Review

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Hepatic encephalopathy: Diagnosis and management

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ABSTRACT

Type C hepatic encephalopathy (HE) is a brain dysfunction caused by severe hepatocellular failure or presence of portal-systemic shunts in patients with liver cirrhosis. In its subclinical form, called "minimal hepatic encephalopathy (MHE), only psychometric tests or electrophysiological evaluation can reveal alterations in attention, working memory, psychomotor speed and visuospatial ability, while clinical neurological signs are lacking. The term "covert" (CHE) has been recently used to unify MHE and Grade I HE in order to refer to a condition that is not unapparent but also non overt. "Overt" HE (OHE) is characterized by personality changes, progressive disorientation in time and space, acute confusional state, stupor and coma. Based on its time course, OHE can be divided in Episodic, Recurrent or Persistent. Episodic HE is generally triggered by one or more precipitant factors that should be found and treated. Unlike MHE, clinical examination and clinical decision are crucial for OHE diagnosis and West Haven criteria are widely used to assess the severity of neurological dysfunction. Primary prophylaxis of OHE is indicated only in the patient with gastrointestinal bleeding using non-absorbable antibiotics (Rifaximin) or non-absorbable disaccharides (Lactulose). Treatment of OHE is based on the identification and correction of precipitating factors and starting empirical ammonia-lowering treatment with Rifaximin and Lactulose (per os and enemas). The latter should be used for secondary prophylaxis, adding Rifaximin if HE becomes recurrent. In recurrent/persistent HE, the treatment options include fecal transplantation, TIPS revision and closure of eventual splenorenal shunts. Treatment of MHE should be individualized on a case-by-case basis.

Key words: hepatic encephalopathy, minimal hepatic encephalopathy, Spontaneous Portal-systemic Shunts, transjugular intrahepatic portosystemic shunt, cirrhosis, rifaximin, non-absorbable disaccharides

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INTRODUCTION

Type-C hepatic encephalopathy (HE) is a complex neurological syndrome typical of patients with cirrhosis as a consequence of severe hepatocellular failure or the presence of large portal-systemic shunts, which causes a wide spectrum of nonspecific neurological and psychiatric manifestations. This condition ranges from a subclinical entity (minimal hepatic encephalopathy, MHE) to a most severe form characterized by a complete alteration of consciousness (overt HE, OHE).

OHE occurs in 30%–40% of patients with liver cirrhosis during the natural history of their disease,[1] but the real epidemiology is not easy to estimate. Prevalence rates of HE may be much higher in transjugular intrahepatic portosystemic shunt (TIPS),[2] as well as in spontaneous[3,4] or surgical shunting carriers.[5]

MHE is "apparently" lacking any clinical evidence, in fact it can be detected only through psychometric evaluations or electrophysiological and other functional brain tests. MHE prevalence is also still debated but is considered very frequent (20%–80% of patients). Nevertheless, MHE is clinically relevant because it is related to patients' falls, fitness to drive, working ability, sarcopenia, prognosis[6–8] and worsening patients and caregivers lives by altering their quality of life and socioeconomic status.

Recently, the term "covert" has been coined to unify MHE and Grade I HE in order to refer to a condition that is not unapparent, but also not overt. Both MHE and CHE are considered strong risk factors for the development of OHE (5%–25% of patients develop OHE within 5 years after cirrhosis diagnosis).[9–10]

According to its time course, HE is subdivided into three types: episodic HE if precipitated, recurrent HE if denotes bouts of HE occurring with a time interval of 6 months or less and persistent HE when shows continuous neurological alterations interspersed with relapses of OHE.[1–5, 11]

CLINICAL PRESENTATION AND DIAGNOSIS OF HEPATIC ENCEPHALOPATHY

Type C OHE should be suspected in case of personality changes occurring in a cirrhotic patient, such as apathy, irritability, disinhibition or obvious alterations in consciousness and motor function. Moreover, asterixis, as well as alterations of sleep wake cycle with excessive daytime sleepiness, can be frequently observed in this condition. Patients with OHE can further develop progressive disorientation in time and space, inappropriate behavior, acute confusional state with agitation or somnolence, stupor and finally coma. This can occur as a progressive alteration of state of consciousness, from mildest to serious forms, or as a direct fall in deeper stage of HE.

Episodic HE is often characterized by the presence of one or more precipitating events, both new or superimposed, that should be found and treated. So, searching for them is mandatory in all patients with OHE. When multiple precipitating events coexist, failure to identify and correct all precipitating factors can worsen the management.[12] Most common precipitating factors are infections, constipation, dehydration, hypokalemia and/or hyponatremia, gastrointestinal (GI) bleeding and use of psychoactive drugs (opioids or benzodiazepines). In addition, recent evidences suggest that low serum albumin level are significantly associated with the development of OHE in liver cirrhosis and that long-term albumin administration to patients with decompensated cirrhosis significantly reduces the incidence rate and severity of type C OHE (grade 3–4), while improves 18-months survival.[11, 13–15]

The differential diagnosis for patients not responding to standard pharmacological approach should exclude the presence of alcohol withdrawal, meningitis and encephalitis.[16]

Some patients may present chronic HE, which is refractory to conventional medical therapy and often lacks evident precipitating events. The presence of unrecognized large Spontaneous Portal-Systemic Shunts (SPSSs) can be responsible for chronic course of HE. In fact, 46–70% of cirrhotic patients with refractory HE shows SPSSs at radiological imaging.[3,4,17–19]

TIPS opens an artificial link between portal and hepatic veins, shifting blood from splanchnic circulation into systemic vascular system in order to avoid the major complications of portal hypertension. Polytetrafluoroethylene (PTFE)-covered stents significantly reduce the incidence of shunt insufficiency[20] but is unfortunately counterbalanced by the development of OHE.[21] Strategies of HE testing range from simple clinical scales to more complex psychometric and neurophysiological tools; however, the entire spectrum of HE, being the severity as a continuum, cannot be studied using only one test. Clinical examination and clinical decision are the cornerstone of OHE diagnosis, while clinical scales analyze its severity; West Haven criteria (WHC)[22] as reported in Table 1[1] are still widely adopted for this purpose, and more recently, a simple clinical scale has been proposed[11] as shown in Table 2.

OHE still remains an exclusion diagnosis of other mental status abnormalities. Therefore, as clinically indicated, and as explained previously, exclusion of precipitants and other aetiologies by laboratory and radiological assessment is needed.[1,11]

DIAGNOSIS OF MINIMAL HE

MHE is the mildest form of HE and can affect up to 80% of patients with liver cirrhosis, depending on the population studied and the type of diagnostic tool used.[23]

Ideally, each patient at risk should be tested for this condition because it constitutes a significant health problem and, despite its minimum expression, it is associated with burden on caregiver, poor prognosis, increased risk of developing episodes of OHE, inability to drive, sleep disorders, falls and therefore poor quality of life.[24,25]

The optimal measure for diagnosing MHE is still debated. In fact, none of the methods proposed cover the complexity and the heterogeneity characteristic of MHE cognitive impairment; moreover, appropriate norms are often needed and MHE is still ignored or underdiagnosed by most clinicians.[6–8]

Diagnosis of MHE can often be overlooked for several reasons:

- MHE is difficult to diagnose with objective neurological examination, so specific neuropsychological and/or neurophysiological tests are necessary.[23]

Table 1: West Haven criteria and clinical description and ISHEN modifications[1]

West-Haven criteria including MHE	ISHEN	Description	Suggestive operative criteria
Minimal	Covert	Alterations in psychometric or neuropsychological tests exploring attention, working memory, psychomotor speed, visuospatial ability and executive functions. No clinical neurological signs.	Abnormal tests without clinical manifestations.
Grade I		Euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm and lack of awareness.	Cognitive/behavioral decay with respect to his/her standard on clinical examination or to the caregivers.
Grade II	Overt	Lethargy or apathy, disorientation for time, obvious personality changes, inappropriate behavior, dyspraxia, asterixis.	Disorientation for time (at least three of the following are wrong: day of the month, day of the week, month and season or year) ± the other mentioned symptoms.
Grade III		Somnolence to semi-stupor but response to stimuli, confusion, gross disorientation, bizarre behavior.	Disorientation also for space (at least three of the following are wrong: country, state or region, city or place) ± the other mentioned symptoms.
Grade IV		Coma	Lacking response to painful stimuli.

Table 2: Algorithm for OHE grading[11]

1. Animal Naming Test (ANT)

List all possible animals in a minute. Number of animals_____

Simplified ANT: if yrs. of instructions < 8, add 3 animals
if yrs. of instructions < 8 add and age > 80, add 6 animals

No HE: > 15 animals
Covert HE (MHE or grade I): 10–15 animals
Overt HE (grade II-IV): < 10 animals

2. Orientation in time

	FALSE	CORRECT
What year are we?	☐	☐
What month are we?	☐	☐
Which day of the week is it?	☐	☐
What is today's date?	☐	☐

3. Orientation in space

	FALSE	CORRECT
Which country are we in?	☐	☐
Which region are we in?	☐	☐
Which city are we in?	☐	☐
Where are we now?	☐	☐

4. Glasgow Coma Scale	**Scores**
Eye opening response	
The patient does not open eyes	1
The patient opens eyes in response to painful stimuli	2
The patient opens eyes in response to voice	3
The patient opens eyes spontaneously	4
Verbal response	
The patient makes no sounds	1
The patient makes incomprehensible sounds	2
The patient pronounces inappropriate words	3
The conversation is confused, disoriented	4
The patient is oriented and converses normally	5
Motor response	
The patient makes no movements	1
Extension to painful stimuli (decerebrate response)	2
Abnormal flexion to painful stimuli (decorticate response)	3
Flexion/withdrawal to painful stimuli	4
The patient localizes painful stimuli	5
The patient obeys commands	6

Continued Table 2: Algorithm for OHE grading[11]

5. Overall assessment results	
	Staging
NO HE (grade 0)	Oriented in time
	Oriented in space
	ANT > 15 animals
Covert HE	Oriented in time
	Oriented in space
	ANT 10–15 animals
Overt HE grade II	Disoriented in time
	Oriented in space
Overt HE grade III	Disoriented in time
	Disoriented in space
	GCS = 8–14
Overt HE grade IV (coma)	Disoriented in time
	Disoriented in space
	GCS < 8

- Cognitive impairment involves the areas of overall performance and psychomotor activities, while verbal functioning is usually preserved.[23]

- Some tests are time consuming, expensive and require highly specialized personnel and specific testing equipment.[23,26]

- Diagnostic criteria and normal distribution values corrected for age and educational level are missing.[26]

- There is no single optimal method for assessing the presence of MHE because none of the tests proposed covers all the aspects of HE; in fact each method explores different brain functions.[6]

Diagnosis of MHE can be made with psychometric tests (computerized and non-computerized) and electrophysiological tests (Electroencephalogram [EEG], Event related potentials, [ERP]).

Electrophysiological tests suffer from methodological problems, require sophisticated equipment and analysis and have less sensitivity than psychometric tests.[27] For this reason, they could be used in patients with poor performance on screening tests.[28]

Computerized tests are generally based on repeating a large number of trials, and therefore, give more precise results than paper-pencil tests.[29]

A preferable strategy for MHE diagnosis is to screen cirrhotic patients with rapid and highly sensitive computerized psychometric tests, and then use PHES for further validation.[30]

Testing strategies for MHE, as summarized in Table 3, are:

- **PHES** (psychometric hepatic encephalopathy score): It consists of a battery of paper-pencil psychometric tests developed specifically for MHE and validated in this population group.[23] The subtests are: NCT-A (number connection test A), NCT-B (number connection test B), SDT (serial dotting test), LTT (line tracing test), DST (digit symbol test). It lasts for about 15 minutes. PHES score is calculated as the sum of all the subtests' score, corrected for age and educational level.[6] A final score < -4 points is suggestive for MHE.[26]

  This test evaluates psychomotor speed, set shifting, attention, visual perception, visuospatial orientation, visuomotor ability, concentration and memory.[23]

  PHES is recommended as the gold standard for MHE diagnosis because it covers the spectrum of cognitive alterations involved in HE, it is inexpensive[26] and simple to administer;[6] moreover, it has good external validity and has prognostic value since it can predict OHE development and survival.[23]

  However, it is not sensitive to early neurological changes in a cirrhotic patient, results are influenced by age and educational level and some subtests have learning effect.[30]

- **CFF** (critical flicker frequency): Light pulses are presented in decreasing frequency (from 60 Hz downwards) and patient has to press a button as soon as the impression of fused light switch to oscillating light. After a training phase, the test is repeated 8 times and the mean value of this run is calculated as CFF, which is a measure of visual temporal resolution. The cut-off value is 38–39 Hz and it takes about 10 minutes.[31]

  This test is based on the hypothesis that retinal gliopathy, a consequence of astrocyte swelling, is a marker of

Table 3: Summary of the most widely diagnostic tools used for MHE diagnosis

Test	Tested domain	Copyright	Dedicated (Europe-Asia/ USA)	Time required for administration and interpretation (min)	Comments
NCT-A	Psychomotor speed	Yes	No/No	1–2	Poor specificity
NCT-B	Psychomotor speed, set shifting and divided attention	Yes	No/No	1–3	Poor specificity
BDT	Visuospatial reasoning, praxis and psychomotor speed	Yes	No/Yes	10–20	It can be used for dementia testing as well
DST	Psychomotor speed and attention	Yes	No/Yes	4	Tends to be very sensitive and is an early indicator
LTT	Psychomotor speed and visuomotor ability	Yes	No/Yes	2–4	Outcomes are errors and time; tests balance between speed and accuracy
SDT	Psychomotor speed	Yes	No/es	1–2	Only tests psychomotor speed but has a higher sensitivity than DST
PHES	Psychomotor speed, set shifting, attention, visual perception, visuospatial orientation and visuomotor ability	Yes	No/Not for all tests	15	Inexpensive, easy to administer, good external validity, prognostic value (predictive of survival and OHE development); performance influenced by age and educational level
R-BANS	Verbal/visual/working memory; visuospatial, language and psychomotor speed	Yes	No/Yes	25–35	Primarily studied in dementia and brain injury. Limited HE experience
ANT	Semantic fluency test and verbal retrieval and recall	No	No	1	Simple to administer; good sensitivity for screening of MHE; prognostic value (predictive of survival and OHE development); easy tool for caregivers for identify mental status alterations; useful for illiterate patients
ICT	Response inhibition, working memory, vigilance and attention	Yes	No/No	15–20	Need highly functional patients and familiarity with computers
SCAN test	Working memory, vigilance and attention	Yes	No/No	15–20	Prognostic value (predictive of mortality)
CRT	Motor reaction speed, sustained attention and inhibitory control	NA	NA	10	Not affected by age and educational level; no learning effect; simple software are required
Stroop Test	Psychomotor speed, cognitive flexibility, executive control and functioning of anterior attention system	No	NA	5	Simple to explain, administer and interpret; good sensitivity for screening of MHE; highly accessible by web (available in app-form); influenced by age, educational level and training
CFF	Measure of visual temporal resolution	NA	NA	10	Simple to administer and interpret; prognostic value (predictive of survival and OHE development); partially influenced by training, setting and etiology; requires specialized equipment
EEG	Generalized brain activity	No	Yes/Yes	10–15	Can be performed in comatose patients; alterations not specific for HE
VEPs	Interval between visual stimulus and activity	No	Yes/Yes	May vary	Highly variable and poor overall results
BAEPs	Response in brain cortex after auditory click stimuli	No	Yes/Yes	May vary	Inconsistent response with HE testing/prognostication
P300 Cognitive evoked potentials	An infrequent stimulus embedded in irrelevant stimuli is studied	No	Yes/Yes	Different ranges	Correlates with severity of hepatic encephalopathy (high latency and low amplitude of P300 waves)

ANT: animal naming test; BAEPs: brainstem auditory evoked potentials; BDT: block design test; CFF: critical flicker frequency; CRT: continuous reaction time; DST: digit symbol test; EEG: electroencephalogram; ICT: inhibitory control test; LTT: line tracing test; NCT-A: number connection test A; NCT-B: number connection test B; PHES: psychometric hepatic encephalopathy score; SDT: serial dotting test; VEPs: visual evoked potentials.

brain gliopathy in patients with HE; so the flicker fusion frequency analysis reflects not only the efficiency of visual apparatus, but also the functional efficiency of cerebral cortex.[27]

It is simple to administer and interpret and is highly reproducible. It is not influenced by age and educational level,[27] language, verbal fluency and numbering and is not subject to learning effect.[29] It can predict mortality and OHE development[29] and it correlates with severity of neurological deficit in cirrhotic patients. In fact, the CFF value decreases in parallel with mental and psychomotor impairment, and therefore, this test can be useful for the quantification of MHE and its evolution over time.[6]

CFF is partially influenced by training,[23] setting (color and brightness of the stimuli, distance and angle between light source and subject) and etiology of cirrhosis, since patients with alcoholic disease have lower CFF values.[32] Finally, this test requires intact binocular vision, absence of color blindness and specialized equipment.[6]

- **CRT** (continuous reaction time test): The subject has to press a button in response to one-hundred 500 Hz tones presented at 90 dB in random intervals of 2 to 6 seconds via headphones.[31] CRT-Index is the variation coefficient of the reaction times during test; a high index denotes a low variability (normal) while a low index denotes a loss of stability (abnormal). CRT-index < 1,9 discriminates with good sensitivity and specificity between organic damage and HE, and this value is used as the cut-off.[33]

  This test evaluates the ability to react adequately and for a long time period, so it assesses sustained attention and attention stability.

  Compared to the patients with organic brain damage, those with HE have slower reaction times and increasing intrapersonal variability of reaction times. This increase in variability seems to occur before the appearance of clinical signs of worsening HE; so this test may be able to recognize MHE from loss of stability of reaction times.[33] Moreover, this test is not influenced by age; there is no learning/tiring effect and requires simple software for testing.[4]

  However, it is susceptible to confounding factors such as external distractions, use of psychoactive drugs and sleep disturbances.[33]

- **ICT** (inhibitory control test): Several letters are presented at 500 msec intervals, with X and Y interspersed within these letters. During the initial part of the training run, the subject has to respond to every X and Y; in the latter part of this, he has to respond only when X and Y are alterning (called targets) and to inhibit from responding when X and Y are non alterning (called lures). After the training run, 6 tests run are administered;[34] each test lasts approximately 2 minutes, so it takes about 14 minutes overall.[32] At the end of the test, lure and target response rate and lure and target reaction time are automatically calculated. A good psychomotor response in characterized by lower lure response, higher target response and shorter target and lure reaction time.[30]

  This test evaluates working memory, vigilance, attention and inhibition, which are cognitive domains affected in patient with MHE.[34]

  Errors of inhibition, identified by a higher number of lures response, can be responsible for serious wrong decisions in daily life (such as during driving); patients with MHE tend to respond to a higher number of lures than healthy subject or cirrhotic patients without MHE.

  Errors of omission/attention are characterized by a lower target detection rate; errors of omission and longer lure and target reaction times, are associated with impairment of processing speed and visuomotor functions.[34]

  The ICT has good external validity, has prognostic value because it can predict the development of OHE, it is simple to administer, has high sensitivity/specificity and appreciable test-retest reliability.[35] Results are influenced by therapy, TIPS implantation and educational level, but not by age and alcoholic etiology.[30,34] However, performing this test requires highly functional patients and familiarity with computers.[6] Further studies are needed to determine its ability to predict survival.[30]

- **Stroop test**: This test includes two components, ON and OFF state, based on concordance or discordance of the stimuli. In the OFF state, the subject sees a neutral stimulus and has to respond as soon as possible by touching the matching color of the stimulus to the color displayed at the bottom of the screen; if the subject makes a mistake, he has to start over and continue until five complete correct runs. In the ON phase, the subject sees discordant stimuli and has to touch the color of the word presented, which is the name of the color in discordant coloring. The patient has to continue until five complete correct runs. At the end of the test, the time and number of runs necessary to complete the five correct runs in both phases are automatically measured.

  The Stroop test evaluates the anterior attention system, which modulates inhibitory responses (ON state) and

executive control, psychomotor speed and cognitive flexibility (OFF state).[28]

This test is simple to explain, administer and interpret; it has good sensitivity for the screening of MHE and can predict OHE development.[30] However, it requires familiarity with smartphone and results are influenced by age, educational level and training; in fact, patients without previous episodes of OHE, improve in ON phase with repetition (but not in the OFF state).[28]

- **SCAN test**: This test is performed by randomly displaying a series of 72 sorted pairs of numbers for 3 seconds on a computer screen. Patient has to press the appropriate number on a keyboard if he identifies a common digit in the sequence of numbers presented. At the end of the test, the mean reaction time and the percentage of errors are recorded, and results are evaluated using the reaction times weighted by the number of errors. This test takes about 15–20 minutes.

  It evaluates working memory, vigilance and attention, and has prognostic value, because it can predict mortality at one year of follow-up.[30]

- **ANT** (animal naming test): This test consists of listing as many animals as possible in a minute. Depending on the number of animals listed, two threshold values have been proposed; in this way, it is possible to identify three scores: 0 if ANT >= 15, 1 if ANT is between 10 and 15, and 2 if ANT < 10.

  Adequate performance on the ANT requires adequate executive functions and memory, because patient has to keep track of responses already given.[36]

  The ANT explores functions of pre-frontal and anterior cortex that influenced semantic fluency and verbal and retrieval recall[6] that are affected in the early stages of HE. Therefore, it can be a useful first-line test for diagnosis of MHE.

  This test is simple to administer and well accepted; it has good sensitivity for screening of MHE and prognostic value since it can predict the risk of OHE development and mortality at one year of follow-up. Results are marginally influenced by age and educational level (< 8 years of education and > 80 years of age) but not by sex. Learning effect is minimal.[36]

- **RBANS** (repeatable battery for the assessment of neuropsychological status): This test explores verbal, visual and working memory, visuospatial functions, language and psychomotor speed. It lasts about 25 minutes.[25]

  In the United States, it has been used extensively for screening of various cognitive disorders such as stroke, Alzheimer, dementia and schizophrenia. So, its diagnostic value in MHE requires further validation.[32]

- **EEG** (electroencephalogram): It is used to identify the changes in cortical activity even in uncooperative patients.[6]

  In patients with OHE, EEG shows a progressive slowing of general activity, an initial increase and then decrease of the wave's amplitude and the presence of three-phase waves, which however are not specific for HE (these are found in other types of metabolic encephalopathy or in drug intoxication). Delta waves appear in comatose patients.

  In patients with MHE, the quantitative EEG (q-EEG) analysis shows an increase in the relative power of the theta band and a decrease in the MDF (mean dominant frequency) in the posterior derivations. These changes correlate with indices of hepatic dysfunction and predict OHE development and liver-related death.[37]

  EEG study during sleep may be helpful in cirrhotic patients because changes in MDF during sleep represent an early marker of brain dysfunction in a subject with MHE. In this situation, q-EEG shows alterations in slow oscillatory activity, with an increase in frequency of dominant delta-rhythm.[23]

- **Evoked potentials:** They are electrical signals generated through adequate stimulation of excitable tissues using light (visual evoked potentials, [VEPs]), acoustic signals (brainstem auditory evoked potentials [AEPs]) or electrical stimulation of somatosensory nerves.[38]

  Generation of BAEPs is achieved by applying fast sequences of monaural acoustic stimuli (between 1000 and 2000 clicks). Activation of the acoustic nerve is followed by stimulation of several parts of the brainstem. In healthy subjects, seven positive and negative waves can be recorded. Patients with HE stages 0-I, have no significant prolongations of BAEP-peaks I-V or of the interpeak latency I-V. So, BAEPs present an inconsistent response with HE tests.[38]

  VEPs assess the interval between visual stimulus and brain activity, but the results are variable. This variability may depend on the use of a later component (N3) for the assessment of subclinical HE instead of the P100-component commonly used in routine neurological examinations; moreover, clinical definition of subclinical HE varies between different studies, so comparison

between these results is very difficult. Therefore, use of VEPs in patients with MHE appears to be of little diagnostic value.[39]

P300 wave is an endogenous visual component that is elicited in the decision-making process (ERP). Patients with MHE have high latency and low amplitude waves. This has been linked to the severity of the HE.[23]

TREATMENT OF HEPATIC ENCEPHALOPATHY

General recommendations for the treatment of episodic OHE type C include the following:

- Prompt start of care of hospitalized patients with altered mental status.
- Identify and eventually treat alternative and co-existing causes.
- Identify and correct precipitating factors.
- Consider starting empirical ammonia-lowering treatment.

Moreover, subjects with high HE degree (III and IV)[22] are at risk or unable to protect their airways and should ideally be managed in an intensive care setting.

Common empirical pharmacological approaches are non-absorbable antibiotics (Rifaximin) and non-absorbable disaccharides (Lactulose or Lactitol per os and per enemas). Other agents (branched-chain amino acids-BCAAs, probiotics, other antibiotics or intravenous L-ornithine L-aspartate-LOLA) are available, but evidences supporting their efficacy remain lacking.[1,11] Recent studies have demonstrated that albumin infusion might improve the severity of OHE and might be associated with reduced in-hospital mortality in cirrhotic patients with or without OHE.[14]

Precipitant induced HE benefits from both prompt recognition and elimination of precipitating agents and specific HE therapies. Unfortunately, in majority of cases, it is difficult to understand which of the different approaches has had the decisive role.

Primary prophylaxis of OHE is not generally recommended, except in the case of upper gastrointestinal bleeding adopting therapies able to remove blood from the gastrointestinal tract.[41,42] Rifaximin has been shown to be as effective as lactulose in preventing OHE after upper gastrointestinal bleeding.[43]

Secondary prophylaxis should initiate using non-absorbable disaccharides,[1,11,44,45,46] but overuse of lactulose should be avoided since it can cause complications (dehydration), which can newly precipitate bouts of HE. In case of recurrent OHE, the addition of Rifaximin, a non-absorbable antibiotic, has been demonstrated useful and safe in maintaining remission.[47] To date, there is no evidence about the role of pharmacological prophylaxis of HE after TIPS;[48] the use of shunt with different diameter may be considered,[49,50] but it deserves further studies for validation.

In case of *Recurrent HE* not associated with TIPS or SPSSs, a therapeutic option may be fecal microbiota transplantation (FMT).[51] *Recurrent HE* in TIPS carriers may benefit of shunt revision if a causal relationship between shunt and HE is supposed (*i.e.*, if HE occurs in a short period after TIPS or when the procedure leads to a significant reduction of portal-systemic gradient). This decision requires caution due to a possible recurrence of complications of portal hypertension (ascites or varices) after shunt reduction.[21]

Recurrent or persistent HE is also more frequent in patients bearing splenorenal shunt. Therefore, CT scan for SPSSs detection in patients with advanced liver disease is recommended in order to prevent, treat or identify the causes of recurrent HE. Recently, new radiological techniques such as plug assisted retrograde transvenous obliteration (PARTO) or coil assisted retrograde transvenous obliteration (CARTO) have been proposed to manage recurrent or persistent HE.[51,53]

TREATMENT OF MHE

Despite a subclinical nature, MHE and CHE seriously impair daily life because of poor quality of life, impairment of cognitive function or of driving skills and work performance. Therefore, the indication to treat patients may be strong. A series of various treatments have been proposed, *that is*, non-absorbable disaccharides, low absorbable antibiotics, probiotics, but no convincing evidences on the effective role of those therapies on MHE have emerged.[1,6,7,11] In fact, because of various concerns on available data and on the design of RCTs on MHE treatment,[54–66] recently published guidelines state that the treatment of MHE and CHE is not routinely recommended apart from on a case-by-case basis.[1,11]

Conflict of Interests

None declared.

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