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CLINICAL REVIEW

Hepatic encephalopathy due to liver cirrhosis

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Overt hepatic encephalopathy affects approximately 20% of patients with liver cirrhosis each year.[1] It is a pathognomonic feature of liver failure and a common cause of admission to emergency departments. It affects the quality of life of both patient and relatives[2] and signifies a poor prognostic indicator for patients with cirrhosis, with a survival of only 23% at three years from onset.[3] Treatments aimed at interrupting the pathogenesis of hepatic encephalopathy are known to reduce frequency of hospital admissions and improve survival.[4]

Studies suggest that the prevalence of chronic liver disease in the United Kingdom is increasing, in part owing to the increasing prevalence of non-alcoholic fatty liver disease (NAFLD), alcohol related liver disease, and hepatitis C.[5 6] Clinicians therefore need to be able to recognise signs and symptoms of hepatic encephalopathy in patients who might not have a diagnosis of chronic liver disease.

This review aims to highlight the importance of recognising hepatic encephalopathy in chronic liver failure and outlines a practical and evidence based approach to its management, based on the framework of recent guidelines from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD).[4] Hepatic encephalopathy in acute liver failure is managed differently, and will not be addressed.

What is hepatic encephalopathy and what are its signs and symptoms?

Hepatic encephalopathy constitutes a spectrum of neuropsychiatric abnormalities, beginning with subtle psychomotor changes and progressing to confusion with asterixis, somnolence, and then coma, arising in patients with impaired liver function or portosystemic shunting.[7] The first neuropsychological feature to emerge is psychomotor slowing, which can only be detected on psychometric testing, using, for example, the psychometric hepatic encephalopathy score (PHES).[8] Other neuropsychological tests are outlined in table 1⇓. There is no agreed "gold standard" test, and patients may score differently on each. The tests therefore need to be used as part of a wider clinical assessment. Which test is chosen depends on availability of equipment, training of examiner, and local preference.[4]

Psychomotor slowing may progress to subtle cognitive impairment and difficulties in concentration.[14] Reversal of the sleep-wake cycle is an early sign in some patients. In addition, affective changes including depression and occasionally personality changes are observed (such as irritability and inappropriate behaviour).[15] Agitation and aggression can progress to acute confusion leading to progressive stupor and coma. Asterixis (also known as a "liver flap") constitutes an arrhythmic negative myoclonus and loss of postural tone with a frequency of 3-5 Hz. This may be bilateral or asymmetric and is normally seen in the hands but can affect other parts of the body. It may be more easily felt than seen.

Hepatic encephalopathy must be distinguished from other causes associated with a change in cognition—such as electrolyte disturbance, intoxication, cerebral hypoperfusion, hypoxia, and sepsis—as well as more chronic conditions such as dementia. A differential diagnosis for hepatic encephalopathy is given in table 2⇓.

Neurological examination is often normal in stages 1-2 of hepatic encephalopathy, but hyperreflexia and extensor posturing may develop later, together with a positive Babinski sign.[16]

In liver cirrhosis seizures are less common than in acute liver failure (when they warn of developing cerebral oedema)[17 18] and suggest causes such as electrolyte derangement (for example, hypoglycaemia, hypomagnesaemia), alcohol withdrawal, stroke, or encephalitis.[19]

How is hepatic encephalopathy classified?

There are several methods of classifying hepatic encephalopathy. The syndrome can be seen as comprising three separate clinical entities: type A due to acute liver failure, type B due to portal venous bypass with portosystemic shunting, and type C due to cirrhotic liver disease (table 2⇓).[7] Some authorities define hepatic encephalopathy as acute or chronic; or as episodic, recurrent,

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The bottom line

- Hepatic encephalopathy is a sign of poor prognosis and correlates with mortality in both in patients with acute liver failure and those with cirrhosis associated with end stage liver disease
- Patients without overt hepatic encephalopathy can have subtle cognitive deficits affecting quality of life that may be responsive to treatment
- Hepatic encephalopathy is a clinical diagnosis that can be assisted by neuropsychology and neurophysiology
- Evidence based treatments, such as lactulose and rifaximin, influence both length and quality of life

Sources and selection criteria

We searched PubMed up to March 2015 (and updated June 2015) with the terms "hepatic encephalopathy" and "minimal hepatic encephalopathy" targeting reviews and studies published in English since 1990. We searched the references of identified articles as well as our own files. The selection of references was made based on our assessment of relevance to the topic.

or persistent; others differentiate between non-precipitated and precipitated episodes.

Type B hepatic encephalopathy may develop acutely after transjugular intrahepatic portosystemic shunting (TIPS) procedures,[20] in which an iatrogenic portosystemic shunt is created. The likelihood of developing overt hepatic encephalopathy after TIPS varies from 15% to 48%,[21] and is higher in older patients, those with previous episodes of hepatic encephalopathy, and those with a higher Child-Pugh score.[22] If covert hepatic encephalopathy is included the risk is higher. If hepatic encephalopathy does develop, shunt size reduction or embolisation of portosystemic collaterals should be considered.[23]

The most common clinical classification used to describe the severity of hepatic encephalopathy is the West Haven criteria (table 3⇓).[7] This describes the continuum of hepatic encephalopathy progressing through its four stages, from mild lack of awareness to coma.

Covert hepatic encephalopathy refers to subtle neuropsychological problems, psychomotor slowing, and difficulty with activities of daily living that can be detected on neuropsychological assessment (see table 1⇓). It is not reliably detected by the clinician without investigations. Recent studies have demonstrated that covert hepatic encephalopathy affects up to 50% of cirrhotic patients.[8] Many patients develop covert hepatic encephalopathy in a chronic manner, with subtle neuropsychological changes that may have devastating effects on the patient's ability to function independently.[24] Assessment for covert hepatic encephalopathy using psychometric tests may be particularly considered in patients with known or suspected liver cirrhosis who complain of difficulties functioning in everyday life, whose relatives have noticed attentional difficulties, or when employment is directly affected by cognitive impairment.[4] Covert hepatic encephalopathy also has a poor prognosis, with increased risk of hospitalisation and progression to overt hepatic encephalopathy or mortality.[25]

What causes hepatic encephalopathy?

Hepatic encephalopathy can develop due to liver failure from any cause. It is postulated that its pathogenesis is related to the effects of nitrogenous waste products on the brain, particularly ammonia and glutamine.[26] Glutamine is normally metabolised by glutaminase in the small intestine to ammonia and glutamate; ammonia is then converted to urea in the liver.[27] High levels of ammonia in the serum lead to cerebral oedema, which acts synergistically with an inflammatory response in the central nervous system to cause complex cortical and subcortical dysfunction. In cirrhotic patients, portosystemic shunting allows ammonia and other neurotoxins to bypass the liver and enter the systemic circulation, and this may also occur after transjugular intrahepatic portosystemic shunting. Hyponatraemia, common in cirrhosis, may also exacerbate cerebral oedema and astrocyte dysfunction.[28] Muscle volume depletion (sarcopenia) contributes to the development of encephalopathy, since muscle represents an alternative site of ammonia detoxification.[29] Patients with a concomitant systemic inflammatory response syndrome, such as from infection, are predisposed to developing hepatic encephalopathy.[30 31] The gut microbiota has also been implicated in pathogenesis, and there is evidence for gut dysbiosis and small bowel overgrowth,[32] hence the possibility of therapies modulating microbiota, such as probiotics.

Which investigations aid diagnosis?

There is no specific test for hepatic encephalopathy, and the diagnosis should be made on clinical grounds through the exclusion of other conditions that can mimic or be confused with hepatic encephalopathy (see table 2⇓). Testing of arterial or venous ammonia levels is commonly performed, but levels correlate poorly with the grade of hepatic encephalopathy[33] and should not be used alone for establishing the diagnosis as they are not consistently raised.[34]

Computed tomography or magnetic resonance imaging should be performed in all patients in whom a diagnosis of hepatic encephalopathy is being considered, in order to exclude other conditions such as intracranial haemorrhage or space occupying lesions. Hyperintensity of the basal ganglia on magnetic resonance imaging is suggestive of portosystemic shunting.[35] Positron emission tomography has been used experimentally and may have a role, but this remains undefined.[36]

Electroencephalography is used to investigate for the presence of seizures and should be considered if subclinical seizures are suspected.[37] It may show characteristic changes in overt hepatic encephalopathy in the form of triphasic waves, as well as more subtle signs in covert hepatic encephalopathy.[38] It may be used together with neuropsychological assessments (see table 1⇓) to aid the diagnosis of covert hepatic encephalopathy.[4] However, the findings are generally non-specific and may be influenced by metabolic and drug factors.

How is hepatic encephalopathy managed?

The management of hepatic encephalopathy depends on its type and severity. Many patients with covert hepatic encephalopathy may not require treatment unless the condition is thought to be adversely affecting quality of life.[4] Episodes of overt hepatic encephalopathy can be shortened with appropriate treatment, and further events prevented.

Many patients presenting acutely with overt hepatic encephalopathy will have an underlying precipitant, such as gastrointestinal bleeding, infection, diuretic overdose, or use of sedating medication.[39] The first stage in management is to address these—that is, by stopping precipitating drugs, treating infection, etc. However, a substantial proportion of patients will have no identified cause.

All patients with evidence of hepatic encephalopathy should be advised to stop driving and inform the Driver and Vehicle Licensing Authority (DVLA).[4] Studies have shown that even patients with covert hepatic encephalopathy are more prone to road traffic accidents.[40] Failure of the patient to inform the DVLA about the condition may result in a fine. Patients are likely to have their licence revoked until satisfactory recovery is demonstrated.[41]

Nutrition

Historically, dietary protein restriction has been advised for patients with hepatic encephalopathy as this was thought to decrease intestinal ammonia production, but a small randomised trial suggests that normal protein diets are safe, and protein malnutrition may contribute to sarcopenia, potentially worsening the condition.[42 43] Thus it is recommended by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism that 1.2-1.5 g/kg of protein is given in small meals distributed throughout the day, with a late night snack of complex carbohydrates.[44] A nasogastric feeding tube should be considered if the patient is unable to achieve the dietary targets.

Non-absorbable disaccharides and probiotics

Lactulose is a non-absorbable disaccharide that is metabolised to lactic and acetic acid in the colon, reducing the pH and promoting the excretion of ammonia as well as the utilisation of ammonia in the metabolism of gut bacteria.[45 46] Although a Cochrane review did not find a significant difference in outcomes associated with its use in acute hepatic encephalopathy,[47] results from a well conducted randomised controlled trial support the use of lactulose in the secondary prophylaxis of hepatic encephalopathy.[48] The EASL-AASLD guidelines recommend that lactulose is used as a first line agent in episodes of overt hepatic encephalopathy and then continued to prevent further episodes.[4] The patient should take 25 mL of lactulose twice daily, aiming to achieve three soft bowel motions a day.[4] Lactitol is an alternative and is used in some centres on the basis of poor quality evidence from a small meta-analysis of four small trials suggesting that it may be better tolerated than lactulose.[49]

Probiotic therapy was found to decrease overt hepatic encephalopathy in a meta-analysis of six randomised controlled trials.[50] Probiotics can be administered in yoghurt drinks or tablets, commonly containing *Lactobacillus rhamnosus* and *Saccharomyces boulardii*. A Cochrane review examining seven trials found insufficient evidence to recommend the routine use of probiotics, largely because of methodological concerns.[51]

Polyethylene glycol is a purgative laxative agent which produces catharsis of the gut, theoretically reducing the numbers of ammonia producing bacteria. In a recent well designed randomised controlled trial, it was shown to be as effective as, and possibly superior to, lactulose in terms of speed of resolution of hepatic encephalopathy and reduction in length of hospital stay.[52] However, more data are required before it can be routinely recommended in preference to lactulose.

Neomycin and rifaximin

Advances in treatment in recent decades have been due to the use of oral antibiotics to modulate gut flora, thus reducing ammonia production. Neomycin is an aminoglycoside antibiotic which is poorly absorbed and reaches high concentrations in the gut, acting as a glutaminase inhibitor.[53] It was the first antibiotic agent to be widely used in hepatic encephalopathy, although significant adverse events compared with newer agents now preclude its use.

Rifaximin is a semisynthetic antibiotic derived from rifamycin. The National Institute of Health and Care Excellence (NICE) recently recommended rifaximin for the prevention of episodes of overt hepatic encephalopathy based on evidence from a large well conducted randomised controlled trial.[54 55] Both NICE and the EASL-AASLD guidance recommend rifaximin for secondary prophylaxis of overt hepatic encephalopathy in patients who have had further episodes while taking lactulose.[4] There is no evidence for the use of rifaximin alone.

What treatments are available for resistant hepatic encephalopathy?

Patients whose hepatic encephalopathy does not respond to optimal medical treatment, in the form of lactulose and rifaximin, may be considered for embolisation of portosystemic shunts, which can be undertaken percutaneously. Evidence from two retrospective studies suggests that the procedure decreases hospital admissions and improves survival, but adverse effects include de novo gastro-oesophageal varices, worsening ascites, and renal dysfunction due to contrast-induced nephropathy.[56 57]

Liver transplantation should be considered in all suitable candidates presenting with hepatic encephalopathy, and discussion with a liver transplant centre initiated.[58] Patients can be considered for a transplant if they have had two admissions for hepatic encephalopathy in the past six months in the absence of comorbidities that would preclude surgery.[59] Patients with alcoholic liver disease must be abstinent and sign an agreement indicating intention of continued abstinence.[60]

Hepatic encephalopathy and end of life care

For patients who are not candidates for liver transplantation, particularly those for whom hepatic encephalopathy is refractory to treatment or leads to an increasing number of hospital admissions, it is important that clinicians recognise that a switch in the emphasis of care may be required. Discussions with the patient, family members, and carers are important to inform them what hepatic encephalopathy is, what causes it and, importantly, what its implications are. In the context of liver cirrhosis and in the face of clinical deterioration, the clinician may ask the "surprise" question—that is, "Would I be surprised if this patient were not alive in 12 months' time?"[61] If the answer is no, then consider placing the patient on an end of life registry, informing his or her general practitioner and the community palliative care team.

The "Amber care bundle" is a set of evidence based interventions which provides a framework for clinicians to follow to ensure that the correct steps are taken.[62] The emphasis of care may then shift to maintaining the patient's comfort, wishes, and dignity, providing support to the family and carers, and trying to avoid hospital admissions. Carers should be educated about the causes of hepatic encephalopathy and how to prevent them, such as by preventing constipation and avoiding

sedating medications. If constipation develops, then increasing doses of laxatives should be considered. If this does not lead to an improvement, carers should either be taught how to administer phosphate enemas or contact a district nurse to assist with this. For patients who wish to be cared for at home, when they enter the dying phase of their disease, their carers and the primary care team should be fully informed and receive written information as to how to respond to the complications of end stage disease such as variceal bleeding, ascites, worsening hepatic encephalopathy, and sepsis. At this stage the main aim is to reduce distress rather than preserve lucency, thus administering opiates, benzodiazepines, and other sedating medications can be considered where appropriate.

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Future prospects in the treatment of hepatic encephalopathy

L-ornithine-L-aspartate (LOLA)—A preparation containing the amino acids ornithine and aspartic acid, given by intravenous infusion
Evidence: A meta-analysis including 20 randomised controlled trials showed LOLA to be as effective as non-absorbable disaccharides, with a trend towards superiority, with few adverse effects[63]

Branched chain amino acids (BCAA)—A preparation of amino acids (valine, leucine, and isoleucine) normally given orally or by nasogastric tube, postulated to alter the balance of amino acids in the brain as well as to provide energy supplementation
Evidence: A recent Cochrane review considered 16 randomised clinical trials and found high quality evidence of clinical benefit but no effect on mortality, quality of life, or nutrition parameters[64]

Human albumin solution (HAS)—Albumin is a crucial plasma protein that is reduced in liver failure. Supplementing albumin intravenously may help to address circulatory dysfunction
Evidence: A small randomised trial suggested that intravenous HAS does not improve resolution of hepatic encephalopathy, but it may improve survival[65]

Glyceryl phenylbutyrate—An oral preparation which provides an alternative for waste nitrogen excretion, reducing ammonia production
Evidence: A recent randomised controlled trial showed a reduction in episodes of hepatic encephalopathy and hospital admissions[66]

Ornithine phenylacetate—L-ornithine acts as a substrate for glutamine synthesis from ammonia in skeletal muscle, and phenylacetate excretes ornithine-related glutamine as phenylacetylglutamine in the kidneys[67]
Evidence: A trial is currently recruiting to examine safety and efficacy versus standard of care in hospitalised patients (NCT01966419)

A patient's story

I will attempt to provide an account of the impact of HE by recounting actual occurrences. Most of these have a comic element which disguises the severe anxieties I experienced. In most cases I am paradoxically able to remember what was happening at the time, and, although I think I was aware of the distress I was causing to others, I was unable to change my behaviour until the effects wore off.

My episodes of hepatic encephalopathy usually started with the onset of confusion and a state of disorientation. I would start to shake, hold my head in my hands, and become argumentative, unreasonable, and uncooperative. Bizarre behaviour usually followed, such as:

- Dressing to go out to a dinner party, I presented downstairs with my trousers on back to front.
- Returning from buying a newspaper I stood in the dark on a freezing winter's night trying to unlock the back door without success until my partner returned home from shopping.
- I once spent 20 minutes trying to figure out how to put on a pair of gardening clogs (no laces).
- I forgot how to brush my teeth despite having the brush loaded with paste put in my hand and the tap turned on.
- I went downstairs one morning to make my partner her cup of tea and returned inexplicably with a knife and no tea.
- I didn't recognise best friends whom my partner had called for help during one of my episodes.
- I offered my phone as payment in a shop.
- I couldn't work out how to read a book.
- I forgot how to use the computer
- My handwriting became illegible.

Prior to my admission to hospital, I experienced a variety of attempts to diagnose my condition. While I understand the need to cover every possibility before arriving at hepatic encephalopathy, greeting a confused and anxious patient with "Hello again, Mr Crawford. Been drinking again have we?" cannot help. Hepatic encephalopathy is an awful experience for the patient and the carer. It is unpredictable and challenging and mystifying in the early stages because it is usually impossible to ascribe the episodes to any particular cause.

Generally, I was aware of what was happening and what I wanted to say, but I was unable to make myself clear. This was especially frightening in hospital without my partner to help and decipher. I cannot overemphasise the importance of seeking the views and opinions of the patient's carer in trying to assess the impact the condition has on their lives.

I had many awful experiences alone on a ward. For example, when I was in bed and wanted a blanket I resorted to miming to a nurse that I was cold because I couldn't retrieve the necessary words. I remember hallucinating and developing irrational fears of what might be planned for me. I even planned an elaborate plot to escape from hospital. Patients are usually seen alone on the wards when they are confused and disorientated. I remember trying to remember key facts for my partner's benefit when she visited. Usually I was unable to recall what I'd been told which caused anxiety and embarrassment. Hepatic encephalopathy prohibits clear thought and articulation. Once, I tried to write things down for her benefit, but what I thought was a lucid account was illegible.

At this point, I had not been given a formal account of what hepatic encephalopathy was and what I might expect to happen to me. An explanation given to my partner was: "Toxins which your liver cannot process travel to your brain and distort its functioning." Clarity is vital if the patient and carer are expecting to come to terms with hepatic encephalopathy. A simple, definitive explanation is beneficial for patients as soon as one is available.

Rifaximin worked for me. Being prescribed it during a consultation with my specialist certainly made me feel that I was being dealt with properly at last.

Informing the DVLA is really important. I did drive on occasions when I was affected by hepatic encephalopathy. Defiance and bravado were to blame, and I did have one minor collision which could have been avoided.

Tips for non-specialists

- Patients with previously undiagnosed liver disease are increasingly likely to present to primary or secondary care with hepatic encephalopathy, and it should be part of the differential diagnosis of confusion. Screening for risk factors such as alcohol misuse, exposure to bloodborne viruses, obesity, and diabetes will help to identify these patients
- Seizures in patients with cirrhosis usually have another cause: evaluate for electrolyte imbalances, infection, alcohol history and stroke
- Early nutritional review is vital for patients with hepatic encephalopathy and can improve outcome
- If patients fail to respond to medical therapies, discussion with a liver transplant centre is advised when clinically appropriate for the patient
- For patients who are not fit for transplant and who are clinically deteriorating, consider shifting the emphasis of care to maintaining comfort
- Patients who are diagnosed with hepatic encephalopathy should stop driving and inform the Driver and Vehicle Licensing Authority (DVLA)

Questions for future research

- What is the most appropriate diagnostic strategy in covert hepatic encephalopathy?
- Do patients with covert hepatic encephalopathy benefit from treatment, and if so which treatment is most effective?
- Are probiotics an effective treatment for hepatic encephalopathy?
- What is the role of neuroinflammation in hepatic encephalopathy, and can it be targeted with anti-inflammatory drugs?

Additional educational resources

Resources for health professionals

- EASL clinical practice guideline *Hepatic Encephalopathy in Chronic Liver Disease: 2014*—www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/hepatic-encephalopathy-in-chronic-liver-disease-2014
  Useful guide to diagnosis, management, and follow-up.
- Felipo V. Hepatic encephalopathy: effects of liver failure on brain function. *Nature Reviews Neuroscience* 2013;14:851-8—www.nature.com/nrn/journal/v14/n12/full/nrn3587.html
  Accessible recent review of pathophysiology and new approaches to treatment. Requires institutional access rights.

Resources for patients

- British liver trust—www.britishlivertrust.org.uk
  Provides information and support for patients with liver disease and their families

How patients were involved in the creation of this article

We consulted one of our patients who had experienced hepatic encephalopathy who kindly reviewed our manuscript and made suggestions about aspects of care that were especially important for patients with the condition

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Tables

Table 1| Psychometric tests for diagnosis of covert hepatic encephalopathy

Test name	Description	Equipment required	Problems
Psychometric hepatic encephalopathy score (PHES)[8]	Six tests evaluating cognitive and psychomotor processing speed and visuo-motor coordination	Pencil and paper	Vision must be intact
Stroop test[9]	Tests interference between a coloured field and a written colour name	Computer, pencil and paper, or mobile phone app	Vision must be intact
Critical flicker frequency (CFF) test[10]	Assessment of ability to detect a light source flickering	Specialised equipment	Vision must be intact
Continuous reaction time (CRT) test[11]	Motor reaction time to auditory stimuli	Computer equipment and additional hardware	Hearing must be intact
SCAN test[12]	Computerised digit recognition task	Computer equipment	Vision must be intact
Inhibitory control test (ICT)[13]	Test of attention and response inhibition to presented letters	Computer equipment	Requires patients to be familiar with computer use

Table 2| Differentials differential diagnosis for hepatic encephalopathy

Category and diagnosis	Distinguishing factors
Metabolic: Diabetic ketoacidosis Hypoglycaemia Hyperosmolar states	Patient's history and results of blood and urine investigations will help to exclude metabolic and endocrine causes
Endocrine: Hyponatraemia Hypercalcaemia Hypothyroidism	
Drugs and toxins: Alcohol intoxication or withdrawal Wernicke's encephalopathy Opioids Benzodiazepines	Alcohol withdrawal often causes tremor, sweating, and prominent hallucinations. A collateral history of alcohol intake can be helpful Constricted pupils and depressed respiratory drive may indicate opiate toxicity
Infection: Encephalitis Sepsis related encephalopathy	Look for prodromal personality change, fever, focal neurological signs, and seizures as signs of encephalitis Evaluate carefully for a source of underlying sepsis: consider chest x ray and urine microscopy
Vascular: Ischaemic stroke Intracranial haemorrhage Cerebral hypoperfusion	Sudden onset focal neurological signs point to a cerebral vascular event Cerebral hypoperfusion can occur secondary to cardiac failure or reduced circulating volume: consider echocardiography
Others: Non-convulsive status epilepticus Brain lesions Dementia Obstructive sleep apnoea Psychiatric disorder	Electroencephalography and brain imaging are vital if non-convulsive status or a space-occupying lesion are considered Overnight pulse oximetry and early morning arterial blood gas analysis can point to obstructive sleep apnoea Depression can cause psychomotor slowing and may coexist with other pathologies: psychiatric evaluation may be warranted

Table 3| **West Haven criteria for grading severity of hepatic encephalopathy**

Grade	Clinical features
Covert hepatic encephalopathy	
Minimal hepatic encephalopathy (MHE)	Evidence of cognitive impairment on neuropsychology Evidence of altered psychomotor speed or executive function Requires psychometric tests to make the diagnosis
Grade I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction (for example, serial 7s test) Altered sleep rhythm
Overt hepatic encephalopathy	
Grade II	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behaviour Dyspraxia Asterixis
Grade III	Somnolence to semi-stupor Response to stimuli Confused Gross disorientation Bizarre behaviour
Grade IV	Coma