Diagnosis and Management of Hepatic Encephalopathy

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KEYWORDS

• Cirrhosis • Minimal hepatic encephalopathy • Hepatic encephalopathy
• Transjugular intrahepatic portosystemic shunt • Ammonemia

KEY POINTS

- Hepatic encephalopathy is a very common, life-threatening complication of cirrhosis.
- Clinicians become more and more interested in this clinical situation with the widespread use of TIPS in the management of portal hypertension-related complications.
- Liver transplantation should be discussed in case of refractory hepatic encephalopathy; in this setting, differential diagnosis have to be ruled out in order to maximize the chance of complete recovery.

INTRODUCTION

The prevalence and cumulative incidence of hepatic encephalopathy (HE) are difficult to state precisely. Thirty percent to 45% of cirrhotic patients could be affected by overt hepatic encephalopathy (OHE), and the prevalence of minimal hepatic encephalopathy (MHE) may be as high as 85% in some case series.[1] The joint American-European guidelines[2] define HE as "a brain dysfunction caused by liver insufficiency and/or portosystemic shunts." This definition highlights the importance of the causal relation between neurologic abnormalities, from subtle neuropsychological abnormalities to coma, and liver dysfunction and/or portosystemic shunts.

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According to the underlying liver disease, HE is divided into type A (resulting from acute liver disease), type B (resulting from portosystemic shunting without any liver disease), and type C (resulting from cirrhosis).[1] This review focuses on type C HE. The clinical impact of HE is of major importance for both the patient and their caregivers. A first episode of OHE is associated with a survival rate at 1 year of 35% to 45%.[3] HE is also associated with altered work capacity, an increase in falls, more car accidents, and poor quality of life.[4,5] After an episode of OHE, cognitive status often remains impaired, and patients display MHE. Thus, this condition represents a major burden for affected families/caregivers and health care systems.[6]

The peculiar medical presentation of HE, encompassing the specialties of both hepatology and neurology, renders a multidisciplinary approach to the disease very useful both to better describe the neurologic presentation and to rule out differential diagnoses. With this in mind, in 2012, the authors created a unique study group dedicated to the neurologic complications of liver diseases at the Pitié-Salpêtrière University Hospital in Paris: The Brain Liver Pitié-Salpêtrière Study (BLIPS) group. This group, which includes hepatologists, neurologists, liver surgeons, liver transplant specialists, neuroradiologists, neurophysiologists, neuropsychologists, pharmacists, biochemists, immunologists, and sleep medicine specialists, follows both outpatients and inpatients, from patients with MHE to patients with OHE in the intensive care unit (ICU). This multidisciplinary approach to HE patients appears to be fundamental in the diagnosis and management of both the patients and their caregivers.

In this review, the authors first focus on the pathophysiology of HE in cirrhosis and the diagnosis of HE and discuss the different therapeutic options. They summarize the available recommendations and suggest an algorithm based on the clinical experience of the BLIPS group.

Pathophysiology of Hepatic Encephalopathy in Cirrhosis

The pathophysiology of HE in cirrhotic patients is still not totally understood. Even if its correlation with the importance of neurologic impairment is regularly challenged, the implication of hyperammonemia has been well established for decades.[7,8] Recent works have highlighted the synergic effect of hyperammonemia and systemic inflammation[9,10] (**Fig. 1**). Only patients with systemic inflammation, signs of systemic inflammatory response syndrome, and/or elevated levels of proinflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]) were found to develop HE in the presence of hyperammonemia. Hyperammonemia is the result not only of the increased intestinal production of ammonia by the enterocytes but also of liver failure responsible for decreased urea cycle function and/or the presence of portosystemic shunting. Once the liver metabolism of ammonia is impaired, only muscle cells and astrocytes can metabolize ammonia into glutamine through the glutamine synthase enzyme. This pathophysiological aspect probably explains why HE is more frequent in patients with major sarcopenia.[11,12] Astrocytes extrude osmotic compounds, such as myoinositol and taurine, to compensate for glutamine osmotic power in order to prevent swelling.[13] Of note, this is not the case in the setting of acute liver failure, whereby such compensatory mechanisms have no time to be initiated, thereby generating brain edema.[14] Whereas the presence of systemic inflammation is clearly established in HE, the existence and the pattern of neuro-inflammation are less understood. Microglial activation is incriminated, which could be associated with other pathophysiologic mechanisms. An increase in glutamine levels associated with neuroinflammation leads to an increase in the glutamatergic and GABAergic tones.[15,16] The accumulation of other substances in the central nervous system has been found in HE: aromatic amino acids, mercaptans, manganese, benzodiazepine-like

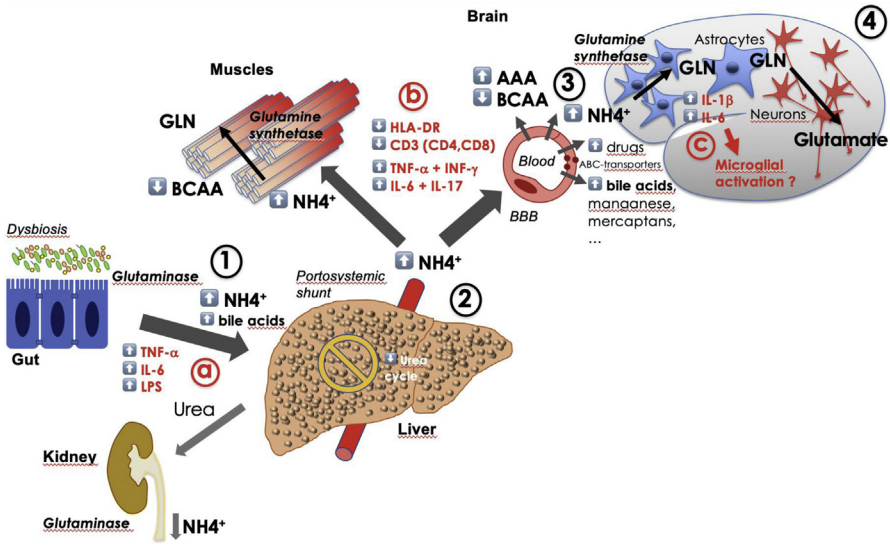

Fig. 1. Pathophysiology of HE. Intestinal microbiota dysbiosis and increased intestinal ammonia production through the enterocytes lead to hyperammonemia, increased secondary to primary bile acids (1), and increased inflammatory markers (lipopolysaccharide [LPS], IL-6, TNF-α) in the portal vein (A). Liver failure responsible for a decreased urea cycle function and the presence of portosystemic shunting will worsen hyperammonemia (2), systemic inflammation (with increased levels of IL-6, IL-17, TNF-α, and decreased expression of HLA-DR and T-lymphocytes count), (B) but also in several other substances that cannot be any longer metabolized by the liver. Ammonia can be metabolized in muscle cells into glutamine through glutamine synthetase but has a side effect to decrease BCAA levels. Ammonia and most of the inflammatory markers cross the blood-brain barrier (3) and can thus be metabolized into glutamine through glutamine synthetase in astrocytes cytosol. Glutamine osmotic power is compensated by the extrusion of other osmotic compounds (myoinositol and taurine) outside the astrocytes. Whereas the presence of systemic inflammation is clearly established in HE, the existence and the pattern of neuroinflammation are less well understood (C). Microglial activation is incriminated, which could be associated with other pathophysiologic mechanisms. Taken together, an increase in glutamine levels associated with neuro-inflammation led to both an increase in the glutamatergic and GABAergic tones that explain neurologic symptoms (4). Several substances accumulate in the central nervous system: aromatic amino acids, mercaptans, manganese, benzodiazepine-like compounds, and drugs (3). Some are due to impaired liver metabolism (mercaptans, manganese), whereas others are due to an abnormal imbalance in transport through the blood-brain barrier (aromatic amino acids) or modulation of ABC-transporters efflux pump associated with impaired liver metabolism. GLN, glutamine; IFN-γ, interferon-γ.

compounds, or xenobiotics.[8,17] In particular, the accumulation of bile acids brings some new insights to HE pathophysiology and accounts for the link between intestinal microbiota dysbiosis and neuroinflammation.[18] Whether the accumulation of xenobiotics is part of HE pathophysiology or a feature of drug-induced encephalopathy is still unclear.[17] The implication of dysbiosis in the pathophysiology of HE is outlined by the recent randomized control trial of fecal microbiota transplantation (FMT) compared with standard of care or placebo.[19,20] This trial showed that FMT was able to lower inflammatory cytokines levels, hyperammonemia, and the secondary/primary bile acid ratio.[19]

Diagnosis of Hepatic Encephalopathy

The diagnosis of OHE is relatively standardized and includes a wide range of clinical manifestations according to the severity of HE. Other diagnoses should be ruled out. The diagnosis of MHE is more complicated, as there is no applicable gold standard, and there are many differential diagnoses. Accurately phenotyping neurocognitive disorders is particularly important when liver transplantation is being considered.

Diagnosis of overt hepatic encephalopathy

Clinical diagnosis. The clinical presentation of OHE ranges from asterixis to coma. The most frequent/typical symptoms of OHE are asterixis, which is the first manifestation of OHE, and psychomotor slowing.[21] Lethargy, extrapyramidal syndrome,[22] seizures,[23] and coma[24] are less frequently observed. Of note, the clinical manifestations of OHE fluctuate over time, and this explains why the diagnosis is sometimes not easy to make and not always reproducible in a given patient.

Paraclinical diagnosis. Some tests are useful to support the diagnosis of HE, especially on initial presentation and when a differential diagnosis is difficult. In the authors' team, they tend to perform a complete workup as often as possible. This workup includes measurement of the plasma ammonia level, electroencephalogram (EEG), and cerebral imaging, especially MRI (Appendix 1).

The role of the plasma ammonia level in HE has been largely debated for decades. As discussed earlier, it is known that a high plasma ammonia level plays a crucial role in the pathophysiology of HE.[25,26] The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver guidelines,[2] as well as the recent French guidelines,[20] recommend reconsideration of the diagnosis of HE if the plasma ammonia level is normal,[1] with the negative predictive value being approximately 80%. However, the positive predictive value of the ammonia level is still debated in the setting of cirrhosis, and the plasma ammonia level is not useful for a positive diagnosis. The prognostic value of a high plasma ammonia is still debated in the setting of cirrhosis.[26–29] Recently, in a large retrospective series of patients who were included prospectively in 3 different cohorts, some investigators pointed out that ammonia level was an independent prognostic factor of mortality in patients with or without OHE.[30] This finding suggests that normalization of ammonemia should be a therapeutic target. Outside of the acute setting, it has been suggested that the fasting plasma ammonia level predicted the risk and frequency of HE episodes.[31] This phenomenon was shown in the past in a very different setting also implicating ammonia overload, that is, urea cycle disorders.[32] A recent retrospective study of more than 100 patients reported that inpatient management of OHE with lactulose was not influenced by either the presence or the level of ammonia, suggesting that ammonia levels do not presently guide physicians in clinical practice.[33] In the authors' opinion, the issue of ammonia response-guided therapy has to be solved in the future. Appendix 2 delineates the pros and cons of the measurement of the plasma ammonia level.

The real issue with ammonia measurement is that this test is unreliable. It is not routinely performed in every center, and some conditions need to be fulfilled for it to be interpretable. Recommendations include collecting the blood sample with no venous stasis (ie, ideally without use of a tourniquet), completely filling the tube, transporting it quickly to the laboratory on ice, and cautiously interpreting the measurement (for example, it may be distorted if hemolysis or severe jaundice was present) (see Appendix 2). The only risk incurred when the test is not correctly performed is abnormally high values (>100 μmol/L). In this case, the most likely diagnosis is false

hyperammonemia. After control, if the ammonia values stay very high, inborn errors of metabolism, especially urea cycle disorders, should be ruled out.[34] The authors' team performs ammonia measurements at each episode of encephalopathy in a cirrhotic patient.

EEG typically displays a slowing of basic rhythmic activity with triphasic waves and anterior-predominant abnormalities in HE (**Fig. 2**A). These abnormalities may be observed in OHE or MHE and correlate with the severity of HE and the severity of cirrhosis.[35] EEG enables one to rule out epilepsy, which may be useful when patients have abnormal movements or coma. EEG reading needs to be performed by experienced neurophysiologists to ensure an accurate diagnosis.[36–38] Moreover, EEG abnormalities are sometimes missing and, above all, are not specific to HE; these abnormalities may be present in any metabolic encephalopathy, including sepsis, hypercapnia, or drug-induced encephalopathy.[2,39] Last, the issue of EEG availability is a major obstacle to its use in general practice.

Cerebral imaging is mostly useful to rule out other disease processes. It should be performed at least for the first episode of HE and should be repeated for each episode of HE with atypical symptoms, especially if focal central nervous system symptoms

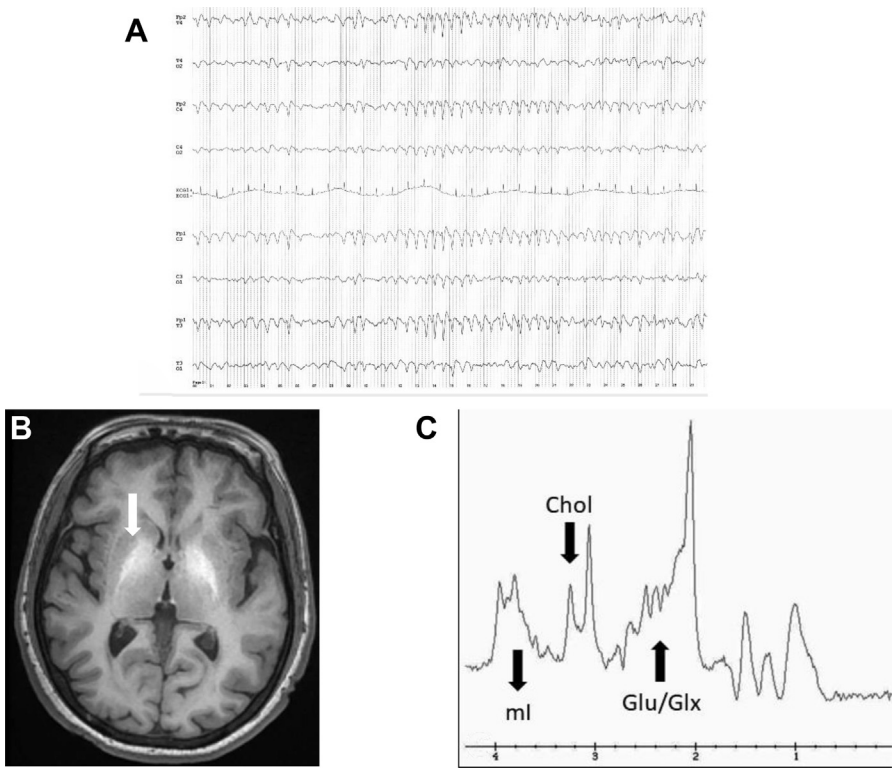

Fig. 2. Typical signs of HE with EEG and cerebral MRI. (*A*) The EEG shows a slowing of basic rhythmic activity, triphasic waves, anterior-predominant abnormalities, and worsening if hearing or painful stimulation. (*B*) Cross-section of cerebral MRI, T1 acquisition: spontaneous hypersignal in basal ganglia (*arrow*). (*C*) Magnetic resonance spectroscopy of corona radiata: increase of glutamine + glutamate (Glu/Glx), decrease of myoinositol (mI), and decrease of choline (Chol).

are present. Brain imaging cannot be done in some patients displaying confusion, except under anesthesia, and this is a major concern. This limitation considerably hampers the diagnostic process, at least in the acute phase. Cerebral MRI is the best test option, but cerebral computed tomographic (CT) scan should be done if MRI is not available. Cerebral MRI typically shows spontaneous T1 hypersignal in the basal ganglia, probably because of manganese overload (**Fig. 2**B), but this may reflect portosystemic shunting more than HE.[40,41] Performing magnetic resonance spectroscopy, which analyzes metabolic spectra in specific areas of cerebral tissue, may be useful to reinforce the diagnosis of HE.[42–45] It typically shows an increase in glutamine and glutamate, a decrease in myoinositol, and a decrease in choline in the corona radiata (**Fig. 2**C). However, brain spectroscopy is only available in a few centers. Its diagnostic and prognostic values have not been studied; thus, its use cannot be recommended in clinical practice. In the authors' experience, if a typical profile is seen, particularly an increase in glutamine and glutamate, this can suggest ammonia hypermetabolism in the astrocytes and may be of interest in cases whereby ammonia levels are not constantly increased. Conversely, if spectroscopy is normal, the diagnosis of HE should be reconsidered.

In summary, the need for a paraclinical workup will depend on the clinical presentation (typical or not), medical history (first bout or not), and protocols of the center. The usefulness of different paraclinical testing is shown in Appendix 1.

Differential diagnosis. The main differential diagnosis of HE types and their characteristics is presented in **Table 1**. In the authors' experience, in the absence of any focal sign, the main differential diagnoses of OHE are other causes of metabolic encephalopathy, alcohol withdrawal, and, more rarely, nonconvulsive status epilepticus.

When nonconvulsive status epilepticus is suspected, EEG is very useful to confirm or rule out the diagnosis and to avoid overprescribing benzodiazepines, which may worsen HE. Other causes of metabolic encephalopathy include sepsis,[46] drug-induced encephalopathy, dysnatremia, hyperuricemia, and hypercapnia. The relationship between sepsis and encephalopathy in the setting of cirrhosis has been known for years.[46] Numerous medications are neurotoxic, and this is of even more concern in cirrhotic patients, as the blood-brain barrier is probably more permeable. As a matter of fact, in a study of the cerebrospinal fluid in cirrhotic patients with encephalopathy, the authors showed the presence of several compounds that are known to be neurotoxic, such as antibiotics.[18]

Other differential diagnoses must be investigated, especially if patients have focal central nervous system signs (see **Table 1**). In some situations, encephalopathy may reveal inborn errors of metabolism, with urea cycle defects occurring frequently.[34,47,48] Although rare, these diagnoses are essential because they lead to specific treatments in an emergency, such as protein restriction, hypercaloric carbohydrate and lipid intake, the use of ammonia-scavenging drugs, and sometimes renal replacement therapy. Inborn errors of metabolism should particularly be considered in cases of severe neurologic symptoms with high hyperammonemia (>150 μmol/L), subnormal hepatic blood tests, and family history of hepatic or neurologic disease. In **Fig. 3**, the authors suggest an algorithm in case of suspicion of OHE.

Diagnosis of minimal hepatic encephalopathy

Clinical diagnosis of minimal hepatic encephalopathy. MHE is still difficult to diagnose in many cases because of (1) the absence of a diagnostic gold standard that can be

Table 1
Main differential diagnosis of hepatic encephalopathy

	Differential Diagnosis	Circumstances	Neurologic Signs and Diagnosis Confirmation	Comments
OHE	Epilepsy/status epilepticus	Sometimes due to alcohol or drug withdrawal, sometimes due to a focalized cerebral lesion, sometimes spontaneous	Seizures Sometimes coma if nonconvulsing: diagnosis with EEG	
	Metabolic cause of delirium			
	Drug-induced encephalopathy	Several drugs, HIV	Drug dosage in the blood	Possible in the absence of an obvious drug known to be neurotoxic and with drugs concentrations in the normal ranges in the blood
	Other metabolic encephalopathies (uremic or hypercapnic or septic encephalopathy, hyponatremia or hypernatremia)	Renal failure, respiratory insufficiency, sepsis	Blood tests (urea level, blood gases, inflammatory syndrome), known identified infection Same EEG as HE (slowing and triphasic waves)	
	Alcohol withdrawal	Sometimes due to hospitalization	History Tip tremor, sweat, hallucinations, seizures	Treatment with benzodiazepines despite the risk of worsening HE
	Benzodiazepines withdrawal	Sometimes due to hospitalization	History Seizures Urinary toxic analysis	
	Carential encephalopathy (Gayet-Wernicke-Korsakoff syndrome, folic acid or vitamin B12 deficiency, vitamin PP deficiency)	Severe undernourishment and alcohol intake, autoimmune disease, hematologic disease, or overweight surgery	Oculomotor abnormalities, nystagmus, amnesia, false recognition, delirium, hypothermia, paraesthesia Specific vitamin dosage Normal ammonia level	Progressive worsening most frequently, but acute onset is possible, little fluctuation, associated systemic signs

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Table 1
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Differential Diagnosis	Circumstances	Neurologic Signs and Diagnosis Confirmation	Comments
Osmotic demyelination syndrome (formerly centropontine or extrapontine myelinolysis)	Rapid fluctuation of natremia	Tetraparesis and/or facial palsy FLAIR hypersignal in cerebral MRI (pontine in the case of centropontine myelinolysis, diffuse if extrapontine)	Large interindividual sensitivity
Focal cerebral lesion			
Subdural or epidural haematoma	Falls with head injury,	Hyperdensity on brain CT scan	Do not hesitate to perform a cerebral imaging if atypical clinic signs of HE
Cerebral thrombophlebitis	Thrombophilia	Vein obstruction on brain CT scan with contrast-enhancement agent injection or on brain MRI angiogram	
Ischemic or hemorrhagic stroke	Arterial hypertension, cardiovascular risk factor, male sex	Cerebral MRI	
Miscellaneous			
Reversible posterior leukoencephalopathy syndrome	Especially when immunosuppression (post–liver transplantation) in the context of arterial hypertension and renal function impairment	Delirium, headache, seizures, cortical blindness White matter vasogenic edema affecting the posterior occipital and parietal lobes of the brain on MRI	
Autoimmune or paraneoplastic encephalitis	Known cancer or autoimmune disease	Delirium, seizures, mouth and face dyskinesia Lymphocytic meningitis on lumbar puncture Autoimmune antibodies specific for encephalitis (anti-NMDA-R, anti-LGI-1, anti-Caspr-2, anti-Hu)	

	Inborn error of metabolism (urea cycle disorders are the most frequent)	Family history	Highly elevated ammonia levels Blood amino acid chromatography Urinary organic acid, including urinary orotic acid	High value of ammonemia discordant with the absence of icterus and low level of transaminases Treatment with diet rules
MHE	*Neurocognitive disorders*			
	Vascular dementia	Metabolic cause of cirrhosis	Brain imaging (vascular leukopathy on cerebral MRI), neuropsychologic testing, neurodegenerative biomarkers (normal), normal ammonia level	Progressive worsening, absence of fluctuation
	Alcoholic dementia	Chronic alcohol intake	Neuropsychologic assessment, atrophy on brain imaging with important cerebellar atrophy, normal ammonia level	Progressive worsening, absence of fluctuation
	Carential encephalopathy (Gayet-Wernicke-Korsakoff syndrome, folic acid or vitamin B12 deficiency, vitamin PP deficiency)	Severe undernourishment and alcohol intake, autoimmune disease, haematological disease or overweight surgery	Oculomotor abnormalities, nystagmus, amnesia, false recognition, delirium, hypothermia, paraesthesia Specific vitamin dosage Normal ammonia level	Progressive worsening, little fluctuation, associated systemic signs
	Neurodegenerative disorder (Alzheimer disease or frontotemporal dementia)	Family history sometimes	Neuropsychologic assessment, hippocampus atrophy on cerebral MRI, neurodegenerative biomarkers in lumbar puncture, PET-FDG scanning Normal ammonia level	Progressive worsening, absence of fluctuation
	Endocrinal encephalopathies (Hashimoto encephalopathy, Addison disease) (rare)	Thyroiditis, autoimmune disease, tuberculosis	TSH, T4, cortisol Normal ammonia level	Rapid response to corticosteroids in the case of Hashimoto encephalopathy
	Psychiatric disorders			
	Depression	Previous history of mental or depressive disorder, anxiety	Elimination diagnosis	Sometimes in the context of Wilson disease

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Table 1
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Differential Diagnosis	Circumstances	Neurologic Signs and Diagnosis Confirmation	Comments
Toxic encephalopathies			
Over-the-counter use of sedatives (opioids, benzodiazepines)	Several prescription drugs, previous history of addiction	Urinary or blood testing, normal ammonia level	Possible despite the theoretic counterindication of cirrhosis
Alcohol intake	History of alcohol addiction	Blood testing, normal ammonia level	Some fluctuation, importance of the discussion with relatives
CNS infection (rare)			
Syphilis	Hepatitis C or B cirrhosis	Specific blood and cerebrospinal fluid testing	Reversible with antibiotics
HIV	Hepatitis C or B cirrhosis	HIV serology	Slowly progressive
Lyme disease	Specific regions, outdoor activities or work	Specific blood and cerebrospinal fluid serology and Western blot	Other organ involvement
Hepatitis B and C	Hepatitis B or C cirrhosis	Possible abnormalities on MR spectroscopy	Discussed
Miscellaneous (rare)			
Obstructive sleep apnea syndrome and other sleep disorders	Frequently associated with obesity and arterial hypertension	Headache, need for naps Hypercapnia Apnea-hypopnea Index >5 if obstructive sleep apnea	Questioning relatives may be helpful
Autoimmune disease with neurologic involvement (lupus, sarcoidosis, Gougerot-Sjogren, Behçet disease)	Autoimmune disease	Specific blood abnormalities, meningitis on lumbar puncture	Rare in the context, other organ involvement
Autoimmune or paraneoplastic encephalitis	Known cancer or autoimmune disease	Autoimmune antibodies specific for encephalitis (anti-NMDA-R, anti-LGI-1, anti-Caspr-2, anti-Hu)	

Abbreviations: CNS, central nervous system; FLAIR, fluid-attenuated inversion recovery; HIV, human immunodeficiency virus; TSH, thyroid-stimulating hormone.

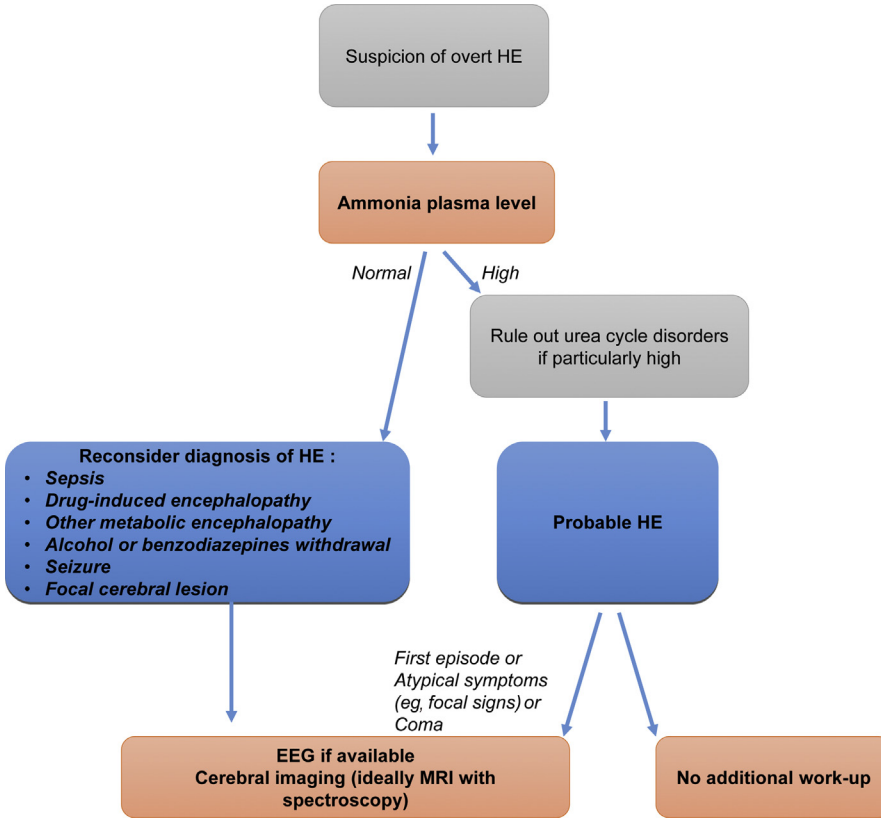

Fig. 3. Algorithm if suspicion of OHE.

performed routinely in clinical practice, (2) the fluctuating character of symptoms, and (3) the fact that many patients are not aware of (anosognosia) or tend to hide their symptoms. Special attention should be paid to the caregivers, as they often relay subtle abnormalities not mentioned by the patients. Of major importance is comparison with the previous cognitive status. Indeed, to diagnose MHE when seeing a patient with cognitive symptoms, it is mandatory to assess a deterioration of cognitive status over time along with worsening of liver disease, and fluctuation of symptoms. Last, one must be aware of the many differential diagnoses of cognitive disorders (see later discussion under the differential diagnosis section). Among the differential diagnoses, only seizures could present with fluctuating symptoms. Thus, in the absence of any fluctuations, MHE should be suspected.

MHE includes psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiologic alterations without clinical evidence of mental change. Clinical presentation can also include a trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, and altered sleep rhythm. These symptoms are sometimes outlined by the caregiver. In this case, it is recommended by some experts to classify HE as stage 1 and not MHE (see later discussion under classification).

A neuropsychological assessment is necessary to confirm the diagnosis of MHE. The psychometric hepatic encephalopathy score[48] is considered by many the gold

standard. It includes 5 tests that enable one to assess psychomotor speed and visuospatial ability. Other tests may be used,[2,49] such as the critical flicker frequency test, which assesses the patient's ability to discriminate a discontinuous light with decreasing frequency[50–52]; the inhibitory control test[53]; the scan test[54]; and the Stroop test.[55] Two abnormal tests are usually considered to diagnose MHE.[1,2] However, all those tests are time-consuming. These tests are dependent on the level of education, which renders their interpretation difficult.

Recently, the animal naming test has been suggested to screen easily and quickly for MHE.[56] This test only requires a timer, and the practitioner has to count the number of animals that the patient can name in 1 minute (Appendix 3). In 1 prospective series, naming more than 20 animals in 1 minute could rule out MHE with a negative predictive value of 76% and a specificity of 78%.[57] Of note, cutoffs may differ between languages, and this test must be validated among different countries. The animal naming test can be considered a good screening test and is recommended by the French guidelines to screen for MHE.[58]

Paraclinical diagnosis of minimal hepatic encephalopathy. Some studies suggest that EEG is more sensitive than psychometric tests[59–61] for the diagnosis of MHE. Moreover, some EEG features may predict OHE occurrence at 1 year.[62] Other paraclinical tests, such as ammonemia and brain imaging, can be useful for the diagnosis of MHE. Their indications and interpretation are the same as for OHE.

Differential diagnosis of minimal hepatic encephalopathy. The differential diagnosis of MHE can be cumbersome. Differential diagnoses are displayed in **Table 1**. Distinguishing between MHE and neurodegenerative disorders at the stage of minimal cognitive impairment (MCI) is particularly difficult. Among the diagnoses, MCI of vascular origin is frequent because of the growing incidence of metabolic cirrhosis. Alcoholic neurotoxicity, Gayet-Wernicke-Korsakoff encephalopathy, and neurodegenerative diseases also must be suspected, especially if patients display persistent temporospatial disorientation, anterograde amnesia, dyspraxia, or speech disorders. In such situations, caregivers often describe progressive worsening of symptoms and little fluctuation. Moreover, distinction between MHE and depression is sometimes difficult. A focal cerebral lesion should be ruled out if there is any doubt in the diagnosis.

If MHE is suspected, 2 options can be proposed: either perform a rather complete workup, or in some centers like the authors' center, perform a therapeutic test. In **Fig. 4**, the authors propose an algorithm in the case of suspicion of MHE.

Classifications

Many classifications of HE have been used over the years, and many revisions have taken place. The authors describe here the latest classification, modified from West Haven, and it includes the different ways of characterizing HE. All the following items should be provided when discussing a patient: type of HE, stage of HE, time course, and precipitating factors.

According to the clinical presentation (see earlier discussion under previous sections). Symptoms depend on the severity of HE, usually described with the West Haven classification (**Table 2**).[2] When the classical neurologic examination is normal, HE is defined as minimal or stage I HE. In stage I HE, the relatives can point out symptoms, whereas in MHE, only neuropsychological/physiologic testing supports symptoms. In the last proposed version of the West Haven classification, covert hepatic encephalopathy (CHE) brings MHE and stage I HE together; in fact,

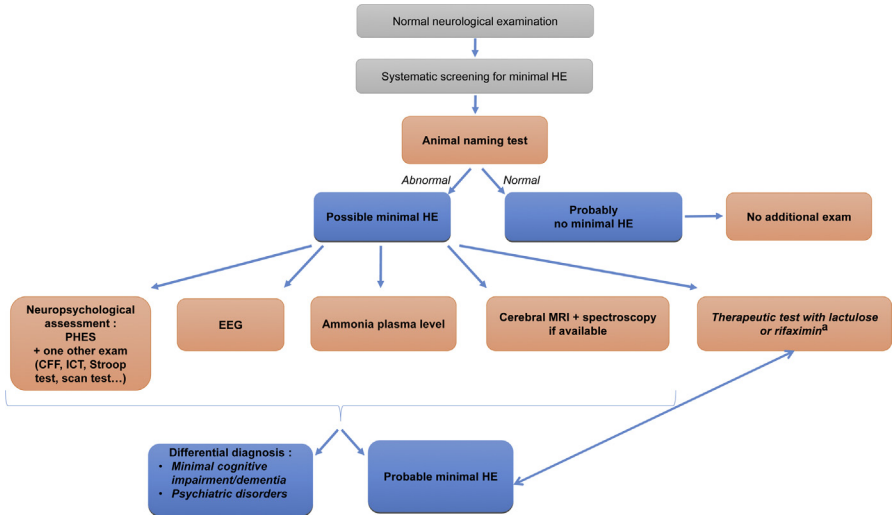

Fig. 4. Algorithm for the diagnosis of MHE. CFF, critical flicker frequency test; ICT, inhibitory control test; PHES, Psychometric Hepatic Encephalopathy Score. [a]Validated in France as first-line treatment of MHE.

Table 2
West Haven classification

	Stage of HE	Symptoms
CHE	Minimal	Psychometric or neuropsychologic alterations of tests exploring psychomotor speed/executive functions or neurophysiologic alterations without clinical evidence of mental change
	I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm
OHE	II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis
	III	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior
	IV	Coma

Adapted from Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998 Hepatology 2002; 35(3)716-21 ; with permission.

whether minimal and stage I HE should be merged into a unique category is still a matter of debate, as the outcome is probably not the same between the 2 entities. However, the distinction between MHE and stage I HE can be cumbersome in clinical practice.

According to time course. Symptoms of HE are classically fluctuant and interspersed with remission phases (episodic HE). HE is defined as recurrent when patients have more than 2 episodes of OHE within 6 months and persistent if behavioral alterations are always present and interspersed with relapses of OHE.

According to the existence of precipitating factors. HE is sometimes contemporary to another insult. Some of those factors can be either triggers or causes of encephalopathy (see later discussion).

Diagnosis of hepatic encephalopathy: remaining issues

Precipitating factor/trigger vs cause of hepatic encephalopathy. Sepsis and medications can induce encephalopathy in patients outside of the setting of cirrhosis/portosystemic shunts. Hence, both can be considered as differential diagnoses or as precipitating factors of HE. Ammonia levels could help in this matter: hyperammonemia in the context of encephalopathy suggests HE with a precipitating factor.

Brain reserve. Cirrhotic patients often display other causes of brain damage than HE, either related to the cause of their liver disease (metabolic syndrome, for example, with vascular risk factors, alcohol abuse) or related to other diseases and age. Hence, HE should, in some cases, be envisioned as an explanation of only part of the neurologic symptoms. This aspect is particularly important when discussing liver transplantation, as "complete neurologic recovery" is a goal that is not always attainable.

Treatment of Clinical Hepatic Encephalopathy

General management of hepatic encephalopathy

The general management of HE is based on several principles: (1) exclusion of other conditions mimicking HE (see later discussion under algorithm for the diagnosis of HE), (2) evaluation of the severity of HE in order to manage patients with altered consciousness in the ICU, (3) identification and treatment of precipitating factors, (4) empirical ammonia-lowering treatment, and (5) prevention of HE recurrence (**Fig. 5**).

Treatment of precipitating factors

Precipitating factors include gastrointestinal bleeding, infection, dehydration/hyponatremia/renal failure, constipation, and use of medications. These factors may precede HE or be contemporary to HE. Identifying and treating the precipitating factors of HE is mandatory, as treatment of the precipitating factors has been shown to improve HE in 90% of cases. Moreover, prevention of HE relies on the elimination of precipitating factors.

Gastrointestinal bleeding. HE is often linked to gastrointestinal bleeding and is related, in this situation, to deteriorating liver function, inflammation, infection, and hyperammonemia. A primary prophylaxis of HE with lactulose is required in cases of gastrointestinal bleeding[63] (see later discussion).

Hyponatremia. Hyponatremia is associated with an increased risk of HE,[64] and there is a correlation between hyponatremia and HE severity. It seems therefore crucial to

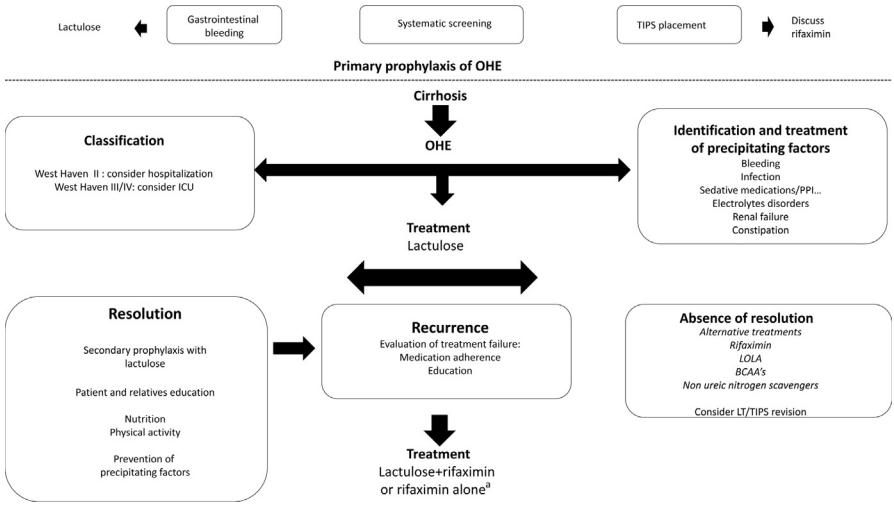

Fig. 5. Proposed algorithm for the prophylaxis and treatment of HE. LT, liver transplantation. [a]In case of lactulose intolerance.

maintain a sodium level greater than 130 mmol/L. Moreover, hyponatremia is associated with a lower response to HE therapy, including lactulose.

Constipation. Patients with cirrhosis often complain of constipation, which is accompanied by ascites, dysautonomia, and prolonged bed rest. Constipation may lead to HE through bacterial overgrowth.

Medications. Several retrospective studies have suggested a link between proton pump inhibitor (PPI) use and HE.[65] PPI cause alterations in gut microbiota. The elimination of the gastric acid barrier may facilitate dysbiosis, leading to bacterial overgrowth. Another hypothesis relies on drug-drug interaction with the blood-brain barrier.[66] In 1 recent prospective series of more than 300 patients, PPI use was associated with MHE, OHE, and increased mortality in patients with cirrhosis.[67] It seems therefore appropriate to regularly evaluate the balance between benefits and risks in such situations. The same results are observed with the use of sedative medications, such as benzodiazepines; several retrospective studies suggested a link between HE and benzodiazepines,[68] which should be considered precipitating factors. Therefore, such medications should not be prescribed to patients with cirrhosis except in cases of delirium tremens, a situation in which the efficacy of benzodiazepines has been clearly demonstrated.[69]

Available therapeutics

Nonabsorbable disaccharides. Lactulose and lactitol are nonabsorbable disaccharides that reduce the intestinal production/absorption of ammonia by different mechanisms[70]: (1) a laxative effect, resulting in an overall decrease in transit time; (2) a reduction in intraluminal pH, leading to increased formation of $NH4^+$ from NH3, with $NH4^+$ not being absorbed; and (3) a decrease in bacteria-producing ammonia.

Recently, a meta-analysis including 31 randomized controlled trials (RCTs)[71] showed that lactulose improved the resolution of HE episodes (relative risk [RR] = 0.62, 95% confidence interval [CI]: 0.39–0.99), as well as survival (RR = 0.49, 95% CI: 0.23–1.05) when compared with placebo/no intervention. Lactulose is also superior to placebo in secondary prophylaxis of HE,[72,73] in primary

prophylaxis in patients with gastrointestinal bleeding,[63] and in MHE.[71] Lactulose is approved for the treatment of OHE episodes, secondary prophylaxis, and primary prophylaxis in cases of gastrointestinal bleeding. The French guidelines also recommend lactulose for the treatment of MHE.[58] Clinical tolerance remains the main issue.

Polyethylene glycol (PEG) is an osmotic laxative that increases ammonia excretion. PEG has been studied in 2 RCTs in OHE alone[74] or in association with lactulose.[75] PEG was associated with improvement of HE at 24 hours, faster resolution or greater improvement of HE versus placebo at 24 hours, and shorter hospitalization duration versus lactulose alone. Nevertheless, these RCTs were conducted in a small series of patients with a short follow-up.

Rifaximin. Rifaximin is a broad-spectrum, poorly absorbed antibiotic that is thought to reduce ammonia production by eliminating ammonia-producing colonic bacteria. In a recent meta-analysis[76] comparing rifaximin and placebo or lactulose, rifaximin improved the probability of HE resolution (RR = 1.34, 95% CI: 1.11–1.62) and survival (RR = 0.64, 95% CI: 0.43–0.94). Noteworthy, this meta-analysis included studies published more than 15 years ago with fewer than 65 patients. It is therefore not indicated to treat an episode of OHE with rifaximin alone. More recently, an RCT[77] demonstrated the efficacy of rifaximin in combination with lactulose versus lactulose alone in OHE grades 2 to 4. The combination showed a higher probability of achieving the resolution of HE, a shorter length of hospitalization, and improvement in survival when compared with lactulose alone. However, the use of rifaximin in the treatment of HE needs further confirmation. Regarding secondary prophylaxis, the efficacy of rifaximin was first evaluated in 1 RCT with 299 patients who were treated with lactulose and suggested that rifaximin reduced the probability of developing HE by 58% when compared with placebo and reduced the rate of hospitalization.[78] Maintenance therapy with rifaximin for 24 months was also associated with better prevention of HE recurrence and with a good safety profile. Two RCTs evaluated the efficacy of rifaximin versus placebo or lactulose in MHE.[79,80] The first RCT found a significant improvement when compared with placebo, whereas the second RCT showed comparable results between the 2 treatment groups. Tolerance was significantly better in the rifaximin group.

Rifaximin is approved for secondary prophylaxis of HE, when lactulose is ineffective (then associated with lactulose), or alone in the case of lactulose intolerance. The French guidelines also recommend rifaximin for the treatment of MHE.[58]

L-Ornithine L-aspartate. L-Ornithine L-aspartate (LOLA) is the salt of the natural amino acids ornithine and aspartate. LOLA demonstrated the capacity to increase ammonia removal by residual hepatocytes and skeletal muscle of patients with cirrhosis. More than 30 studies have been published in the setting of HE that compare LOLA to placebo, lactulose, antibiotics, probiotics, or branched-chain amino acids (BCAAs). The results have been pooled in a meta-analysis of 33 RCTs,[81] and they did not reveal any beneficial effect of LOLA over the other treatments mainly because of bias related to the studies.

Flumazenil. Flumazenil is a specific GABA receptor antagonist. Its efficacy has been suggested in several RCTs and 2 meta-analyses.[82,83] In the first meta-analysis, flumazenil was associated with significant improvement in OHE and in electroencephalographic abnormalities, and in the second meta-analysis, flumazenil significantly improved the resolution of HE without any improvement in survival.

Probiotics. Probiotics have been studied in several small series that have been analyzed in a meta-analysis (21 studies, 1420 patients). Only 2 RCTs evaluated the

efficacy of probiotics in OHE and did not reveal any improvement when compared with placebo.

Branched-chain amino acids. BCAAs, that is, valine, leucine, and isoleucine, are reduced in patients with cirrhosis and impair the conversion of ammonia into glutamine in the skeletal muscle. A Cochrane review of 16 RCTs comparing BCAAs and placebo/no intervention/diet/neomycin or lactulose[84] showed that BCAAs have a beneficial effect on the symptoms of HE but no effect on mortality, quality of life, or nutritional parameters. Data on the prevention of HE are more convincing, as 4 studies suggested a reduction in the number of bouts of HE. The main issue regarding BCAAs is their availability/reimbursement in several countries.

Nonpharmacologic therapeutics. Malnutrition is common in cirrhosis and is associated with an increased risk of sarcopenia. Muscle tissue plays a major role in nitrogen metabolism. Therefore, a low protein diet is not recommended, and optimal daily energy or protein intake should be similar to that of non-HE patients (35–40 kcal/kg/d and 1.2–1.5 g/kg/d, respectively). Physical exercise should be encouraged.

Education of patients with HE and of their relatives or caregivers is a key factor in reducing HE recurrence and, as a consequence, hospital admissions. It includes the effects of medication and potential side effects, the importance of compliance, the recognition of early signs of recurrence, and appropriate actions.

Perspectives in management

Medications

Fecal microbiota transplantation The rationale for the use of FMT in HE is the modulation of gut microbiota composition and function. This treatment was investigated by Bajaj and colleagues,[20] who performed an RCT comparing its efficacy in terms of cognitive improvement, adverse events, microbiota, and metabolic changes versus standard of care in patients with recurrent HE. After 150 days of follow-up, there was cognitive improvement in the FMT group, together with increased microbial diversity and expansion of beneficial taxa. No severe adverse events were registered. Long-term data confirmed sustained clinical improvement and the safety of FMT.[19]

Nonureic nitrogen scavengers Nonureic nitrogen scavengers include sodium benzoate, sodium phenylbutyrate, glycerol phenylbutyrate, and ornithine phenylacetate. Preliminary data suggest that scavengers could be effective in HE; sodium phenylbutyrate was effective in patients with HE who were hospitalized in the ICU in terms of clinical improvement and reduction of ammonemia.[85] Ornithine phenylacetate stimulates glutamine synthetase activity in peripheral organs. One phase 2b RCT compared ornithine phenylacetate to placebo in OHE and suggested clinical improvement in patients with hyperammonemia, although the primary endpoint addressing all the patients was not reached. A phase 3 study will be conducted soon in patients with hyperammonemia.

Other measures

Telemedicine Telehealth and mobile health technologies have been used in several chronic diseases, including liver diseases. Closely monitoring symptoms is part of the management of HE. In a preliminary study,[86] after discharge, home monitoring was done using an iPad with the patient buddy app (monitoring cognition, among other things). This study suggested that many potential readmissions related to HE were prevented via early outpatient interventions.

Shunt obturation/ligation Shunt obturation or ligation can be considered in patients with demonstrated and accessible portosystemic shunts. Current available data are restricted to retrospective studies. This technique should be discussed on a case-by-case basis.

Liver transplantation Liver transplantation is considered the ultimate therapeutic option for refractory HE. Issues regarding HE and liver transplantation are described elsewhere.[87] Prioritization of these patients is currently based on liver function and could therefore underestimate their risk of mortality and hospitalization. Hence, it is important to adequately weight the prognostic impact of persistent/highly recurrent HE in patients on the waiting list for transplantation, possibly adding a quantitative or clinical HE parameter to the available scoring systems.

Proposed algorithm for the prophylaxis and treatment of hepatic encephalopathy

The avoidance of any precipitating factor is part of treatment of HE (see **Fig. 5**). MHE should be screened for in all patients with cirrhosis.

All patients should receive lactulose as a first-line treatment of OHE. Alternative therapeutics may also be attempted. Flumazenil may be an interesting therapeutic option in patients with HE related to benzodiazepine use and in patients with stage IV HE to avoid orotracheal intubation. Secondary prophylaxis of HE includes lactulose and then rifaximin + lactulose or rifaximin alone in cases of lactulose intolerance.

Particular Situation: Hepatic Encephalopathy and Transjugular Intrahepatic Portosystemic Shunt Placement

Prevention of hepatic encephalopathy in patients who are candidates for transjugular intrahepatic portosystemic shunt placement

HE occurs in approximately 35% of cases after transjugular intrahepatic portosystemic shunt (TIPS) placement. Many studies have described the risk factors of HE after TIPS[88,89]: age greater than 65 years, a high model for end-stage liver disease or Child-Pugh score, a previous episode of HE, MHE, and sarcopenia. The best prevention for HE after TIPS is to properly select good candidates for TIPS placement. The authors strongly recommend discussing TIPS placement and liver transplantation at the same time to anticipate the patient's management in the case of TIPS failure or HE after TIPS. Whether pharmacologic treatments should be used as a primary prophylaxis of HE before TIPS placement was investigated. Two RCTs have been published, and they did not reveal any efficacy of lactulose, rifaximin, or LOLA. Recently, 1 RCT[90] evaluated rifaximin and placebo 2 weeks before and then 6 months after TIPS placement: the probability of remaining free of HE was higher in the rifaximin group. Rifaximin will probably be indicated for the primary prophylaxis of OHE before TIPS.

Hepatic encephalopathy management in patients with transjugular intrahepatic portosystemic shunt

In the case of refractory HE after TIPS, reduction or occlusion of the shunt can be attempted, but liver transplantation should always be discussed in this situation.

SUMMARY

HE is the most common complication of cirrhosis and is even life-threatening when progressing to coma. Diagnostic issues remain, especially in the setting of MHE. New pharmacologic therapeutic options are under study. There is growing evidence that telemedicine and mobile health could effectively address unmet needs, especially for therapeutic guidance and monitoring. Most of the patients can be managed with lactulose or rifaximin, education, and the control of precipitating factors. Nevertheless,

liver transplantation should be considered in patients with refractory HE or with poor liver function.

CLINICS CARE POINTS

- The diagnosis of HE should be reconsidered if ammonia in normal.
- The animal naming test is an easy tool for the screening of MHE.
- A differential diagnosis has to be ruled out in case of refractory HE and if liver transplantation is envisioned.

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APPENDIX 1: USEFUL WORKUP FOR THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF HEPATIC ENCEPHALOPATHY

Examinations	Usefulness
Measurement of ammonia plasma level	• Suggests a differential diagnosis if normal • Prognostic value is high (severity of HE, recurrence of HE, other organ failure, mortality)
Electroencephalogram	• May strengthen the diagnosis of HE but may be normal without ruling out HE • May have a better sensitivity than psychometric tests for MHE • Predictive of OHE at 1 y • May diagnose seizures as a differential diagnosis
Cerebral CT scan	• Reveals a differential diagnosis, such as expansive intracranial process
Cerebral MRI + spectroscopy	• Reveals a differential diagnosis, such as vascular leukoencephalopathy, vasculitis, expansive intracranial process, or other metabolic disorders • Spectroscopy acknowledges high glutamine brain content. Normal spectroscopy suggests a differential diagnosis

Appendix 2

APPENDIX 2: PROS AND CONS OF MEASUREMENT OF AMMONIA PLASMA LEVEL

Pros	Cons
• Based on a simple blood test • Available • Inexpensive • Easily interpretable, as opposed to EEG or cerebral MRI and spectroscopy • Diagnostic value: the diagnosis of HE should be reconsidered if the plasma ammonia level is normal • Prognostic value: a high ammonia plasma level is associated with the severity of HE, recurrence of HE, other organ failure, and mortality • Therapeutic target?	• Needs specific conditions of blood collection to be interpretable: ○ No venous stasis (ie, ideally without use of tourniquet) ○ Completely fill the EDTA tube and immediately homogenize by spinning ○ Bring the tube quickly to the laboratory on ice at +4°C ○ Interferes with hemolysis, severe jaundice, physical exercise, tobacco, or high protein diet • Measurement may vary according to laboratories • Correlation with psychometric tests is debated in MHE • Therapeutic target?

Appendix 3

APPENDIX 3: ANIMAL NAMING TEST INSTRUCTIONS

REQUIRED TIME: less than 2 minutes

REQUIRED EQUIPMENT: paper, pen, timer

INSTRUCTION: "Tell me the names of as many animals as you can think of, as quickly as possible, in 1 minute." If the person says nothing for 15 seconds, say "A dog is an animal. Can you tell me more animals?" If the person stops before 60 seconds, say "Any more animals?"

SCORING: Count the total number of animals (not including repetitions or nonanimal words)

INTERPRETATION: A cutoff of 15 to 20 animals in 1 minute seems reasonable to rule out MHE, and MHE is possible below this cutoff. Cutoffs depend on validation studies according to language.