated and multifactorial pathophysiology of this disease makes the downstream process further challenging. Following are some of the major research avenues into pathways involved in the pathogenesis of HE in cirrhosis:

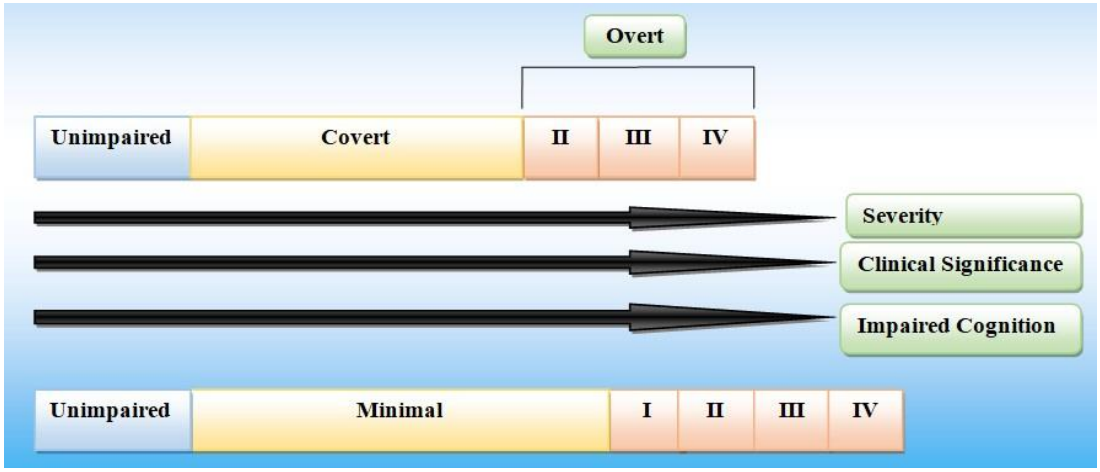
1. By impairing blood brain barrier **(**Quigley, 2017, p. 3-4)
2. Causing Gut microbiota alterations[2] (Wang et al., 2014, p. 9-10) 3. Oxidative stress (Lemberg and Fernandez, 2009, p. 98.)
4. Neurotransmitters (Fogel et al., 1990, p. 286).
5. Hyperammonemia (Haberle, 2011, p. 27).
6. Inflammation (Coltart et al., 2o13, p. 192-194).

Neurotoxic substances like Manganese (particularly involved in the motor disturbances associated with HE), because this heavy metal deposits in the basal ganglia due to its reduced clearance in portal-systemic shunting and cholestasis, may have a pathophysiological function in HE. It's crucial to understand the pathophysiology of hepatic encephalopathy in order to have finer diagnostics and develop new therapeutic strategies.

Epidemiology

Because low-grade HE (grade I) is difficult to identify, a new categorization that combines MHE and Grade I HE has been devised, introducing the term "covert" (Bajaj et al., 2011, p. 741) The goal is to simplify the clinical pattern such that the presence of clinically covert HE (CHE) may be diagnosed quickly and universally, as documented in figure 1. According to a 2007 poll by the American Association for the Study of Liver Diseases, the majority of clinicians believe MHE is a serious condition. However, only 50% of clinicians had evaluated if their patients had MHE, and 38% had never used psychometric testing to study their patients with liver cirrhosis and suggested the simplification of tests in order to increase clinical testings **(**Bajaj et al., 2007, p. 833834).

UGC Approved Journal
© UNIVERSAL RESEARCH REPORTS | REFEREED | PEER REVIEWED
ISSN : 2348 - 5612 | Volume : 05 , Issue : 04 | January - March 2018



The effects of HE are felt not only in the patients' physical well-being, but also in their psychological, economical, and emotional lives. Prior HE, for example, has been found to have a significant impact on employment rates (87.5 percent vs 19 percent). Furthermore, HE places a bigger strain on caretakers than cirrhotic patients who have never had HE (Neff and Zachry, 2018, p. 810). On a driving simulator, patients with MHE show poor sophisticated navigation skills, which coincides with impairments in reaction inhibition and attention (Bajaj, 2007, p. 833-834).

MHE is defined as the presence of quantifiable cognitive deficits in individuals with liver illness and/or portal-systemic shunting that are not discovered effortlessly but by a thorough clinical history and neurological examination like using PHES (Riggio et al., 2011, p. 614**).** MHE is detectable and the whole spectrum of progression into Overt could be made which could aid in limiting MHE to its earlier stage as established by (Bajaj et al., 2007, p. 833-834). Interviews with close relatives could also help MHE to be distinguished. Thus, there was not complete consensus amongst ISHEN for replacing minimal with covert and emphasized on treating the disease progression in spectrum than categorization **(**Bajaj, 2011, p. 742**).** Standard neuropsychological assessment is a time-tested and established methodology for measuring cognitive impairment in patients with MHE (Dhiman, 201o, p. 1033). MHE is considered latent with not really dormant effect on quality of life. From some **sophisticated** studies (Ridola et al., 2018, p. 5449), it could be concluded that MHE has severe effects on prime of daily lives than on the vitality.

Penumbra Casted

There has been constant research and rapid progress to understand the severity of HE that helped in further refining the process, [3] but HE is a disease with synergistic comorbidities. Varying initiation factors might show similar manifestations in the disease spectrum. Due to the lack of balance between the understanding of upstream factors and their correlational alterations, the task of treating HE according to its severity become further complex. Major treatments available focus on curing hyperammonia condition or curing inflammation, focusing on such mainstream factors cause a wriggle in which the mild or covert HE stays unattended therapeutically. The research in area of HE is majorly focused on confounders like ammonia, inflammatory cytokines and others casting a shadow on precipitating factors

UGC Approved Journal
© UNIVERSAL RESEARCH REPORTS | REFEREED | PEER REVIEWED
ISSN : 2348 - 5612 | Volume : 05 , Issue : 04 | January - March 2018

like Thyroid conditions altering metabolites, infection led inflammation, gut microbiota alterations. The management of affected people can be done with the proper identification and treatment of these precipitating factors. To keep a check on it, a multidimensional diagnosis for such multifactorial disease is to be done as to have better treatment options.

Diagnostic tools and principles

Diagnosis of Covert Hepatic Encephalopathy (CHE) is the most significant in the whole episode of HE as, its manifestations are non-homogenous having a plethora of signs and symptoms making it non-specific and misled as any other disorder such as Hepatogenous Diabetes Mellitus (Cheon and Song, 2021, p. 4-8). CHE is arduous to detect as holds a latent position but, the impacts are not latent in terms of financial and psychiatric consequences. By following appropriate norms with personalized approach in considerations with various different upstream factors leading to it might aids in further detection, classification and grading of HE.

Test	Realm	Duration of exegesis	Description
PHES	Analysis of visual and psychometric abilities, Cognitive domain.	Fortnight	A simple diagnostic tool to overcome the resource short bearings of third world countries.
NCT-A	Psycho-muscular co-ordination	About a day	Less specific but readily available tool
NCT-B	Psychomotor consciousness	2 days	Great sensitivity with less specified approach.
SDT	Psychomotor momentum	2 days	Early indicator.
LTT	Psycho-visual motor pace	Half a week	Well befitted tool to check balance.
DST	Psychometric attentiveness	5 days	A suited tool to check cognitive balance.
CFF	Retinal gliopathy[4]	10 days	A synergistic test with brilliant outcomes.
MRI	Microhemorrhages of white matter	A week	A neuroimaging tool to provide brain insights and check neural impairments.
R-BANS	Immediate and Constructional attention	A month	A general test for neurocognitive impairment analysis.
EEG/ERP	Brain electrical activity	Fortnight	A clinical tool to analyse non-specific pre-dormant conditions

UGC Approved Journal
© UNIVERSAL RESEARCH REPORTS | REFEREED | PEER REVIEWED
ISSN : 2348 - 5612 | Volume : 05 , Issue : 04 | January - March 2018

ICT	Response and cognitive inhibition	20 days	A computerized general monitoring tool to keep to progression of HE in check.

**diagnostics available (Table 1)*

Abbreviations: PHES, Psychometric Hepatic Encephalopathy Score; NCT-A, Number Connection Test A; NCT-B, Number Connection Test B; SDT, Serial Dotting Test; LTT, Line Tracing Test; DST, Digit Symbol Test; CFF, Critical Flickering Frequency; MRI, Magnetic Resonance Imaging; R-BANS, Repeated Battery for Assessment of Neuropsychological Status; EEG/ERP, Electroencephalogram/ Event Related Potential; ICT, Inhibitory Control Test.

No single measure available is optimal for diagnosing CHE. The neuropsychological and physiological tests aren't enough as because of the presence of varying etiological upstream events. An elegant study by Montagnese et al. showcased about 61% patients could suffer HE because of the comorbidities and about 39% had it amongst the overt patients. In case of CHE, 54% deemed to have minimal HE and 46% had it ranging from comorbidities coming along. **(**Montagnese, et al., 2014, p. 405-406**).** An Individualized approach if feasible must be used to diagnose CHE because of varying IQ, EQ of individual and might have a clinical history to add on to it. Language limitation is also a constraint in case of neuropsychological testings.

Psychometric Hepatic Encephalopathy Score is a constellation of 5 cognitive, visuomotor and psychomotor pen-pencil based tests encompassing Number connection test A, B, serial dotting test, line tracing test, digit symbol test. This type of easily accessible, low-cost screening test is an important addition to the diagnostic toolbox, enabling patients and providers to diagnose HE early (Agarwal, et al., 2020, p. 3). Critical Flickering Frequency is an opthalamological test with expeditious, non-invasive qualities that uses Hepatonorm analyzer. It has an impressive accuracy at 39 Hz cutoff value. (Metwally et al., 2019, p. 1031). Magnetic Resonance Imaging: HE as involves a spectrum of varying neurological conditions, MRI could be used to provide an insight into brain white matter, edema if present, any structural impairments if persisting (Ridola et al., 2018, p. 156; Bathla and Hedge, 2013, p. 548). Repeated battery for assessment of neuropsychological status: It also is a paper and pencil test to aid neurocognitive disorders diagnosing and holds CHE diagnosing as secondary consequence, and is ISHEN recommended for CHE (Randolph et al., 2009, p. 631). Electroencephalogram is a potent diagnose for whole wide spectrum of HE. By analyzing somatosensory evoked potentials and Brainstem auditory responses (BAEPs), predormant neurological conditions could be reported clinically. (Guerit et al, 2009, p. 793). Inhibitory control test is a computerized test to detect further spectral progression in HE. ICT has proven its reliability in a study by offering moderate sensitivity (65%) and level of specificity was (57%) when compared to PHES. (Stawicka et al., 2020, p. 6).

The use of different metrics can help improve diagnostic accuracy. The evaluation must be done keeping clinical and biochemical profile of individual in sight as is an essential step in to decide the aid for the ailment.

UGC Approved Journal
© UNIVERSAL RESEARCH REPORTS | REFEREED | PEER REVIEWED
ISSN : 2348 - 5612 | Volume : 05 , Issue : 04 | January - March 2018

Probable Treatment Course

Despite the latent clinical manifestations offered by CHE and MHE, its consequences are not really dormant with effects on QOL[5], driving/navigation abilities, cognitive ailments and many others poses a threat on the daily life of a being. In spite of continuous research, reaching a single gold standard treatment has not been achieved yet and the varying signs even demand a person to person approach. There have been a number of studies indicating the effectiveness of current treatment methods **(**Ridola et al., 2018, p. 32-34**).** The treatments are usually required to be long term in order to get a hold onto the spectrum of HE progression. Some extensively used treatments to be summarized as:

Model of treatment	Mode of action	Proven efficacy	Precautions and side effects
1. Probiotics	• Rebalances the gut microflora. • Reduces serum ammonia level within short term use by week 4 and blocks spectral progression by week 8.	Better than placebo or no interventions.	• Requires a long course. • Not standardized
2. Lactulose (Nonabsorbable disaccharide).	• Fermentation is the central process by which it converts to Lactic and acetic acid in anaerobic conditions. • Acidic environment aids in conversion of NH_4^+ from NH_3.	Effectiveness in both primary and secondary prophylaxis of HE has been proven.	Diarrhea, Lactulose distastefulness, Abdomen bloating are some minor signs observes which could be managed by dietary advice.
3. Rifaximin	Binds to bacterial DNA dependent RNA polymerase and inhibits translational machinery.	Full bodied protective effects are seen against HE episodes.	Need a long term use and is mostly started in overt stages.
4. LOLA (L-ornithine L-aspartate)	Breaks into its elemental a.a., L-ornithine then functions as an intermediary of urea cycle and carbomyl phosphate synthase activator. Laspartate by transamination reaction forms glutamate via glutamine in brain, liver and	• Curbs hyperammonia condition. • Hepatoprotective potential aswell.	Though is a mainstream treatment process but hasn't proven its efficiency in early or CHE stages.

UGC Approved Journal
© UNIVERSAL RESEARCH REPORTS | REFEREED | PEER REVIEWED
ISSN : 2348 - 5612 | Volume : 05 , Issue : 04 | January - March 2018

	skeletal muscles.		

**treatments available*

Probiotics play a role in the therapy of HE by altering gut flora by reducing pathogen bacteria counts, intestinal mucosal acidity, decreased ammonia synthesis and absorption, changes in gut permeability, lowered endotoxin levels, and changes in short chain fatty acid synthesis (Sharma and Singh, 2016) Probiotics are likely to promote recovery and may lead to improvements in the development of overt hepatic encephalopathy, quality of life, and plasma ammonia concentrations when compared to placebo or no intervention, but they may have little or no effect on mortality as is proved here by a number of studies (Dalal et al., 2019, p. 1-96**).**

Lactulose Chemically β galactosidofructose along with Lacitol i.e. βgalactosidofructose causes acidification in colon, resulting in changes in the gut microflora. Lactulose cause significant multifold excretion of nitrogen and thus could be considered as first line defense (Sharma et al., 2013, p. 5).

Rifaximin is an orally administered broad spectrum, non-systemic antibiotic. It is an FDA approved drug to cure secondary prophylaxis of HE. Rifaximin causes a decrease in resistant bacterial strains risks in comparison to systemic antibodies in circulation. The non-absorbable nature makes it further efficient as causes a drop in its presence in the plasma levels (Bass et al., 2010, p 1071-1081).

LOLA is a compound salt that act by interfering with various metabolic pathways, lowers hyperammonia condition and thus acting as an effective treatment for HE even for the overt stages. But unilateral use of LOLA only does not hold such significant hold in curing CHE manifestations. Studies have shown LOLA to hold certain neuroprotective properties as-well (Kristiansen, 2016).

A multifaceted approach to HE treatment could prove to be quite effective. After the presence of such treatments, there are a number of other treatments prevailing as well like BCAA which earlier was used as Salvage therapy. As, acting as a great source of Glutamate thus, works in a manner similar as LOLA **(**Goh et al., 2018, p. 32**).** Embolization of shunt to help in detoxification of blood and prevent the hyper accumulation of ammonia. **(**Yanny et al., 2019, p. 611**).** From an elegant study to acquaint Hepatic encephalopathy with Diabetic encephalopathy, Metformin (A drug used for type II diabetes mellitus) has shown protective effects against HE in cirrhotic patients. (Cheon and Song**,** 2021, p. 2**).** Other possible treatment options holding future relevance could be Fecal Microbiota Transplant (FMT**) (**Lv

et al., 2019, p. 5-7) by altering gut microflora, various anti-inflammatories (Cauli et al., 2007, p. 4). A wide spectrum of physiological and neuropsychological manifestations need quantifications from diverse clinical backgrounds ranging from hepatology to psychology with value additions from neurologists and others in order to balance out the clinical latency faced by MHE.

Conclusion and Future Perspectives

So far, with an umbrella perspective into current and past literatures in order to formulate a specific set of standard to diagnose and aid the ailment, no single technique of diagnosis or any specific treatment procedure turn out to set gold standard for spectrum of HE in its covert or overt stages. For the CHE, a prompt diagnosis and keeping a check on threshold causes leading to a stage of HE holds the most crucial and significant place to prevent the progression and the far ranging consequences. A mix of precipitating factors and cofactors, with their interactions differs the neuropsychological and physiological manifestations of the disease. Thus, posing a different result for same techniques used for diagnosing it. So, critical evaluation must be done to avoid any uncertainity caused. CHE, poses delirium in selection of treatment procedure as, throughout the spectrum of HE, similar treatment procedure is used. Probiotics, Lactulose, Rifaximin, BCAA and others in many studies have shown their beneficial effects and a concoction of different methods with a result focused alterations could help set a course ahead. Following an individualized approach, with research engrained clinical preceding with multidimensional orientation and multidisciplinary scientific collaborations from various fields in accordance with practice guidelines definitely is the way ahead. Future studies further holds the potential to address the gaps in study, some approaches holding clinical potential are Minocline (Ibuprofen) by targeting microglial cells activation and normalizing iNOS activity, FMT holds significant potential with demanding trials with varying animal models and if is maintained with other possible treatment options. Compounds targeting neurotransmitters like Gamma aminobutyric acid (GABA) could also favour unmet needs.

[1] An abnormal connection between systemic circulation and porto-vascular system. The blood from abdominal organs rather than being drained to liver is shunted to systemic circulation causing liver atrophy. It when is combined with circulating nutrients, proteins and toxins results to HE.

[2]A diverse and dense consortium of gut residing microorganisms i.e. fungi, bacteria, archae, protozoa and viruses. About 10^{14} such microbial cells reside in human gut. With continuous growing research, a clarity in view that gut dysbiosis plays a significant role in liver disease progression has been established.

[3] Ranging from Hippocrates times (460-371 BCE) up till twentieth century, varying physiological, neurological and pathological mechanisms are unraveled in relationship establishing such axis but, exploiting the axis and adding encephalopathy to any condition must be done after a clear understanding of its upstream etiological events. Without such understanding, shadows are casted upon the cause and causing misinterpretation increasing the gaps from reaching effective cure.

4 A condition affecting the glial cells and is usually benign. Retinal gliopathy could be used as a marker for HE.

5 The QOL in relation to hospitalization, daily livelihood chores, sleep disorders as-well-as recurrent HE severely impacts the QOL of patient suffering and their caretakers too making them a socioeconomic liability.

References

Agarwal, A., Taneja, S., Chopra, M., Duseja, A., & Dhiman, R. K. (2020). Animal Naming Test - a simple and accurate test for diagnosis of minimal hepatic encephalopathy and prediction of overt hepatic encephalopathy. *Clinical and experimental hepatology*, *6*(2), 116–124. https://doi.org/10.5114/ceh.2019.95105.

American Association for the Study of Liver Diseases, & European Association for the Study of the Liver (2014). Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *Journal of hepatology*, *61*(3), 642–659. https://doi.org/10.1016/j.jhep.2014.05.042.

Amodio, P., & Montagnese, S. (2021). Lights and Shadows in Hepatic Encephalopathy Diagnosis. *Journal of clinical medicine*, *10*(2), 341. https://doi.org/10.3390/jcm10020341. Bai, M., Yang, Z., Qi, X., Fan, D., & Han, G. (2013). l-ornithine-l-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials. *Journal of gastroenterology and hepatology*, *28*(5), 783–792. https://doi.org/10.1111/jgh.12142.

Bathla, G., & Hegde, A. N. (2013). MRI and CT appearances in metabolic encephalopathies due to systemic diseases in adults. *Clinical radiology*, *68*(6), 545–554. https://doi.org/10.1016/j.crad.2012.05.021

Bajaj, J. S., Etemadian, A., Hafeezullah, M., & Saeian, K. (2007). Testing for minimal hepatic encephalopathy in the United States: An AASLD survey. *Hepatology (Baltimore, Md.)*, *45*(3), 833–834. https://doi.org/10.1002/hep.21515

Bajaj, J. S., Hafeezullah, M., Hoffmann, R. G., Varma, R. R., Franco, J., Binion, D. G., Hammeke, T. A., & Saeian, K. (2008). Navigation skill impairment: Another dimension of the driving difficulties in minimal hepatic encephalopathy. *Hepatology (Baltimore, Md.)*, *47*(2), 596–604. https://doi.org/10.1002/hep.22032

Bajaj, J. S., Cordoba, J., Mullen, K. D., Amodio, P., Shawcross, D. L., Butterworth, R. F., Morgan, M. Y., & International Society for Hepatic Encephalopathy and Nitrogen Metabolism
(ISHEN) (2011). Review article: the design of clinical trials in hepatic encephalopathy--an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. *Alimentary pharmacology & therapeutics*, *33*(7), 739–747. https://doi.org/10.1111/j.1365-2036.2011.04590.x

Bass, N. M., Mullen, K. D., Sanyal, A., Poordad, F., Neff, G., Leevy, C. B., Sigal, S., Sheikh, M. Y., Beavers, K., Frederick, T., Teperman, L., Hillebrand, D., Huang, S., Merchant, K., Shaw, A.,

Bortey, E., & Forbes, W. P. (2010). Rifaximin treatment in hepatic encephalopathy. *The New England journal of medicine*, *362*(12), 1071–1081. https://doi.org/10.1056/NEJMoa0907893

Cao, Q., Yu, C. B., Yang, S. G., Cao, H. C., Chen, P., Deng, M., & Li, L. J. (2018). Effect of probiotic treatment on cirrhotic patients with minimal hepatic encephalopathy: A metaanalysis. *Hepatobiliary & pancreatic diseases international: HBPD INT*, *17*(1), 9–16. https://doi.org/10.1016/j.hbpd.2018.01.005.

Cauli, O., Rodrigo, R., Piedrafita, B., Boix, J., & Felipo, V. (2007). Inflammation and hepatic encephalopathy: ibuprofen restores learning ability in rats with portacaval shunts. *Hepatology (Baltimore, Md.)*, *46*(2), 514–519. https://doi.org/10.1002/hep.21734

Cheon, S. Y., & Song, J. (2021). The Association between Hepatic Encephalopathy and Diabetic Encephalopathy: The Brain-Liver Axis. *International journal of molecular sciences*, *22*(1), 463. https://doi.org/10.3390/ijms22010463

Coltart, I., Tranah, T. H., & Shawcross, D. L. (2013). Inflammation and hepatic encephalopathy. *Archives of biochemistry and biophysics*, *536*(2), 189–196. https://doi.org/10.1016/j.abb.2013.03.016.

Dalal, R., McGee, R. G., Riordan, S. M., & Webster, A. C. (2017). Probiotics for people with hepatic encephalopathy. *The Cochrane database of systematic reviews*, *2*(2), CD008716. https://doi.org/10.1002/14651858.CD008716.pub3.

Dhiman, R. K., Saraswat, V. A., Sharma, B. K., Sarin, S. K., Chawla, Y. K., Butterworth, R., Duseja, A., Aggarwal, R., Amarapurkar, D., Sharma, P., Madan, K., Shah, S., Seth, A. K., Gupta, R. K., Koshy, A., Rai, R. R., Dilawari, J. B., Mishra, S. P., Acharya, S. K., & Indian National Association for Study of the Liver (2010). Minimal hepatic encephalopathy: consensus statement of a working party of the Indian National Association for Study of the Liver. *Journal of gastroenterology and hepatology*, *25*(6), 1029–1041. https://doi.org/10.1111/j.1440-1746.2010.06318.x

Fogel, W. A., Andrzejewski, W., & Maśliński, C. (1990). Neurotransmitters in hepatic encephalopathy. *Acta neurobiologiae experimentalis*, *50*(4-5), 281–293.

Goh, E. T., Stokes, C. S., Sidhu, S. S., Vilstrup, H., Gluud, L. L., & Morgan, M. Y. (2018). L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. *The Cochrane database of systematic reviews*, *5*(5), CD012410. https://doi.org/10.1002/14651858.CD012410.pub2

Guerit, J. M., Amantini, A., Fischer, C., Kaplan, P. W., Mecarelli, O., Schnitzler, A., Ubiali, E.,

Amodio, P., & members of the ISHEN commission on Neurophysiological Investigations (2009). Neurophysiological investigations of hepatic encephalopathy: ISHEN practice guidelines. *Liver international : official journal of the International Association for the Study of the Liver*, *29*(6), 789–796. https://doi.org/10.1111/j.1478-3231.2009.02030.x.

Häberle J. (2011). Clinical practice: the management of hyperammonemia. *European journal of pediatrics*, *170*(1), 21–34. https://doi.org/10.1007/s00431-010-1369-2Kristiansen R. G. (2016). Current state of knowledge of hepatic encephalopathy (part I): newer treatment strategies for hyperammonemia in liver failure. *Metabolic brain disease*, *31*(6), 1357–1358. https://doi.org/10.1007/s11011-016-9908-9.

Hadjihambi, A., Arias, N., Sheikh, M., & Jalan, R. (2018). Hepatic encephalopathy: a critical current review. *Hepatology international*, *12*(Suppl 1), 135–147. https://doi.org/10.1007/s12072017-9812-3.

Hudson, M., & Schuchmann, M. (2019). Long-term management of hepatic encephalopathy with lactulose and/or rifaximin: a review of the evidence. *European journal of gastroenterology & hepatology*, *31*(4), 434–450. https://doi.org/10.1097/MEG.0000000000001311.

Lemberg, A., & Fernández, M. A. (2009). Hepatic encephalopathy, ammonia, glutamate, glutamine and oxidative stress. *Annals of hepatology*, *8*(2), 95–102.

Lv, W. J., Wu, X. L., Chen, W. Q., Li, Y. F., Zhang, G. F., Chao, L. M., Zhou, J. H., Guo, A., Liu, C., & Guo, S. N. (2019). The Gut Microbiome Modulates the Changes in Liver Metabolism and in Inflammatory Processes in the Brain of Chronic Unpredictable Mild Stress Rats. *Oxidative medicine and cellular longevity*, *2019*, 7902874. https://doi.org/10.1155/2019/7902874.

Montagnese, S., Schiff, S., & Amodio, P. (2015). Quick diagnosis of hepatic encephalopathy: fact or fiction?. *Hepatology (Baltimore, Md.)*, *61*(1), 405–406. https://doi.org/10.1002/hep.27127.

Nardone, R., Taylor, A. C., Höller, Y., Brigo, F., Lochner, P., & Trinka, E. (2016). Minimal hepatic encephalopathy: A review. *Neuroscience research*, *111*, 1–12. https://doi.org/10.1016/j.neures.2016.04.009

Neff, G., & Zachry, W., III (2018). Systematic Review of the Economic Burden of Overt Hepatic Encephalopathy and Pharmacoeconomic Impact of Rifaximin. *PharmacoEconomics*, *36*(7), 809–822. https://doi.org/10.1007/s40273-018-0641-6.

Quigley E. (2017). Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. *Current neurology and neuroscience reports*, *17*(12), 94. https://doi.org/10.1007/s11910-017-0802-6

Randolph, C., Hilsabeck, R., Kato, A., Kharbanda, P., Li, Y. Y., Mapelli, D., Ravdin, L. D., RomeroGomez, M., Stracciari, A., Weissenborn, K., & International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) (2009). Neuropsychological assessment of hepatic encephalopathy: ISHEN practice guidelines. *Liver international : official journal of the International Association for the Study of the Liver*, *29*(5), 629–635. https://doi.org/10.1111/j.1478-3231.2009.02009.x.

Riggio, O., Ridola, L., Pasquale, C., Pentassuglio, I., Nardelli, S., Moscucci, F., Merli, M., Montagnese, S., Amodio, P., & Merkel, C. (2011). A simplified psychometric evaluation for the diagnosis of minimal hepatic encephalopathy. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*, *9*(7), 613–6.e1. https://doi.org/10.1016/j.cgh.2011.03.017.

Ridola, L., Cardinale, V., & Riggio, O. (2018). The burden of minimal hepatic encephalopathy: from diagnosis to therapeutic strategies. *Annals of gastroenterology*, *31*(2), 151–164. https://doi.org/10.20524/aog.2018.0232.

Ridola, L., Nardelli, S., Gioia, S., & Riggio, O. (2018). Quality of life in patients with minimal hepatic encephalopathy. *World journal of gastroenterology*, *24*(48), 5446–5453. https://doi.org/10.3748/wjg.v24.i48.5446

Sharma, P., Sharma, B. C., Puri, V., & Sarin, S. K. (2008). An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. *European journal of gastroenterology & hepatology*, *20*(6), 506–511. https://doi.org/10.1097/MEG.0b013e3282f3e6f5

Sharma, B. C., Sharma, P., Lunia, M. K., Srivastava, S., Goyal, R., & Sarin, S. K. (2013). A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *The American journal of gastroenterology*, *108*(9), 1-6. https://doi.org/10.1038/ajg.2013.219.

Sharma, B. C., & Singh, J. (2016). Probiotics in management of hepatic encephalopathy. *Metabolic brain disease*, *31*(6), 1295–1301. https://doi.org/10.1007/s11011-016-9826-x.

Stawicka, A., Jaroszewicz, J., Zbrzeźniak, J., Sołowianowicz, N., Woszczenko, A., Świderska, M., & Flisiak, R. (2020). Clinical Usefulness of the Inhibitory Control Test (ICT) in the Diagnosis of Minimal Hepatic Encephalopathy. *International journal of environmental research and public health*, *17*(10), 3645. https://doi.org/10.3390/ijerph17103645.

Wang, R., Tang, R., Li, B., Ma, X., Schnabl, B., & Tilg, H. (2021). Gut microbiome, liver immunology, and liver diseases. *Cellular & molecular immunology*, *18*(1), 4–17. https://doi.org/10.1038/s41423-020-00592-6Lemberg, A., & Fernández, M. A. (2009). Hepatic encephalopathy, ammonia, glutamate, glutamine and oxidative stress. *Annals of hepatology*, *8*(2), 95–102.

Weissenborn K. (2019). Minimal/Covert Hepatic Encephalopathy - Impact of Comorbid Conditions. *Journal of clinical and experimental hepatology*, *9*(1), 109–111. https://doi.org/10.1016/j.jceh.2018.08.010.

Weissenborn K. (2019). Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. *Drugs*, *79*(Suppl 1), 5–9. https://doi.org/10.1007/s40265-018-1018-z.

Yanny, B., Winters, A., Boutros, S., & Saab, S. (2019). Hepatic Encephalopathy Challenges, Burden, and Diagnostic and Therapeutic Approach. *Clinics in liver disease*, *23*(4), 607–623. https://doi.org/10.1016/j.cld.2019.07.001.