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Review

REVIEW

Hepatic encephalopathy

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Abstract

Hepatic encephalopathy (HE) is a reversible syndrome of impaired brain function occurring in patients with advanced liver diseases. The precise pathophysiology of HE is still under discussion; the leading hypothesis focus on the role of neurotoxins, impaired neurotransmission due to metabolic changes in liver failure, changes in brain energy metabolism, systemic inflammatory response and alterations of the blood brain barrier. HE produces a wide spectrum of nonspecific neurological and psychiatric manifestations. Minimal HE is diagnosed by abnormal psychometric tests. Clinically overt HE includes personality changes, alterations in consciousness progressive disorientation in time and space, somnolence, stupor and, finally, coma. Except for clinical studies, no specific tests are required for diagnosis. HE is classified according to the underlying disease, the severity of manifestations, its time course and the existence of precipitating factors. Treatment of overt HE includes supportive therapies, treatment of precipitating factors, lactulose and/or rifaximin. Routine treatment for minimal HE is only recommended for selected patients.

Key words: Hepatic encephalopathy; pathophysiology; diagnostic tests; management strategy

Introduction

Hepatic encephalopathy (HE) or portosystemic encephalopathy (PSE) is a reversible syndrome of impaired brain function occurring in patients with advanced liver failure. However, HE is not a single clinical entity. It may reflect either a reversible metabolic encephalopathy, brain atrophy, brain edema or any combination of these conditions. The mechanisms causing brain dysfunction in liver failure are still unknown. These factors are directly related to liver failure (e.g. decreased metabolism of ammonia). Unless the underlying liver disease is successfully treated, HE is associated with poor survival and a high risk of recurrence [1,2]. Even in its mildest form, HE reduces health-related quality of life and is a risk factor for bouts of severe HE [3,4].

Pathogenesis

In spite of more than 100 years of research, the pathogenesis of HE is still not well understood. This reflects the limitation to study the brain of patients with HE *in vivo*. Most of the published data are derived from experimental models of HE, which are far from perfect. The most common suggestions include the role of neurotoxins, impaired neurotransmission due to metabolic changes in liver failure, changes in brain energy metabolism, systemic inflammatory response and alterations of the blood brain barrier. The pathogenesis of HE is not allowed to be reviewed in detail due to the huge number of published data (for a detailed discussion, see [5–7]). The various hypotheses of the pathogenesis of HE are not mutually exclusive. It seems likely that many of the described abnormalities may be present at the

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same time and may ultimately be responsible for the development of HE.

Neurotoxins

Ammonia is the best characterized neurotoxin linked to HE. The gastrointestinal (GI) tract is the primary source of ammonia. Ammonia is produced by enterocytes from glutamine and by colonic bacterial catabolism of nitrogenous sources (such as blood after GI bleeding) [8]. The intact liver clears almost all of the portal vein ammonia, converting it into glutamine and preventing entry into the systemic circulation. The increase in blood ammonia in advanced liver disease is a consequence of impaired liver function and of the shunting of blood around the liver. Muscle wasting, a common occurrence in these patients, also may contribute, since muscle is an important site for extrahepatic ammonia removal.

Swelling of astrocytes as consequence of hyperammonemia may be a key event in the development of HE in patients with cirrhosis [9–12]. One possible explanation for brain edema is an increase in intracellular osmolarity resulting from the metabolism of ammonia in astrocytes to form glutamine [13]. Brain glutamine concentrations are significantly increased in acute liver disease whether assessed biochemically in autopsy material [13] or by ^{1}H-magnetic resonance spectroscopy [14]. These data are supported by *in vivo* measurements in cirrhotic patients in whom proton magnetic resonance spectroscopy of the brain showed depletion of myoinositol (a sign of increased osmolarity) and increased glutamine [14]. One protein strongly implicated in cell swelling is the water channel protein aquaporin-4, which is abundantly expressed in astrocytes [15,16]. Ammonia also directly affects neuronal electric activity by inhibiting the generation of both excitatory and inhibitory postsynaptic potentials [17] and cortical hemichannels [18].

Impairment of neurotransmission

Several neurotransmitter systems have been studied in various experimental models of (mostly) acute liver failure, including investigations of neurochemical, neurobehavioral and electrophysi ological methods. Most reports describe changes in the GABA-benzodiazepine-ergic [19], dopaminergic [20], serotoninerergic and glutamate-ergic neurotransmitter systems [5]. For obvious reasons, very few data exist in humans suffering from HE.

Substances involved in the activation of the $GABA_A$-ergic neurotransmission have been isolated, characterized and positively identified by gas chromatography–mass spectroscopy as benzodiazepines in brain, sera and cerebrospinal fluid of humans with type A and type C HE [21]. Some of them may be of exogenous origin but endogenous benzodiazepine-like compounds such as neurosteroids have been identified [22]. Neurosteroids are potent selective positive allosteric modulators of the $GABA_A$ receptor complex. Allopregnanolone and pregnenolone (a neurosteroid precursor) pathophysiologically relevant concentrations were increased in the brains of hepatic coma patients [22]. Activation of the astrocytic 18-kDa translocator protein (formerly referred to as peripheral-type benzodiazepine receptors) contributes to the pathogenesis of the central nervous system symptoms of HE [23].

Some of the extrapyramidal symptoms in patients with cirrhosis may be due to altered dopaminergic function, which is closely related to accumulation of manganese in basal ganglia [24]. Manganese appears to normalize low striatal levels of dopamine. Thus, manganese accumulation in basal ganglia may represent an attempt of the brain to correct dopamine deficiency in liver disease [25].

Systemic response to infections and neuroinflammation

Other possible causes of brain dysfunction include alterations in cerebral blood flow, brain metabolites and the release of inflammatory mediators; importantly, these processes occur without the direct infection of brain tissue [9,26]. Infection is a well-known precipitant of HE, but the mechanisms involved are incompletely understood [27]. Patients with cirrhosis are known to be functionally immunosuppressed and prone to developing infections. Whether infections themselves or the inflammatory response exacerbate HE is unclear. The systemic inflammatory response syndrome results from the release and circulation of proinflammatory cytokines and mediators. Sepsis-associated encephalopathy is characterized by changes in mental status and motor activity, ranging from delirium to coma [28].

Small bowel bacterial overgrowth may contribute to minimal HE [29,30]. Patients with cirrhosis had significantly fewer autochthonous and more pathogenic genera than controls [31]; *Alcaligenaceae* and *Porphyromonadaceae* were positively associated with cognitive impairment [32]. Dysbiosis, represented by reduction in autochthonous bacteria, is present in both saliva and stool in patients with cirrhosis, compared to controls; thus investigating microbiota in saliva can be used in clinical practice [33].

Clinical presentation

HE produces a wide spectrum of nonspecific neurological and psychiatric manifestations [34]. In its lowest expression [35,36], HE alters only psychometric tests oriented towards attention, working memory, psychomotor speed and visuospatial ability, as well as electrophysiological and other functional brain measures [37,38].

As HE progresses, personality changes, such as apathy, irritability and disinhibition, may be reported by the patient's relatives [39], and obvious alterations in consciousness and motor function occur. Disturbances of the sleep–wake cycle with excessive daytime sleepiness are frequent [40], whereas complete reversal of the sleep–wake cycle is less consistently seen [41,42]. Patients may develop progressive disorientation to time and space, inappropriate behavior, acute confusional state with agitation or somnolence, stupor and, finally, coma [43]. The recent ISHEN (International Society for Hepatic Encephalopathy and Nitrogen Metabolism) consensus uses the onset of disorientation or asterixis as the initial sign of overt HE [44].

In non-comatose patients with HE, motor system abnormalities such as hypertonia, hyperreflexia and a positive Babinski sign can be seen. In contrast, deep tendon reflexes may diminish and even disappear in coma [45], although pyramidal signs can still be seen. Rarely, transient focal neurological deficits can occur [46]. Seizures are very rarely reported in HE [47–49]. Extrapyramidal dysfunction, such as hypomimia, muscular rigidity, bradykinesia, hypokinesia, monotony and slowness of speech, Parkinsonian-like tremor and dyskinesia with diminished voluntary movements are common findings [45].

Asterixis or 'flapping tremor' is often present in the early–middle stages of HE that precede stupor or coma, and is in actuality not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers, or the rhythmic squeezing of the examiner's fingers. However, asterixis can be seen in other areas such as the feet,

legs, arms, tongue and eyelids. Asterixis is not pathognomonic of HE, as it can be seen in other diseases, such as uremia.

Notably, the mental (either cognitive or behavioral) and motor signs of HE may not be expressed or do not progress in parallel in each individual, therefore producing difficulties in staging the severity of HE.

Apart from less usual manifestations of HE, it is widely accepted in clinical practice that all forms of HE and their manifestations are completely reversible, and this assumption still is a well-founded operational basis for treatment strategies. However, research on liver-transplanted HE patients and on patients after resolution of repeated bouts of overt HE casts doubt on the full reversibility.

Classification

HE should be classified according to all of the following four factors [50]:

i. According to the underlying disease:
   a. **Type A** due to **a**cute liver failure;
   b. **Type B** due predominantly to portosystemic bypass or shunting;
   c. **Type C** due to **c**irrhosis.
ii. According to the severity of manifestations:
   The continuum that is HE has been arbitrarily subdivided. For clinical and research purposes, a scheme of such grading is provided (**Table 1**). Operative classifications that refer to defined functional impairments aim at increasing intra- and inter-rater reliability and should be used whenever possible.
iii. According to time course of HE:
   a. **Episodic HE**;
   b. **Recurrent HE** denotes bouts of HE occurring with a time interval of ≤ 6 months;
   c. **Persistent HE** denotes a pattern of behavioral alterations that are always present interspersed with relapses of overt HE.
iv. According to the existence of precipitating factors:
   a. **Non-precipitated**;
   b. **Precipitated:** precipitating factors can be identified in nearly all bouts of episodic HE type C, and should be actively sought and treated when found:
      - excessive protein intake;
      - constipation;
      - hyponatremia;
      - infections (e.g. spontaneous bacterial peritonitis);
      - sedative drugs: benzodiazepines, morphine;
      - azotemia;
      - hypokalemia;
      - alkalosis;
      - dehydration;
      - fluid restriction;
      - diuretics;
      - diarrhea;
      - vomiting;
      - arterial hypotension/hypovolemia;
      - gastrointestinal bleeding;
      - peripheral vasodilatation;
      - shock, operation;
      - hypoxia;
      - anemia.

Table 1. West-Haven criteria (WHC) for hepatic encephalopathy and clinical description

WHC	ISHEN	Description	Suggested operative criteria	Comment
Unimpaired		No encephalopathy at all, no history of hepatic encephalopathy	Tested and proven to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis local standards and expertise required
Grade I		Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis	Disoriented for time (at least three of the following are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		Somnolence to semistupor Responsive to stimuli Confused Gross disorientation Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or portosystemic shunting. ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism.

A fifth classification according to whether or not the patient has acute-on-chronic liver failure (ACLF) has been suggested [51]. Although the management, mechanism and prognostic impact differ, this classification is still a research area [50].

Differential diagnoses

The diagnosis requires the detection of signs suggestive of HE in a patient with severe liver insufficiency and/or portosystemic shunting, who does not have obvious alternative causes of brain dysfunction. The recognition of precipitating factors for HE (e.g. infection, bleeding, constipation) supports the diagnosis of HE. The differential diagnosis should consider common disorders altering the level of consciousness.

The neurological manifestations of HE are nonspecific. Therefore, concomitant disorders have to be considered as an additional source of central nervous system dysfunction in any patient with chronic liver disease. Most important are renal dysfunction, hyponatremia, diabetes mellitus, sepsis and thiamine deficiency (Wernicke's encephalopathy); noteworthy also is intracranial bleeding.

Hyponatremia is an independent risk factor for the development of HE in patients with cirrhosis [52]. An increased risk to develop HE has also been shown in cirrhotic patients with renal dysfunction independently of the severity of cirrhosis [53].

Neurological symptoms are observed in 21–33% of patients with cirrhosis with sepsis and in 60–68% of those with septic shock [54]. Data upon the effect of the underlying liver disease on brain function are sparse except for alcoholism and hepatitis C [55]. About half of the HCV patients suffer chronic fatigue irrespective of the grade of their liver disease [56,57]. Rare but difficult cases may be due to Wilson disease [58].

Patients with alcohol disorder and no clinical liver disease have been shown to exhibit deficits in episodic memory [59], working memory and executive functions [60], visuoconstruction abilities [61] and upper and lower limb motor skills [62]. Likewise, patients with primary biliary cholangitis and primary sclerosing cholangitis may have severe fatigue and impairment of attention, concentration and psychomotor function irrespective of the grade of liver disease [63].

Diagnosis and testing

Judging and measuring the severity of HE is approached as a continuum [64]. The testing strategies in place range from simple clinical scales to sophisticated psychometric and neurophysiological tools; however, none of the current tests is valid for the entire spectrum [11]. The appropriate testing and diagnostic options differ according to the acuity of the presentation and the degree of impairment [65].

Diagnosis and testing for overt HE

The diagnosis of overt HE is based on a clinical examination and a clinical decision. Clinical scales are used to analyse its severity. Specific 'quantitative' tests are only needed in study settings. The 'gold standard' is the West-Haven criteria (WHC) [2]. The detection of disorientation and asterixis has good inter-rater reliability, and thus are chosen as marker symptoms of overt HE [65]. Orientation or mixed scales have been used to distinguish the severity of HE [66,67]. In patients with evidently altered consciousness, the Glasgow Coma Scale (GCS) is widely employed. Diagnosing cognitive dysfunction by clinical observation, neuropsychological or neurophysiological tests is not difficult. The difficulty is to assign them to HE. For this reason, overt HE still remains a diagnosis of exclusion in this patient population that is often susceptible to mental status abnormalities due to medications, alcohol abuse, drug use, effects of hyponatremia and psychiatric disease. Therefore, as clinically indicated, exclusion of other etiologies by laboratory and radiological assessment for a patient with altered mental status in HE is warranted.

Testing for minimal and covert HE

Minimal and covert HE is defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with chronic liver disease who are not disoriented or display asterixis. The term 'minimal' conveys that there is no clinical sign, cognitive or other, of HE. The term 'covert' includes minimal and Grade 1 HE. The testing strategies can be divided into two major types: psychometric and neurophysiological [68,69]. Since the condition affects several components of cognitive functioning, which may not be impaired to the same degree, the ISHEN suggests the use of at least two tests depending on the local population norms and availability, and preferably with one of the tests being more widely accepted so as to serve as a comparator.

Testing for minimal and covert HE is important because it may indicate poor quality of life and reduced socio-economic potential, and help counsel patients and caregivers about the disease. The occurrence of minimal and covert HE in patients with chronic liver disease seems to be as high as 50% [70], so ideally every patient at risk should be tested. This strategy, however, may be considered costly [71] and the consequences of the screening procedure are not always clear and treatment is not always recommended (consult the treatment recommendations). An operational approach may be to test patients who have problems with their quality of life or in whom there are complaints from the patients and their relatives [72]. The testing should be done by a trained examiner. A diagnosis of minimal or covert HE does not automatically mean that the affected subject is a dangerous driver [73].

The most established testing strategies are:

i. **Portosystemic encephalopathy (PSE)—Syndrome—Test** consists of five paper–pencil tests that evaluate cognitive and psychomotor processing speed and visuomotor coordination. The tests are relatively easy to administer and have good external validity [74]. It can be obtained from Hannover Medical School that holds the copyright (Weissenborn.karin@mh-hannover.de).
ii. **The Critical Flicker Frequency test (CFF)** is a psychophysiological tool, which is defined as the frequency at which a fused light (presented from 60 Hz downwards) appears to be flickering to the observer. Studies have shown its reduction with worsening cognition and improvement after therapy. It requires several trials, intact binocular vision, absence of red-green blindness and specialized equipment [75,76].
iii. **The Continuous Reaction Time test (CRT)** relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli. The most important test result is the CRT-index that measures the stability of the reaction times. The test result can differentiate between organic and metabolic brain impairment is not influenced by the patient's age or gender, and there is no learning or tiring effect. Simple software and hardware are required [77].
iv. **The Inhibitory Control Test (ICT)** is a computerized test of response inhibition and working memory [78], and is freely

downloadable at www.hecme.tv. The test has been judged to have good validity but requires highly functional patients. The norms for the test have to be elaborated beyond the few centers that have used it.

v. **The Stroop test** evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a colored field and a written color name. Recently, mobile application software (also referred to as a 'mobile app', or an 'app', for a smartphone or tablet computer) based on the test has been shown to identify cognitive dysfunction in cirrhosis compared to paper–pencil tests [79]. Further studies are underway to evaluate its potential for screening for minimal/covert HE.

vi. **Electroencephalograph (EEG)** examination can detect changes in cortical cerebral activity across the spectrum of HE without patient cooperation or risk of a learning effect [68]. It is, however, nonspecific and may be influenced by accompanying metabolic disturbances such as hyponatremia as well as drugs.

The test recommendation varies depending on the logistics, availability of tests, local norms and cost [64,66,69].

Laboratory testing

High blood ammonia levels alone do not add any diagnostic, staging or prognostic value in HE patients with chronic liver disease [80] . However, in case an ammonia level is checked in a patient with overt HE and it is normal, the diagnosis of HE is in question. For 'ammonia-lowering' drugs, repeated measurements of ammonia may be helpful to test the efficacy. There may be logistic challenges to accurately measure blood ammonia which should be taken into consideration. Ammonia is reported either in venous, arterial blood or plasma ammonia so the relevant normal should be used. Multiple methods are available but measurements should only be employed when laboratory standards allow reliable analyses.

Treatment

General principles

At this time, only overt HE is routinely treated [10] . Minimal and covert HE, as its title implies, is not obvious on routine clinical examination and is predominantly diagnosed by the above-described methods. Despite its subtle nature, minimal and covert HE can have a significant impact on a patient's daily living. Special circumstances can prevail where there may be an indication to treat such a patient, e.g. impairment in driving skills, work performance, quality of life or cognitive complaints.

Patients with higher grades of HE who are at risk or unable to protect their airway need more intensive monitoring and are ideally managed in an intensive-care setting. Alternative causes of encephalopathy are not infrequent in patients with advanced cirrhosis. Technically, if other causes of encephalopathy are present, then the episode of encephalopathy may not be termed HE. In the clinical setting, what transpires is treatment of both hepatic and non-HE.

Controlling precipitating factors in the management of overt HE is of paramount importance, as nearly 90% of patients can be treated with just correction of the precipitating factor [81]. Careful attention to this issue is still the cornerstone of HE management.

Therapy for episodes of overt HE

In addition to the other elements of the four-pronged approach to treatment of HE, specific drug treatment is part of the management. Most drugs have not been tested by rigorous randomized–controlled studies and are utilized based on circumstantial observations. These agents include non-absorbable disaccharides such as lactulose and antibiotics such as rifaximin. Other therapies such as oral branched-chain amino acids (BCAA), intravenous L-ornithine L-aspartate (LOLA), probiotics and other antibiotics have also been used.

Non-absorbable disaccharides

Lactulose is usually used as initial treatment for overt HE [82]. A large meta-analysis of trial data did not completely support the efficacy of lactulose for the treatment of overt HE. In addition, most trials on lactulose have been open-label in nature. Cost considerations alone add to the argument in support of lactulose [83]. Lactitol is similar to lactulose and, based on small meta-analyses of even smaller trials, it appears to be more effective [84,85]. In populations with a high prevalence of lactose intolerance, the use of lactose has been suggested [86]. Stool-acidifying enemas (lactose and lactulose) were superior to tap-water enemas in a very small study [87].

The dosing of lactulose should be initiated with 25 milliliters of lactulose syrup every 1–2 hours until at least two soft or loose bowel movements per day are produced. Afterwards, the dosing is titrated to maintain two to three bowel movements per day [2]. There is a danger for overuse of lactulose leading to complications such as aspiration, dehydration, hypernatremia and severe perianal skin irritation, and overuse can even precipitate HE [88].

Antibiotics

Rifaximin has been used for the therapy of HE in a number of trials comparing it with placebo, other antibiotics, non-absorbable disaccharides and in dose-ranging studies [89]. These trials showed effect of rifaximin that was equivalent or superior to the compared agents with good tolerability. Long-term cyclical therapy over 3–6 months with rifaximin for patients with overt HE has also been studied in three trials (two compared to non-absorbable disaccharides and one against neomycin) showing equivalence in cognitive improvement and ammonia lowering. A multi-national study to maintain remission in patients having two prior overt HE bouts showed the superiority of rifaximin versus placebo (in the background of 91% lactulose use) [90]. No solid data support the use of rifaximin alone.

Neomycin has still its advocates, and was widely used in the past for HE treatment; it is a known glutaminase inhibitor [91].

Metronidazole may be used as short-term therapy [92]. However, long-term ototoxicity, nephrotoxicity and neurotoxicity make these agents unattractive for continuous long-term use.

Other therapies

Many drugs have been used for treatment of HE but data to support their use are limited, preliminary or lacking. However, most of these drugs can safely be used despite their limited proven efficacy.

BCAA: an updated meta-analysis of eight randomized–controlled trials (RCTs) indicated that oral BCAA enriched formulations improve the manifestations of episodic HE whether overt

or minimal HE [93,94]. There is no effect of intravenous BCAA on the episodic bout of HE [95].

Metabolic ammonia scavengers: such drugs have been used for treatment of inborn errors of the urea cycle for many years. Different forms are available and now present as promising investigational agents. *Ornithine phenylacetate* has been studied for HE but further clinical reports are awaited [96]. *Glyceryl phenylbutyrate* (GPB) was tested in a recent RCT on patients who had experienced two or more episodes of HE in the last 6 months and who were maintained on standard therapy (lactulose +/– rifaximin) [97]. The GPB arm experienced fewer episodes of HE and hospitalizations, and longer time to first event. More clinical studies on the same principle are under way and, if confirmed, may lead to clinical recommendations.

LOLA: a RCT on patients with persistent HE demonstrated improvement by intravenous LOLA in psychometric testing and postprandial venous ammonia levels [98]. Oral supplementation with LOLA is ineffective.

Probiotics: a recent open-label study of either lactulose, probiotics or no therapy in cirrhosis patients who recovered from HE found fewer episodes of HE in the lactulose or probiotic arms compared to placebo, but were no different between either intervention. There was no difference in rates of readmission in any of the arms of the study [99].

Flumazenil: this drug is not frequently used. It transiently improves the mental status in overt HE without improvement in recovery or survival. The effect may be of importance in marginal situations to avoid assisted ventilation. Likewise, the effect may be helpful in difficult differential diagnostic situations by confirming reversibility, e.g. when standard therapy unexpectedly fails or when benzodiazepine toxicity is suspected.

Laxatives: simple laxatives alone do not have the prebiotic properties of disaccharides, and no publications have been forthcoming on this issue. The use of polyethylene glycol preparation [100] needs further validation.

Prevention of overt HE

Lactulose is frequently used for the maintenance of remission from overt HE. A single-center, open-label RCT of lactulose demonstrated less recurrence of HE in patients with cirrhosis [101]. A RCT supports lactulose as prevention of HE post upper GI bleeding [102,103].

Rifaximin added to lactulose is the best documented agent to maintain remission in patients who have already experienced one or more bouts of overt HE while on lactulose treatment after their initial episode of overt HE [90].

After transjugular intrahepatic portosystemic shunting (TIPS) placement HE may occur. One study illustrated that neither rifaximin nor lactulose prevented post-TIPS HE any better than placebo [104]. Careful case selection has reduced the incidence of severe HE post-TIPS. If it occurs, shunt diameter reduction can reverse the HE [105]. There is lack of consensus on whether to aim to reduce portal pressure by 50% or below 12 mmHg. The latter is associated with more bouts of encephalopathy [106].

Recurrent bouts of overt HE in patients with preserved liver function consideration should lead to a search for large spontaneous portosystemic shunts. Certain types of shunts, such as spleno-renal shunts, can be successfully embolized with rapid clearance of overt HE in a fraction of the patients in a good liver function status, despite the risk for subsequent variceal bleeding [107].

Treatment of minimal and covert HE

While it is not standard to offer therapy for minimal and covert HE, several studies used a variety of agents including probiotics, lactulose and rifaximin in minimal HE. Most studies have been for less than 6 months and do not reflect the overall course of the condition. Trials span the gamut from small open-label trials to larger, randomized–controlled studies using various treatments. Most studies have shown an improvement in the underlying cognitive status but the mode of diagnosis has varied considerably among studies. A minority of studies used clinically relevant endpoints. It was shown in an open-label study that lactulose can prevent development of the first episode of overt HE but the study needs to be replicated in a larger study in a blinded fashion before firm recommendations can be made [108]. Studies using lactulose and rifaximin have shown improvement in quality of life [109,110] and also in driving simulator performance [111,112]. Probiotics have also been used but the open-label nature, varying amounts and types of organisms and different outcomes make them difficult to recommend as therapeutic options at this time [113–115].

Owing to the multiple methods used to define minimal and covert HE, varying endpoints, short-term treatment trials and differing agents used in trials to date, routine treatment for minimal HE is not recommended at this stage. Exceptions could be made on a case-by-case basis using treatments that are approved for overt HE, particularly for patients with covert HE and West-Haven grade I HE.

Nutrition

Modulation of nitrogen metabolism is crucial to the management of all grades of HE and nutritional options are relevant. Detailed recent guidelines for nutrition of patients with HE are given elsewhere [116]. Malnutrition is often under-diagnosed, and about 75% of patients with HE suffer from moderate to severe protein-calorie malnutrition with loss of muscle mass and energy depots. Chronic protein restriction is detrimental, as the patients' protein requirements are relatively greater than normal patients' and they are at risk of accelerated fasting metabolism. Sarcopenia has been proven to be an important negative prognostic indicator in cirrhotic patients [117]. The therapy is refeeding by moderate hyperalimentation. Small meals evenly distributed throughout the day and a late-night snack [118] should be encouraged, with avoidance of fasting. The hyperalimentation should be given orally to patients who can cooperate, by gastric tube to patients who cannot take the required amount and parenterally to other patients. There is consensus that low protein nutrition should be avoided for patients with HE. Some degree of protein restriction may be inevitable in the first few days of overt HE treatment but should not be prolonged. Oral BCAA-enriched nutritional formulation may be used to treat HE and generally improves the nutritional status of cirrhotic patients, but intravenous BCAA for an episode of HE has no effect [119].

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