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HEPATIC ENCEPHALOPATHY: PATHOGENESIS, DIAGNOSIS AND MANAGEMENT

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Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric syndrome which may be acute, as in fulminant liver failure, or chronic and recurrent, as in cirrhosis. This review will concentrate primarily on HE associated with chronic liver disease.

Acute HE is distinct from HE that accompanies chronic liver disease. It is characterised by encephalopathy that develops within eight weeks of the first symptoms of an acute liver disease, e.g. acute viral hepatitis. The pathological features are cerebral oedema of varying degrees and hydropic change of astrocytes. Cerebral oedema, of cytotoxic origin with a consequent rise in intracranial pressure, is thought to contribute to the rapid deterioration seen in fulminant liver failure. The management of intracranial hypertension is vital in the care of this group of patients.

PATHOGENESIS

HE was observed by Hippocrates in the fifth century BC, but only described in detail in dogs with portocaval shunts (Eck's fistula) fed with large protein meals of meat. There is no unifying concept which explains all the features of HE. It is beyond the scope of this review to discuss in detail the pathogenesis of HE (readers are referred to comprehensive reviews).[1,2]

HE arises from the free passage of gut-derived neurotoxins through a sick or shunted liver which then gain access to the central nervous system by crossing a dysfunctional blood-brain barrier. These neurotoxins interfere with cerebral neurotransmission (Figure 1). Research has centred on identifying these neurotoxins as well as the affected neurotransmitter systems so that appropriate pharmacological intervention at these levels could be devised.

Ammonia appears to be central in the pathogenesis of HE: it is gut-derived (50 per cent comes from bacterial breakdown) and, in health, it is metabolised on first-pass through the liver into urea, a far less harmful substance which can be excreted by the kidneys. Ammonia levels are raised in 90 per cent of patients with HE and measures which reduce ammonia levels result in improvement of HE. Ammonia is directly neurotoxic and indirectly interferes with neurotransmitter systems (in particular the glutaminergic and GABAergic systems). However, 10 per cent of patients with HE have normal plasma ammonia levels and the correlation between ammonia levels and severity of HE is poor, indicating that it is likely that ammonia is not the sole neurotoxin.

Other neurotoxins implicated include methionine derivatives, e.g. mercaptans, phenols and fatty acids. There is no consistent evidence that they are of major importance and they possibly exert a synergistic effect with ammonia. Food and gut-derived substances such as false neurotransmitters, e.g. octopamine, benzodiazepine ligands and GABA, have been shown to be elevated in HE and blamed for disturbing

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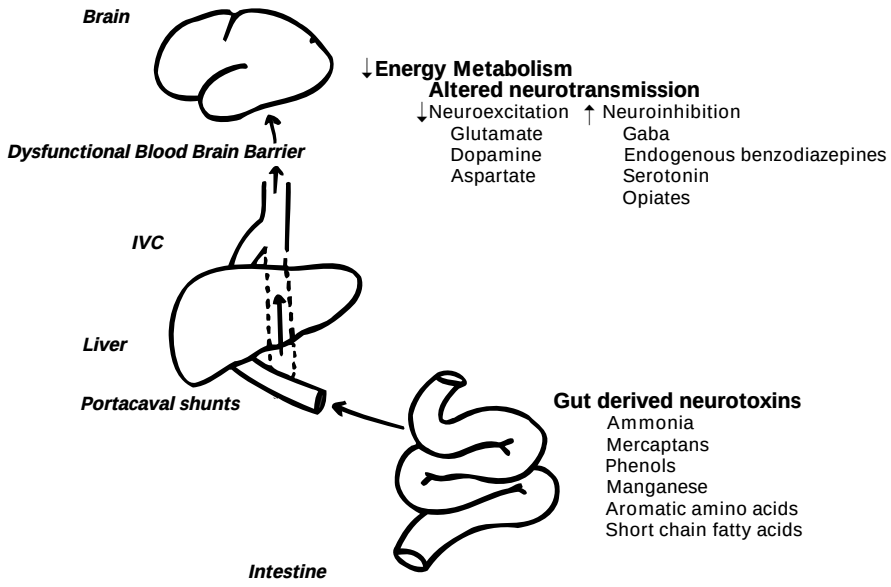

FIGURE 1
Pathogenesis of hepatic encephalopathy.

neurotransmission. However, their significance in the pathogenesis of HE is not clear.[4] Increased levels of aromatic amino acids (e.g. trytophan), and normal or decreased levels of branched-chain amino acids are well documented in HE.[5] Tryptophan is a precursor of serotonin, which may account for the state of increased neuroinhibition seen in HE. Neurotransmitter abnormalities have been identified in the glutaminergic, monoaminergic systems, and latterly in the gamma-amino butyrate and endogenous opioid systems.[6] Manganese is excreted in bile and in cirrhotics it is raised in the serum and accumulates in the *globus pallidus* and this may account for the extrapyramidal signs observed in HE.

Magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are noninvasive tools which enable cerebral metabolism and neurobiology of HE patients to be studied in ways not possible previously.[7]

PATHOLOGY[6]

Astrocytes occupy one third of cortical volume and appear to have a central role in the pathogenesis of HE. They are also responsible for neurotransmitter uptake and the metabolism of neurotoxins. In HE the pathological hallmark is the finding of astrocytes which are swollen, each containing an enlarged pale nucleus, prominent nucleoli and margination of chromatin; these changes are termed as Alzheimer's type II astrocytosis. Manganese deposition is increased in the *globus pallidus*.[8] Cerebral atrophy is not a feature of HE and, when present, it is the result of the underlying cause of the liver disease, e.g. alcohol.

CLINICAL FEATURES

The clinical spectrum ranges from mild impairment of psychomotor skills and altered personality (which is difficult to diagnose at the 'bedside') to obvious

drowsiness and altered muscular tone. HE is classified clinically into subclinical (occult) and overt forms.

Subclinical hepatic encephalopathy (SHE)[8]

This condition, first described in the early 1970s in patients with porto-systemic shunts, is increasingly recognised, and occurs in a large proportion (30-84 per cent) of patients with cirrhosis.[9] Clinical 'bedside' assessment, which relies heavily on obvious abnormal signs and changes in verbal skills, will not detect any abnormality because HE preferentially affects visuo-spatial and psycho-motor abilities rather than verbal ability and intelligence.

The diagnosis of SHE rests on psychometric and electrophysiological testing. Psychometric tests of diagnostic value for SHE are the digit symbol test (DST), the block design test, the number connection test (NCT) and reaction times to light or sound (RT).[10] Of these NCT-A (Figure 2) is the most commonly applied.

These tests are not infallible and are influenced by age, repetitive testing and educational status. Electrophysiological tests comprise visual-evoked potentials (VEP), brain stem auditory-evoked potentials (BAEP), somatosensory-evoked potentials (SSEP), P300 event-related potentials (P300) and electroencephalography (EEG). Expansive specialised equipment and highly-trained personnel are required to carry out these tests, which therefore remain largely research tools.

Evoked potentials look at the functional integrity of the afferent pathway between the cortex and stimulated peripheral tissue. Of the evoked potentials, P300 has emerged as the most reliable. Electrophysiological tests are more specific but less sensitive when compared with psychometric tests, and any overlap between healthy and cirrhotic subjects makes interpretation difficult.

The clinical significance of SHE is that impaired psychomotor function affects the ability of these patients to perform manual work and to drive safely. One study concluded that 60 per cent of cirrhotics were unfit to drive, with another 25 per cent having questionable driving capacity.[11,12]

'Overt' Hepatic Encephalopathy

HE often appears in predisposed individuals following on an adverse episode, but can occur spontaneously in patients with poor liver function and significant portacaval shunting. Table 1 lists the common precipitants of HE.

Clinically, HE involves changes in consciousness, personality and speech.[13] Altered consciousness ranges from a disordered sleep cycle in the early stages to hypersomnia, then coma. Personality changes are similar to those occurring with frontal lobe lesions,

TABLE 1
Common precipitants of hepatic encephalopathy.

- Uraemia
  - Spontaneous
  - Diuretic induced
- Drugs
  - Sedatives, tranquillisers, anaesthetics, analgesics, alcohol
- Gastrointestinal bleeding
- Hypokalaemic alkalosis
- Excess nitrogen intake
- Constipation
- Infection
- Liver failure
- Others
  - Trauma (surgery), shock, hypoxia, paracentesis, porto-systemic shunts

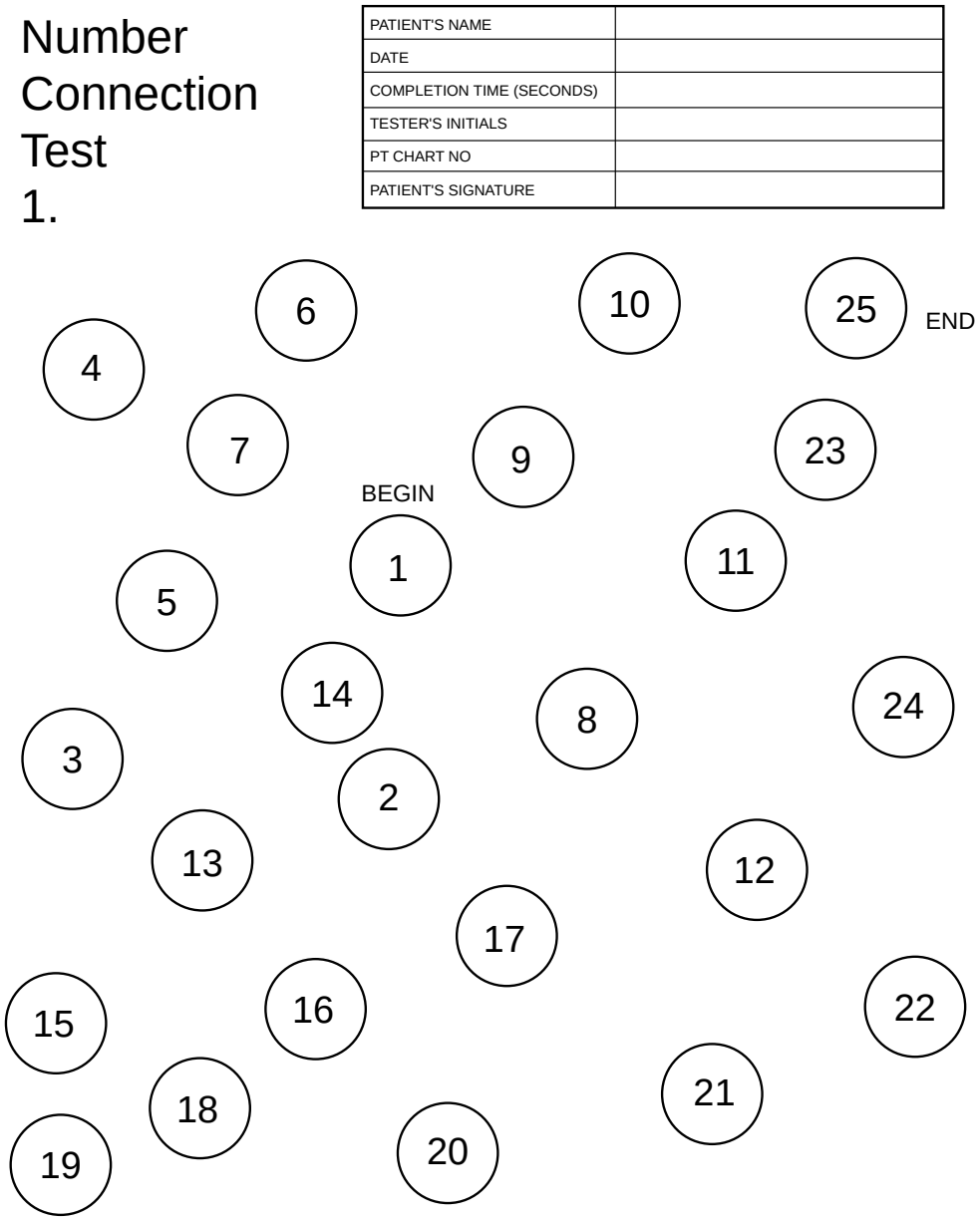

FIGURE 2
Number Connection Test part A (NCT-A): subjects have to connect the numbers consecutively from 1-25, as quickly as possible. Errors are not counted, but subjects are instructed to return to the preceding correct number and then carry on. The test score is the time needed to perform the test, including the time needed to correct all errors.

i.e. disinhibition and childishness. Other changes include euphoria, mania and paranoia. Speech is often slurred and repetitive (perseveration).

Important signs include *fetor hepaticus* - a musty or sweet smell of the breath resulting from unmetabolised mercaptans excreted through the lungs. The hepatic flap - *asterixis* - is characteristic of HE but can also be seen in other conditions, e.g. uraemia, acute CO_2 retention. Other neurological signs include hyperreflexia, hypertonia and extensor plantar responses but these progress to a flaccid state and deep coma. These changes may be due to failure of function of the reticular formation.

Classifications based on the continuum of signs and symptoms that are found in HE are available to grade its severity. Among these, the West-Haven criteria are widely applied (Table 2).

TABLE 2
West Haven criteria for grading mental state in hepatic encephalopathy.

Grade 0	No abnormality detected
Grade 1	Trivial lack of awareness, euphoria, anxiety Shortened attention span Impaired performance in mathematical addition or subtraction
Grade 2	Lethargy, apathy, disorientation for time and place Obvious personality change Inappropriate behaviour
Grade 3	Somnolence to semi-stupor, but responsive to stimuli Confusion Gross disorientation
Grade 4	Coma Mental state not testable

Investigations are generally not essential; fundamentally this is a clinical diagnosis. Changes in psychometric and electrophysiological tests have been mentioned above. EEG shows bilateral synchronous reduction in frequency, from the alpha rhythm down to the theta range of 4-7 Hz, and eventually to the delta range of below 4 Hz, initially involving the fronto-parietal region before spreading globally. This 'encephalopathic pattern' can be seen in many metabolic problems but, in the context of an individual with liver disease, it is highly suggestive of HE. However, both the sensitivity and specificity of EEG for the diagnosis of HE are low: its role is to support the clinical diagnosis of HE if there is doubt.

Cerebrospinal fluid studies, when carried out, serve to exclude other causes of altered consciousness. In HE, the CSF levels of protein, glutamine and glutamate may be elevated, but these have no diagnostic or prognostic value. Blood arterial ammonia is often raised but a normal level does not exclude HE (see pathogenesis). It is important to note that focal neurological signs are an unusual feature of HE and their presence should prompt appropriate investigations, e.g. CT scan to include concomitant pathology such as intracranial bleeding.

MANAGEMENT

As the pathogenesis of HE is uncertain, the many treatments which have evolved associated with varying success. The mainstay of the management of HE are summarised in Table 3:

1. Identifying and removing the precipitating cause (see Table 1) by appropriate therapy as required.
2. Reducing absorption of ammonia.

TABLE 3
Treatment of hepatic encephalopathy.

1.	Identify and remove precipitating factor	
2.	Reduce ammonia absorption	
	i)	Reduce nitrogenous load - protein restriction Acute - 20 g/day and 10 g/day increments Chronic - 40-60 g/day; vegetable proteins; ?BCAA
	ii)	Lactulose/Lactitol - to achieve two soft stools a day
	iii)	Enemas
	iv)	Antibiotics
	v)	Prophylaxis against GI bleeds - H_2 antagonists

i) Reduction of nitrogenous load. In severe HE, protein intake is restricted to 20 g/day (or the diet rendered protein-free). Once recovery appears imminent, protein is added in 10 g increments, on alternate days up to a normal protein diet. Caloric intake is maintained at 2,000 kcal/day. In patients with long-term chronic HE, long-term protein restriction to 40-60 g/day may be needed to control symptoms at the risk of protein malnutrition. Vegetable protein is less ammoniagenic, allowing a larger intake of protein.[14] This may be due to the increased fibre content, which promotes regular bowel movements and the consequent elimination of nitrogenous wastes, but with the drawbacks of an increased incidence of flatulence, bloating and diarrhoea.

Branched-chain amino acids (BCCA) supplements allow protein intake of up to 80 g/day without HE developing, but this is an expensive alternative and results from clinical trials are unclear.[15] However, a subset of protein-intolerant patients may benefit.

ii) Nondigestible disaccharides (lactulose/lactitol). These act by lowering colonic pH, thereby discouraging growth of ammonia-producing bacteria and thus absorption of ammonia and by hyperosmolar catharsis further promoting faecal nitrogen elimination.[16] The dose of lactulose, usually 10-30 mls, is titrated to achieve two soft stools a day. Side effects are diarrhoea and bloating. Lactitol (Beta galactosidosorbitol) at 0.3-0.5 g/kg/day is as effective as lactulose with fewer side-effects.[17]

iii) Purgatives. Enemas, e.g. phosphate and magnesium sulphate enemas, are administered in severe HE when the bowels have not opened spontaneously: tap water enemas are less effective.

iv) Antibiotics. Gut flora constitute the principal source of neurotoxins, especially ammonia. Although gut sterilisation with neomycin (a poorly absorbed aminoglycoside) 4-6 g/day is effective in improving HE in up to 80 per cent of patients,[18] its long-term use should however be avoided because of the risks of ototoxicity and nephrotoxicity. Other antibiotics that have proved effective include vancomycin and metronidazole.

(Lactulose on its own has been shown to be as effective as neomycin in clinical trials and because of the lower toxicity of the former, it should be preferred.)
v) Prophylaxis against gastrointestinal bleeding. H2 blockers such as ranitidine have a role in preventing gastric erosions and ulcers which are potential sources of upper GI bleeding.

Newer treatments and their proposed mechanisms of action and efficacy, are listed in Table 4.[19] Promising among these are sodium benzoate, L-ornitine-L-aspartate and possibly, flumazenil. Sodium benzoate has proved to be as effective as lactulose and is 30 times cheaper, affording clinicians an economical alternative to long-term lactulose.

TIPSS AND HEPATIC ENCEPHALOPATHY

Since its availability in the early 1980s, Transjugular Intrahepatic Porto-Systemic Stent-Shunt (TIPSS) has been used increasingly to treat variceal haemorrhage, ascites and, infrequently, hepatic hydrothorax; the results of long-term follow-up are now becoming available.[22] Newly acquired or worsened HE occurs in 15-25 per cent of TIPSS patients, and the problem is more severe immediately after TIPSS, with improvement to be expected later (presumably because of shunt stenosis).

Chronic HE is seen in 10-15 per cent of TIPSS patients. In this group, HE can be reversed by TIPSS occlusion using a balloon or steel coil, although a return of the initial condition for which TIPSS was required, e.g. varices, should be expected. Increasing age, pre-existing HE, low albumin levels, post-TIPSS portal pressure gradient, female gender, non-alcohol aetiology of the portal hypertension are among factors that may predict post-TIPSS HE (but accurate prediction is not possible).[23]

TABLE 4
Newer treatments for hepatic encephalopathy.

Treatment	Mechanism of Action	Results
Sodium benzoate	Promotes urinary excretion of NH_3	As effective as lactulose in controlled studies
L-ornithine-L-aspartate	Promotes hepatic removal of NH_3	Better than placebo (controlled trial)
Flumazenil	Inhibitor of benzodiazepine ligands	Better than placebo but only subgroup may benefit
Branched Chain Amino Acids (BCAA)	Redress imbalance of BCAA with aromatic amino acids, a potential source of false neurotransmitters	Unclear. Meta-analysis does not show benefit
Naloxone	Opioid antagonist	Animal studies promising. No human trials
L-Dopa, Bromocriptine	Promote dopaminergic neurotransmission	No benefit in controlled trials
Zinc	Corrects zinc deficiency (common in cirrhotics)	No benefit in controlled trials

LIVER TRANSPLANTATION

As HE is a metabolic problem resulting from a diseased liver, liver transplantation offers the definitive treatment for correcting the pathophysiological mechanisms behind HE. This is the only definitive treatment that fully reverses HE. Encephalopathy is a marker of poor prognosis in liver disease and its presence should make clinicians consider the option of transplantation.

SUMMARY

Hepatic encephalopathy spans a wide clinical spectrum from subclinical stages through to deep coma. The pathogenesis is incompletely understood although gut-derived ammonia as a neurotoxin is believed to be important. Management still relies on time-tested principles of removing precipitants and reducing the potential ammonia load, although new pharmacologic agents are under assessment. Non-invasive neuro-investigative tools will hopefully point the way to better understanding of this disabling condition and to the effect of the therapies in current use, leading to more effective treatment.

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