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Hepatic Encephalopathy in Liver Cirrhosis

Pathogenesis, Diagnosis and Management

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Abstract

The pathogenesis of hepatic encephalopathy (HE) is unknown. Many theories have been proposed. Most established therapies are based on such theories but since no theory has have ever been proved, therapies have to be considered empiric. The spectrum of HE ranges from minimal cerebral functional deficits, which can only be found by sensitive psychometric tests, to coma with signs of decerebration. HE has arbitrarily been divided into stages. A number of precipitating factors are known and the first line of therapy should always be the elimination of these factors. The differential diagnosis includes all states of impaired consciousness and deficits in cerebral function in patients with chronic liver disease, and clinical and biochemical tests to differentiate are indicated.

The therapeutic options for HE include: protein restriction only for a limited time in comatous patients; nonabsorbable antibiotics (aminoglycosides), which because of adverse effects are also limited to higher grades of HE; intestinal cleansing which is applicable in all degrees of HE; lactulose, branched chain aminoacids and ornithin aspartate which have been proven to be effective and can be applied long term in patients with lower grades of HE.

1. Definition

Most papers on hepatic encephalopathy (HE) are devoted to portosystemic encephalopathy (PSE). To what extent the pathogenetic models discussed for portosystemic encephalopathy are also applicable to the encephalopathy associated with fulminant hepatitis is uncertain.

The general term HE covers all the neurological and psychological symptoms in patients with liver disease that cannot be explained by the presence of other pathologies. The symptom complexes are classified into severity grades and can arise as a result of different underlying hepatic disorders. This is a clinical syndrome with a wide range of variability extending from minimal impairments of intellectual function only detectable by psychometric testing to profound coma with signs of decerebration.[1] HE is reversible and can exhibit a fluctuating course.

2. Pathogenesis

The pathogenesis of HE is still obscure and thus an exact description of the clinical symptomatology is the only non-speculative way of approaching this clinical phenomenon. HE is one of the best-described metabolic encephalopathies for the very reason that the precise pathomechanisms are still not fully understood. The most frequently discussed pathogenic explanatory models are as follows.

2.1 Endogenous Neurotoxins

2.1.1 Ammonia

In the healthy body an equilibrium exists between ammonia production and ammonia detoxification. The main sites of ammonia synthesis are the intestine, muscle and kidneys, although the majority is produced in the intestine. The main source of energy for the mucosal cells of the small intestine is the amino acid glutamine, which on degradation produces ammonia. In the large intestine, ammonia is formed as a product of the breakdown of proteins and urea by the physiological intestinal flora. Part of the urea is hydrolysed to ammonia by the colonic flora and becomes systemically available.

The amount of ammonia produced in muscle is proportional to muscular work. When the muscle is at rest, ammonia production and breakdown are in a state of balance. The amount of ammonia produced in the kidney is small. An increase in ammonia synthesis occurs during diuretic treatment and in hypokalaemia. When this equilibrium is intact, a nontoxic ammonia level of 30 μmol/L is measurable in the peripheral blood.

Large amounts of ammonia are produced in the liver from the breakdown of proteins, but the am-

monia is immediately metabolised again with the result that hardly any ammonia is released from the liver when hepatic function is intact. Ammonia is detoxified by the formation of urea and glutamine.

The increase in portal vein pressure in liver cirrhosis results in the formation of collateral circulations. External collaterals are the 'typical' accessory venous channels such as esophageal and fundic varices, caput medusae and spontaneous splenorenal shunts. Internal collaterals develop in the form of hepatoportal venous anastomoses. Thus, part of the intestinal ammonia bypasses the liver. In the presence of liver disease, metabolic resources are compromised by the reduced hepatocyte count and the biotransformation of ammonia to urea and glutamine may be reduced by as much as 80%.

The associated hyperammonaemia has a neurotoxic effect mediated by a still partly unexplained mechanism.[2-4] The brain detoxifies ammonia by synthesising glutamate and glutamine, which are ATP-dependent processes. In hyperammonaemia, therefore, more glutamate and glutamine are produced, resulting in an increased energy consumption.[5] Swelling of astroglial cells is another speculative effect of hyperammonaemia. The only morphological change seen in HE is swelling of astroglial cells, although the functional significance of these changes is not fully understood. Studies on other cell systems that change their metabolic functions according to their state of swelling suggest that astroglial cells may be functionally impaired.[6]

Certain correlations exist between ammonia level and HE, but there is no direct dependence. For example, about 10% of patients with encephalopathy have normal blood ammonia levels.[7,8] Both arterial and venous ammonia values correlate with HE, arterial ammonia values more so than venous. HE is very unlikely if there are normal arterial levels.[7]

2.1.2 Mercaptans

Mercaptans are formed as bacterial degradation products of sulphur-containing amino acids (e.g. methionine), and are the cause of the typical 'foetor hepaticus'. These compounds exert their neurotoxic effect by inhibition of Na^+/K^+-ATPase, thereby potentiating the neurotoxic action of ammonia.[9,10]

2.1.3 Phenols

Phenols are also synthesised intestinally as derivatives of the aromatic amino acids (phenylalanine and tyrosine) and are regarded as neurotoxins.[11]

2.1.4 Short- and Medium-Chain Fatty Acids

Short- and medium-chain fatty acids are products of the physiological intestinal flora, and may possibly also be produced in the liver itself. These products also inhibit Na^+/K^+-ATPase, but also inhibit hepatic urea synthesis. They may also cause increased uptake of tryptophan into the brain.[12]

As with ammonia, there is no strict correlation between HE and the serum levels of the other neurotoxins discussed in this section.

2.2 Increased Permeability of Blood-Brain Barrier

The blood-brain barrier describes a complex physiological process evolved to protect the brain against metabolic changes occurring in the rest of the body. In acute liver failure, the permeability of the blood-brain barrier is nonspecifically increased,[13,14] which also explains the tendency to cerebral oedema.[15] Certain changes in the blood-brain barrier are also observed in chronic liver diseases. Increased amounts of neutral amino acids are absorbed (see section 2.3.1), whereas the amounts of glucose, ketone bodies and basic amino acids that cross the blood-brain barrier are reduced.[16] Increased cerebral glutamine synthesis also leads to an increased output of glutamine from the brain, again with an associated increase in uptake of neutral amino acids.[17]

2.3 Change in Neurotransmitters and Receptors

2.3.1 'False Neurotransmitter' Hypothesis

Liver cirrhosis is characterised by alterations in amino acid metabolism.[18] The quantitative ratio between aromatic amino acids and branched-chain amino acids in plasma is shifted in favour of aromatic amino acids. This observation gave rise to

the hypothesis that the levels of aromatic amino acids and tryptophan also increase in the brain, while the levels of branched-chain amino acids decrease. Both amino acid groups compete for a common carrier system at the blood-brain barrier. The reduced levels of branched-chain amino acids in the blood therefore results in an increased blood-to-brain transfer of aromatic amino acids.[19,20] The increased production and elimination of glutamine resulting from augmented intracerebral ammonia metabolism is itself believed to induce an increased inflow of aromatic amino acids.[17] The aromatic acids are precursors of neurotransmitter synthesis. According to this hypothesis, neurotransmitter synthesis is modulated by the oversupply of precursors. Via secondary metabolic pathways other substances such as tyramine, octopamine and phenylethanolamine are formed which, as false neurotransmitters, compete with the normal transmitters for the same receptors. Octopamine is also produced outside the brain, by intestinal bacteria, resulting in a further rise in the systemic levels.[21]

2.3.2 γ-Aminobutyric Acid

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter with receptors on the neurons and astroglial cells. Benzodiazepines and barbiturates can also bind to the GABA receptor complex and induce activation of the Cl^- channel. In people with HE, the levels of receptor agonists in the brain are elevated,[22] with a resulting increase in GABAergic tone.[23] This theory explains why benzodiazepines can induce the neurodepressive disorder of HE. Benzodiazepine antagonists, on the other hand, appear to be able to improve HE (see section 5.4).

2.3.3 Serotonin (5-Hydroxy-Tryptamine; 5-HT)

Increased cerebral uptake of tryptophan is observed in HE. As a result, the cerebral formation of serotonin (5-hydroxy-tryptamine; 5-HT), and its degradation product 5-hydroxyindolacetic acid, is increased. The density of serotonin receptors is believed to decrease, but with an accompanying increase in affinity. This applies particularly to the reticular formation, which explains the altered sleep-wake rhythm in patients with HE.[24]

2.4 Other Theories

Some of the various catecholamines have important neurotransmitter functions. Changes in noradrenaline levels have been detected.[25,26]

More recent hypotheses have attempted to establish a link between zinc deficiency[27] or manganese[28] and HE. In the presence of reduced zinc levels, the activity of urea cycle enzymes is evidently reduced. Hyperintense basal ganglia are seen on T1-weighted nuclear magnetic resonance (NMR) images in patients with HE, an effect attributed to increased manganese deposits.

3. Clinical Aspects

The clinical course of HE can be extremely variable. Acute remitting, chronic remitting and chronic persisting – or even chronic progressive – forms of the disease have been described. With the acute and remitting forms it is usually possible to identify precipitating factors which, when treated, allow the severity of the clinical condition to be reduced. The probability of relapse or deterioration of HE increases after each episode. The particularly unfavourable chronic persisting course of HE is seen only very rarely; one risk factor for this condition is an extensive, and especially a surgically created, portosystemic shunt.

HE is a continuum that is arbitrarily divided into different stages.[29] Originally this condition was classified only into clinical stages, i.e. stages of evident pathological significance. Characteristically for a continuum, however, changes in cerebral performance also occur below the threshold of the overtly pathological. These changes are subsumed under the heading latent or subclinical encephalopathy; in fact, since these changes are now readily detectable – e.g. using psychometric test procedures – it is more accurately termed minimal HE.

3.1 Minimal Hepatic Encephalopathy (HE)

The stage of minimal HE is devoid of clinical symptoms and usually goes unnoticed in daily life. Even when specifically questioned, people with minimal encephalopathy usually do not consider

Table I. Stages of hepatic encephalopathy

Degree	Consciousness	Intellectual function	Behaviour	Neuromuscular function	EEG
0	Normal	Actional IQ reduced	Normal	Psychomotor tests impaired	SEP,VEP P300
I	Absent minded	Calculation impaired	Accentuation of normal behaviour	Handwriting impaired (asterixis)	7-8/sec
II	Drowsy	Loss of time orientation	Disinhibition; apathy	Asterixis; ataxia	5-7/sec
III	Sleeping but arousable	Loss of spatial orientation	Delusion; aggression	Pyramidal signs; muscular rigidity	3-5/sec
IV	Coma	Loss of self	–	Dilated pupils; opisthotonus	<3/sec

EEG = electroencephalography; **IQ** = intelligence quotient; **P300** = a form of VEP; **SEP** = somatosensory evoked potentials; **VEP** = visually evoked potentials.

themselves to be experiencing complaints such as sleep disturbances, lack of concentration, reduced performance or mood changes. Electroencephalogram (EEG) abnormalities are also absent. Only psychometric/neuropsychological tests can disclose deficits. An overall slowing reflecting compromised cerebral performance is apparent. Up to 60% of patients with liver cirrhosis and portocaval collaterals without clinical evidence of cerebral functional deficits have minimal encephalopathy. Psychomotor rather than verbal abilities tend to be affected, and therefore people with manual occupations tend to experience work activity impairment earlier than those in sedentary occupations. 60% of those affected show impairments in psychometric tests used to assess fitness to drive.[30]

3.2 The Stages of Overt HE

Conventionally 4 different stages of clinically apparent HE are distinguished, although within a continuum these are somewhat artificial (see table I).

Stage I is characterised by sleep disturbances, sometimes with inversion of the sleep-wake rhythm[31] as well as general restlessness, mood fluctuations, loquacity, impaired attention and concentration. Many patients show slight finger tremor which has not yet progressed to the typical form of flapping tremor.

In stage II, neuromuscular disturbances are detectable, one typical form being flapping tremor. Asterixis describes the inability to sustain muscle tone.[32] Attempts to sustain muscle tone result in fluttering movements reflecting a sudden decrease in electromyographically measurable muscular activity. Flapping tremor is usually bilateral, although not necessarily synchronous and possibly more pronounced on one side. Ataxia, changes in reflexes (usually diminution) and dysarthria are further symptoms. The great majority of cases are characterised by lethargy and rarely by an excitatory form of HE.

Stage III shows a more pronounced impairment of consciousness, with somnolence and disorientation. Aggressive behaviour is observed. The voice is monotonous and perseverations are apparent. Neurological signs tend to be increased reflexes, also with clonic spasm, pyramidal symptoms and rigor-like increases in muscle tone.

In stage IV, the patient enters coma. A stage IVa with intact undirected pain responses distinguished from stage IVb without pain responses has been described. In this stage, hyperventilation and hyperthermia may possibly be terminal signs. In stage III and IV additional assessment using the Glasgow Coma Scale is useful.

3.3 Precipitating Factors for HE

Episodes of HE during chronic liver disease are usually induced by a clinical event or the spontaneous development of a portosystemic shunt. Often several factors are involved simultaneously. Attempts to explain this development have generally focused on ammonia. Elevated ammonia levels can occur as a result of excessive protein intake and fluid restriction accompanied, for example, by constipation. Gastrointestinal bleeding is accom-

panied by increased production of ammonia by intestinal bacteria. Stored blood contains about 30 μg/100ml ammonia. Hypokalaemia and metabolic alkalosis, which often also develop during ascites mobilising diuretic therapy,[33] result in elevated renal ammonia production and – according to at least one theory – an increase in the diffusion of ammonia through the blood-brain barrier. Infections result in elevated ammonia levels, leading to hypovolaemia and hypoxia, which in turn restricts the metabolism of toxins by the liver and causes protein breakdown. During diuretic therapy, electrolyte disturbances can develop, with reduced hepatic and renal blood flow. Furthermore, hepatic urea synthesis may be compromised. Neurodepressive drugs can naturally also trigger an episode of HE. Because of the impaired hepatic function, the half-lives of most psychotropic medications are prolonged. Therefore, sleep disturbances should only be treated with sedatives or hypnotics in exceptional circumstances. Alcohol plays an important role in liver disease, firstly as an injurious agent responsible for cirrhosis and secondly as a precipitating factor of HE. Alcohol causes a deterioration in hepatic function with all the associated complications and is also a neurodepressant. Alcoholics have an increased susceptibility to infections and for this reason also tend to experience episodes of HE (see table II).

Table II. Precipitating factors for hepatic encephalopathy

Precipitating factor	Possible mechanism
Excessive protein intake Constipation Anorexia Fluid restriction Gastrointestinal bleeding Infection (e.g. spontaneous bacterial peritonitis) Blood transfusion Azotemia Hypokalaemia Surgery	Increased ammonia production
Alkalosis	Increased diffusion of ammonia through blood-brain barrier?
Acidosis	Inhibition of urea synthesis
Dehydration fluid restriction diuretics excessive paracentesis diarrhoea (also due to laxatives) vomiting	Reduced metabolism of toxins due to hepatic hypoxia Protein catabolism
Arterial hypotension/hypovolaemia gastrointestinal bleeding peripheral vasodilatation shock, operation Hypoxia Anaemia Fever	
Psychotropic medications benzodiazepines, morphine (antidepressants, antipsychotics)	CNS depression Binding to GABA receptors
Portosystemic shunts spontaneous surgical (including TIPS)	Reduced hepatic metabolism
Alcohol	Susceptibility to infections Hepatic dysfunction

GABA = γ-aminobutyric acid; **TIPS** = transjugular intrahepatic portosystemic shunt.

3.4 Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure for creating a portocaval anastomosis which, although distinguished from surgical methods by its low invasiveness, is nevertheless comparable with surgical procedures in its effects on HE.

There is a deterioration in HE during the first month after TIPS placement but this is followed by an improvement in the later course.[34] The development of HE depends on the diameter of the shunt; with a shunt diameter below 8mm the risk of HE is low.[35] Additional risk factors for HE after TIPS placement are age over 60 to 65 years, medical history of portosystemic encephalopathy and active alcoholism.[35,36] The results of other studies are relatively consistent, with either relapse or deterioration of HE in 20 to 30% of cases after TIPS placement.[37-39] Compared with TIPS, the rate of HE after portosystemic shunt operations is variable, 50% after portocaval shunt and 10 to 15% after splenorenal shunt.[40]

Relapse or deterioration of HE can be explained firstly as resulting from the enlarged shunt volume,

allowing increased amounts of neurotoxins to enter the systemic circulation. Secondly, a flow reversal occurs in the liver lobules which is associated with a reduction of hepatic clearance function.

3.5 *Helicobacter pylori*

No consensus exists regarding the relevance of gastric colonisation with *Helicobacter pylori* in patients with HE.[41,42] *H. pylori* infection does not appear to increase the rate of portal hypertensive gastropathy, and the relationship between duodenal ulcers and *H. pylori* is also not as strict as in people without HE.[43] Conflicting research evidence has been obtained regarding the relationship between *H. pylori* infection and hyperammonaemia as precipitating factors of HE, and also regarding eradication therapy.[41,44] In addition to the theory of increased ammonia levels with *H. pylori* infection there could be a direct hepatotoxicity caused by a toxin produced by *H. pylori*.[43]

3.6 Differential Diagnosis

All diseases that impair cerebral function can be considered as potential diagnoses. On the other hand, patients with coexisting liver disease and neuropsychiatric symptoms are not necessarily experiencing HE, since these conditions can exist independently of each other.

Some of these impairments such as intracerebral lesions can be diagnosed by computed tomography (CT), and most of the others by blood tests. All disorders of cerebral performance of toxic or metabolic origin should be considered, such as renal failure/uraemia, electrolyte disturbances, hypoglycaemia, hypoxia, alcohol withdrawal delirium or intoxication, and endocrine disorders. Neuropsychiatrical disorders should be also be excluded by differential diagnosis. Psychotropic medications can induce symptoms similar to those observed in HE. Tranquilisers may wrongly be prescribed to treat the unrecognised initial symptoms of HE, which only exacerbate the symptoms. Wernicke-Korsakoff syndrome is associated with nystagmus, ophthalmoplegia and ataxia, almost always in patients with alcoholism and malnutrition. Hyperammonaemia can also develop without liver disease, e.g. in congenital hyperammonaemia syndrome or in people with ureterosigmoidostomy (see table III).

Table III. Differential diagnoses for hepatic encephalopathy

Disease	Diagnostic resources
Intracranial	CT/NMR, angiography, CSF microbiology and serology
trauma (e.g. subdural haematoma)	
subarachnoid hemorrhage	
intracerebral bleeding	
stroke	
tumour	
infection	
abscess	
meningitis	
encephalitis	
Epilepsy	EEG
Neuropsychiatric	Psychiatric examination
depression	
schizoaffective psychosis	
Metabolic	Clinical laboratory tests
hypoxia	
hypoglycemia	
ketoacidosis (e.g. diabetic)	
uraemia	
CO_2 anaesthesia	
azotaemia	
electrolyte disorder	
elevated ammonia level without liver disease	
congenital urea cycle disorder	
Reye's syndrome	
ureterosigmoidostomy	
Wilson's disease	
Endocrine disorders	
hypothyroidism	
Toxic	Toxicological investigations
alcohol	
acute intoxication	Neurological investigations
Wernicke-Korsakoff encephalopathy	
alcohol withdrawal	
drugs of abuse/medicines	
benzodiazepines	
morphine	
barbiturates	
antidepressants	
antipsychotics	
salicylates	

CSF = cerebrospinal fluid; **CT** = computed tomography; **EEG** = electroencephalography; **NMR** = nuclear magnetic resonance.

4. Diagnosis

4.1 Psychometric/Neuropsychological Tests

HE is classified on the basis of the clinical symptoms described in section 3. Minimal HE is not

accessible to this diagnostic approach. This is the domain of neuropsychological test procedures.[45,46] Recognising minimal HE is important since it may considerably compromise everyday life activities while remaining undetectable at clinical examination. Making this diagnosis is important for the further occupational life of the patient, as a basis for therapeutic decision making and possibly also for prognostic reasons.[47,48] A prospective study has shown that 50% of people with minimal HE go on to develop clinically apparent HE within the next 6 months.[49] Typical impairments associated with latent HE relate to psychomotor speed, visual-spatial orientation and visual-constructive ability.

A number of simple neuropsychological tests have been used: retelling and interpreting a fable to assess short term memory and logical thinking, forward digit span for short term memory, and backward digit span for working memory. Reproduction of simple geometric figures evaluates visual short term memory and visuomotor functions. Other tasks are simple coordination exercises such as creating a star with five matchsticks, or writing down a short sequence such as one's name, to document psychomotor function. These original tests are simple, practicable and illustrative. They are not standardised or validated, however, and thus do not allow an objective assessment.[50]

The most widely used test system is the Wechsler Adults Intelligence Test (WAIS) which (especially the second part) reveals early deficits (performance IQ).[1] These changes are unspecific, however, and are also present in patients with other forms of diffuse brain damage.

A discriminant analysis study has shown that psychomotor variables in particular are affected.[50] The following tests are age-normed, validated and quantifiable.

The line tracing test (LTT) evaluates mainly psychomotor functions. In this test a 5mm wide 'street system' has to be negotiated without crossing the boundary line. The time taken to complete the test and the error rate are measured. Another important test procedure is the Reitan number connection test (NCT), also known as the trailmaking test (TMT).[51,52] In the number connection test A (NCT A) numbers have to be connected in arithmetical order (1-2-3-. . .). This test evaluates cognitive processing speed. A more sensitive test is the NCT B, probably because it also assesses divided attention and flexibility in addition to speed of information processing and psychomotor speed. In the NCT B numbers and letters have to be connected alternately in arithmetical or alphabetical order (1-A-2-B-3-C-. . .). The digit-symbol test (DST) also evaluates divided attention. Patients are required to assign various symbols to certain numbers as quickly as possible. Another simple test is the serial dotting test. A sheet of paper shows a number of adjacent identical circles. The test person is requested to dot the centre of the circles with a pencil as quickly as possible. This test evaluates motor speed and coordination, i.e. complex neurological and muscular processes.

A valuable combination of test procedures is the PSE syndrome test; the total point score used to assess the degree of HE is obtained from the individual evaluations of the number-symbol test, the NCT A and B, the serial dotting test and the line-tracing test.[53]

Reaction times and choice reaction times to stimuli such as light and noises can also be recorded. These procedures, however, require elaborate hardware.

In some cases a learning effect has been observed during testing, which has led to the development of parallel forms for psychometric tests. Certain test results have been shown to be dependent on educational status.[54]

It has been debated whether a history of heavy alcohol consumption has an impact on psychometric tests.[55] Asymptomatic patients with liver cirrhosis (without EEG abnormalities) have been shown to differ significantly in their test results from the control group and from patients with alcoholic pancreatitis without liver cirrhosis, but no differences are seen between the groups of non-alcoholic liver cirrhosis and patients with alcoholic liver cirrhosis. Symptomatic individuals (patients with liver cirrhosis and EEG abnormalities and pa-

tients with alcohol-related cerebral atrophy without liver cirrhosis) performed significantly worse than the control group. Analysis of variance has revealed that liver cirrhosis and alcohol have an additive, but not a synergistic effect. From this it was concluded that there is a wide range of alcohol consumption which can cause damage to internal organs such as the liver and pancreas but has no notable effects on cerebral function until typical signs of cerebral alcohol damage occur (e.g. delirium).[50]

4.2 Electrophysiological Studies

Any impairment of cerebral function can in principle cause EEG changes.[56]

The database for establishing the extent to which a correlation exists between EEG abnormalities and HE staging is inconsistent. In general, bilateral synchronous normal alpha rhythm (8 to 13/sec) is initially transformed into slow theta waves (5 to 8/sec). In advanced HE delta waves (2 to 3/sec) are observed, especially in the frontal and central brain areas, and these waves can flatten out even further culminating in an isoelectric line in coma. Regression of HE is characterised by an improvement in the EEG changes in reverse sequence.[57] The EEG abnormalities observed in HE are not pathognomonic, since similar EEG features are also observed in other diseases such as uraemia, CO_2 intoxication, vitamin B12 deficiency, hypoxia or hypoglycaemia.

Moreover, EEG is difficult to use as a diagnostic instrument since in most cases no reference EEG is available for the patient and there is pronounced overlap between normal and pathological findings. A further development of the EEG is computer-assisted evaluation of mean dominant frequency (MDF) and the power spectrum. These investigational methods provide further discrimination of cerebral function and consequently staging of HE, but extensive technical equipment is needed.[58]

Studies on visually evoked potentials (VEP) have been used for the diagnosis of HE. VEP are changed in this as in other diseases, such as multiple sclerosis, Friedreich's ataxia and Parkinson's disease. In this test procedure, stimuli with a defined stimulus pattern, intensity and magnitude are applied to the retina. Leads are attached to the occipital lobe where a number of positive (P1,P2,P3) and negative (N1,N2,N3) waves can be recorded. In most cases the latency of the first large positive wave is evaluated, which normally occurs after 100 msec. Varying degrees of correlation between results of VEP testing and HE have been shown.[59,60] VEP testing has been used as diagnostic aids in minimal HE.[61] However, because of the inconsistent database, psychometric tests are certainly more sensitive and specific and routine VEP testing is unnecessary, particularly since it is routinely available.

Investigation of visual and auditory event-related cerebral potentials (P300) is probably more informative than VEP testing.[62,63] In this procedure the test person is exposed to stimuli and is required to respond only to certain optical stimuli that are offered between other, similar stimuli (choice reaction time). In patients with dementia, the appearance of this positive wave is delayed. Patients with liver cirrhosis and HE show a change in P300 latency. A recent study has shown that P300 is a sensitive method for detecting latent HE which is barely apparent clinically. Several patients with liver cirrhosis without abnormal psychometric tests showed changes in P300, with the result that P300 is now under discussion as possibly more sensitive than psychometric tests for the diagnosis of minimal HE.[64]

4.3 Imaging Techniques

The domain of native CT or contrast enhanced CT is the differential diagnosis or exclusion of other cerebral diseases such as bleeding or abscess.[65,66]

Positron emission tomography (PET) is based on the measurement of positron radiation and is used particularly in the field of cerebral performance deficits. The incorporation of a positron radiation source allows CT recording of activity distribution. PET is thus a quantitative technique generating images of biological and physiological processes. PET studies support the hypothesis

whereby the changes in neurotransmission and astrocyte function known to occur in HE appear to impair basal ganglia function.[67] Studies on cerebral glucose metabolism with fluoroglucose (FDG) have also shown that patients with liver cirrhosis exhibit bilaterally reduced FDG uptake in the frontal, parietal and interhemispheric cortical areas and increased uptake in the inferomedial temporal region, cerebellum and posterior thalamus. This frontal hypometabolism is associated with performance deficits in neuropsychological test procedures.[68] Studies with ^{11}C-flumazenil have revealed higher concentrations and longer persistence of the benzodiazepine receptor antagonist in the brain of patients with HE compared with a control group.[69]

NMR can also be used to detect generalised cerebral atrophy.[70] T1-weighted magnetic resonance images show hyperintensive signals in the basal ganglia,[71] while more recent studies have shown that this occurs especially in the globus pallidus.[72] Signal accumulation in the basal ganglia are considered to be associated with manganese deposits. However, this change appears not to be specific for HE. Studies have shown that basal ganglia predominance is also present in portal venous thrombosis without liver cirrhosis. Basal ganglia intensity is seen to progress after TIPS placement[73] so that shunt formation is also assumed in pathophysiological terms to be the cause of the increased basal ganglia involvement.[74] Magnetic resonance spectroscopy has also revealed an increase in intercerebral levels of glutamine, glutamate and aspartate in patients with HE, accompanied by a fall in myoinositol, choline and hypotaurine.[6,75,76] This could be due to altered osmoregulation in the astrocytes.

Summarising, imaging techniques have not yet become established as routine diagnostic instruments for HE, except for differential diagnosis in relation to other intercerebral changes.

4.4 Clinical Laboratory Tests and Cerebrospinal Fluid

Hepatic function can be evaluated from clinical laboratory parameters; the causes of impaired liver function and the associated disorder of cerebral function should also be clarified. Precipitating factors for HE should be screened for and ruled out: renal function disorders, electrolyte imbalance, acid-base metabolism changes, diabetes mellitus, inflammatory parameters, alcohol levels and possibly drugs of abuse. Clinical laboratory tests provide no direct proof of HE: blood ammonia levels correlate very well with the stage of HE in some patients, but not at all in other patients (see table IV).

Table IV. Clinical laboratory tests for hepatic encephalopathy

Liver function tests
transaminases (ALT, AST)
cholestasis parameters (AP, γGT)
bilirubin
total protein with electrophoresis / albumin
Quick test
Blood glucose
Electrolytes (with calcium and phosphorous)
Creatinine, urea
Drugs of abuse screening (urine and blood)
Alcohol level
Blood gas analysis
Fasting ammonia level
Cultures (blood, urine, sputum, faeces)
Hepatitis and HIV
Ascites (cell count and culture)
Blood count, CRP, ESR

CRP = C reactive protein; **ESR** = erythrocyte sedimentation rate; **Quick test** = global clotting test for extrinsic and common pathways of the coagulation system.

Glutamate and glutamine levels in the cerebrospinal fluid (CSF) may be elevated in HE. However, patients with HE often have impaired liver function with disorders of blood coagulation contraindicating lumbar puncture.

5. Treatment

A precondition for the treatment of HE is the diagnosis and treatment of precipitating factors. In 80% of patients with liver cirrhosis, relapse or deterioration of HE is caused by exogenous factors. Frequent causes are gastrointestinal bleeding, infection or iatrogenic causes such as administration of sedatives or diuretic therapy. The objective should be to treat these factors since in many cases the HE will improve as a result. Gastrointestinal

bleeding should preferably be stopped endoscopically, and pronounced anaemia should be compensated (target haematocrit: 30%). Bacterial infections should immediately be treated with antibacterials. Not infrequently there may be spontaneous bacterial peritonitis (8 to 18% of all patients with cirrhosis develop this complication), which can manifest clinically as only HE. Treatment after ascites puncture and preparation for culture should comprise a cephalosporin or DNA gyrase inhibitor (fluoroquinolone). Metabolic acidosis, occurring for example during an infection, should be compensated at an early stage since acidosis impairs hepatic urea synthesis. Diuretics can cause hypokalaemia, azotaemia and inhibit urea synthesis; diuretic-induced hypovolaemia further compromises hepatic and renal function. Sedatives and other psychotropic medications should always be discontinued and abstention from alcohol should be ensured. Hypoglycaemia can develop during acute liver failure; timely initiation of carbohydrate supplementation is thus advisable. The basic therapeutic principles are presented in the following subsection, followed by a discussion of the currently recommended therapeutic regimens for acute and chronic encephalopathy.

5.1 Diet

Since the suspected toxins are thought to arise from the gut and its contents, diet should assume a position of central importance in the treatment of HE. However, dietary modification is extremely difficult as it implies the reversal of lifelong habits; dietary recommendations are therefore interesting but very difficult to implement in daily practice. Protein restriction or even abstinence was once recommended for this condition but is no longer practised, as it creates a protein catabolic situation in which ammonia formation is increased and the reduction of muscle mass also restricts the extent of extrahepatic ammonia detoxication. General susceptibility to infection is also increased due to the catabolic conditions.

Patients with liver cirrhosis require a daily intake of 0.8 to 1.0 g/kg,[77] or even 1 to 1.2 g/kg, bodyweight protein to maintain a satisfactory nitrogen and energy balance since hepatic protein synthesis depends heavily on substrate supply for export and structural proteins. Susceptibility to infections also decreases under these conditions.

Only in acute episodic encephalopathy will it be temporarily necessary to initially limit protein supply to 20 g/day. After an improvement in HE, protein supply should be increased by 10g every 3 to 5 days until the patient's protein tolerance has been reached. During the period with insufficient protein supply, an adequate caloric intake should be ensured, preferably by increasing dietary carbohydrate.

Increased intake of vegetable proteins is recommended. In patients with protein intolerance below 1 g/kg bodyweight, an increase in total protein intake can usually be achieved by switching to more vegetable proteins. Vegetable proteins are considered to improve the nitrogen balance without causing a deterioration in HE. They are better tolerated than fish, meat or milk proteins.[78-80] This beneficial effect appears to be due to the higher dietary fibre content of vegetable as compared with animal protein diets. Dietary fibres accelerate gastrointestinal transit and, by promoting fermentation by intestinal bacteria, induce a reduction in the pH of the intestinal lumen similar to that observed with non-absorbable disaccharides. Most patients accept a diet containing 30 to 40g vegetable protein daily. A small group of patients with HE exhibit pronounced protein intolerance and cerebral function is adversely affected by increasing protein intake. Patients are titrated to maximal daily protein intake, for which the clinical symptoms are evaluated and appropriate psychometric tests are performed after test meals. In patients with proven protein intolerance, branched-chain amino acids should also be administered orally in amounts of up to 0.25 g/kg bodyweight to create the best possible nitrogen balance.

The hypothesis of amino acid imbalance in HE is the rationale for treatment regimens comprising administration of branched-chain amino acids. A meta-analysis of infusion therapy with branched-

chain amino acids has revealed a significant improvement in cerebral performance, but no influence on survival.[81] Oral administration of branched-chain amino acids has also been observed to induce improvements in psychometric tests and has been proven statistically in prospective studies.[82] In an 8-week course of treatment in patients with minimal HE, the results of psychometric tests used to assess fitness to drive were improved; discontinuation of the branch-chained amino acids usually resulted in a worsening of HE.[83] Since the clinical relevance of minimal PSE is still partly unclear, treatment with branched-chain amino acids cannot be generally recommended. However, branched-chain amino acids are of proven value in patients with protein intolerance, as mentioned in the previous paragraph.[84] In patients with malnutrition who respond to the intake of normal desirable protein diet with a deterioration of HE, the total protein intake can usually be increased by administering branched chain amino acids, which results in a good nitrogen balance.

5.2 Intestinal Cleansing

The aim of intestinal cleansing is to remove nitrogen-containing substances as a potential source of ammonia. This is particularly important in patients with constipation and gastrointestinal bleeding. Oral laxatives and enemas are used for this purpose. Suitable laxatives are saline products (e.g. $MgSO_4$) and non-absorbable disaccharides, the latter being the agents of choice.[85,86] Lactulose is one of these disaccharides; in addition to its laxative effects the following other effects are discussed in the next section.

5.2.1 Disaccharides

Lactulose (β-galactosidofructose) and lactitol (β-galactosidosorbitol) are synthetic disaccharides; they are neither cleaved nor absorbed in the small intestine and are degraded in the colon to short-chain organic acids (e.g. lactic acid, propionic acid) by the physiological bacterial flora.[87-89] This results in pH reduction and an increased osmotic pressure in the intestinal lumen. Lowering the pH has a bacteriostatic effect believed to reduce the number of ammonia-producing bacteria. Diffusion of ammonia from the blood into the intestine is also considered to be facilitated in the acidic environment, while the absorption of ammonia is reduced. The ammonia burden of the body is reduced. The increased osmotic pressure in the intestinal lumen has a laxative effect resulting in intestinal cleansing. Carbohydrates like lactulose are an energy source for the intestinal flora. It is an established fact that bacterial ammonia uptake is enhanced, resulting in an increase in bacterial mass associated with increased excretion of fecal nitrogen.[90] Lactulose is usually administered orally, the dosage being based on clinical signs; 2 to 4 soft stools should be passed daily. It can be assumed that at this defecation frequency a desired pH of below 6 will be achieved. In most patients 30 to 60g daily is sufficient to achieve this. Rectal administration is also effective and is preferred when oral administration is not possible or combined with oral administration when there is a marked deterioration in HE. If enemas are given, it is important to ensure that the patient is adequately repositioned to optimise intestinal distribution.

The disaccharide lactitol can also be used to treat patients with HE, but offers no advantages over lactulose; the daily dose is 30 to 45g.[91-93] For people with lactose intolerance, almost 10% of the population of central Europe and 80% worldwide, the effect can also be achieved with lactose; the dose is up to 100g daily.[94]

Adverse effects accompanying therapy with synthetic disaccharides can include flatulence, diarrhoea and abdominal pain. Pronounced diarrhoea should be avoided since this causes electrolyte imbalance and hypovolaemia which can worsen HE.

Recent studies have used the disaccharidase inhibitor voglibose (AO-128) which reduces the enteral uptake of disaccharides.[95] The resulting malabsorption produces effects similar to fermentation as observed with the synthetic disaccharides. The results of further studies are awaited.

5.3 Antibacterials

Antibacterial agents were originally used to influence the physiological ammonia producing flora in the large intestine, and do in fact reduce blood ammonia levels.[96] However, it is not established whether the altered composition of the intestinal bacteria or a direct action of the antibiotics on the enterocytes is responsible for this effect.[97]

Antibacterials are as effective as disaccharide therapy. A possible potentiating effect achieved with a combination of disaccharides and antibacterials has not been conclusively established. Non-absorbable aminoglycosides such as neomycin and paromomycin are used for antibacterial therapy.[98] For neomycin the total daily dosage is 2 to 4g divided into 4 doses, and the daily dosage for paromomycin is 1 to 2g. However, it should be remembered that about 3% of the dose may be absorbed. Aminoglycosides are ototoxic and nephrotoxic and their toxicity is cumulative. Treatment should not be given for longer than one month.[99] Caution is advised in patients with renal insufficiency. Available alternatives to aminoglycosides are metronidazole[100] (500mg twice daily; most adverse effects are gastrointestinal symptoms), aminopenicillins (2 to 4g; allergy and gastrointestinal discomfort), rifaximine[101] or vancomycin[102] (1 to 2g; ototoxic), although these agents offer no major advantages over aminoglycosides.

5.4 Antipsychotics

One theory of the development of HE predicates the presence of increased GABAergic tone. GABA is an inhibitory neurotransmitter of the brain. Substances that bind to benzodiazepine receptors were detectable in the CSF from rabbits and from patients with HE.[103] These substances were identified by gas chromatography–mass spectrometry as endogenous benzodiazepine ligands.[104-106] Furthermore, HE may be associated with increased cerebral benzodiazepine receptor availability, as can be shown by ^{11}C-flumazenil positron emission tomography.[107] On this premise, attempts at therapy have been made with benzodiazepine receptor antagonists (flumazenil) which bind to the GABA receptor complex.[108-110] The infusion of flumazenil seems to result in an improvement in the EEG grading of HE.[108] Studies conducted to date have had short treatment and follow-up periods and have yielded inconsistent results. However, a new study has revealed benefits in some patients over prolonged periods. Treatment with benzodiazepine receptor antagonists cannot be generally recommended at the present time, and is only relevant for a selected patient subgroup with HE.[111] The increased sensitivity to benzodiazepines in cirrhosis is important to remember in the treatment of neurological/psychiatric disorders.[23] Treatment with benzodiazepine receptor antagonists should be initiated when there is strong suspicion of intake of benzodiazepines in a patient with cirrhosis and HE.

Levodopa,[112] bromocriptin,[113,114] serotonin agonists and antagonists,[115] as well as opioid antagonists,[116] are not currently used in the treatment of HE since the pertinent data are still inconclusive.

5.5 Stimulation of Ammonia Metabolism

The predominant ammonia detoxification mechanisms are the hepatic urea cycle and the formation of glutamine. Attempts to increase ammonia metabolism consist of either administering glutamate and α-ketoglutarate with the aim of enhancing glutamine synthesis, or administering metabolites of the urea cycle to increase urea synthesis.[117] Ornithine is one such substrate of the urea cycle. Ornithine aspartate lowers the ammonia level and thereby improves HE.[118-120]

Benzoate is used in paediatrics to treat hyperammonaemia syndromes in patients with congenital defects of ammonia metabolism. Benzoate (and phenylacetate) binds ammonia to produce hippurate which is excreted as a complex in the urine. Benzoate is not available as a medicine in Europe, although it has no appreciable adverse effects (except not inconsiderable sodium loading). Its odour and taste are reportedly unusual. In one study, benzoate was equally effective as lactulose in the treatment of HE.[121,122]

Table V. Therapy recommendations for patients with hepatic encephalitis (HE)

Disease stage	Diet/protein intake	Disaccharides	Purgation	Antibiotics	Branched-chain amino acids	Flumazenil	Stimulation of ammonia metabolism
Minimal HE	No restriction	+ +	+	0	+ +	0	+ +
Stage I	As tolerated	+ +	+ +	(+)	+ +	(+)	+ +
Stage II	As tolerated	+ +	+ +	(+)	+ +	(+)	+ +
Stage III	0	+ +	+ +	+ +	?	(+)	?
Stage IV	0	+ +	+ +	+ +	?	(+)	?
Chronic persistent HE	No restriction	+ +	+	0	?	(+)	?

0 = not recommended; **+** = to be considered; **(+)** = might be useful in some cases; **+ +** = recommended; **?** = usefulness unclear.

Two of the five enzymes in the urea cycle are zinc dependent.[123] Administration of zinc to patients with HE has yielded contradictory results but in some cases an improvement of HE during zinc substitution was seen.[124] To this extent, zinc treatment is recommended at least in the proven presence of zinc deficiency.[27,125]

5.6 Liver Transplantation

Orthotopic liver transplantation is performed with increasing frequency as a therapeutic principle for end-stage liver cirrhosis. Many of these patients have HE associated with other signs of liver decompensation. Liver transplantation is indicated in a small group of patients with severe, treatment refractory encephalopathy, including symptoms such as dementia, spastic paraparesis, cerebellar degeneration and extrapyramidal disorders. Other diseases, e.g. chronic alcohol abuse or degenerative brain disease, should be excluded as cause of the before said neurological symptoms in order to decrease the morbidity and mortality after liver transplantation. In addition, the expected improvement after liver transplantation is endangered by these diseases. Patients with acute liver failure with initial signs of HE should especially be considered as candidates for liver transplantation, since these patients, in particular, have a poor prognosis.[126] After successful liver transplantation HE will be improved, there are not only changes in psychometric tests but there is also a renormalisation of HE specific brain metabolite changes detected at magnetic resonance spectroscopy.[127] However, it is unclear if imaging techniques which examine brain metabolism can help detect candidates for liver transplantation.

5.7 Other Therapeutic Options

Surgical treatment has been employed to reduce intestinal ammonia production, and specifically, colectomy or colon bypass surgery have been attempted in the treatment refractory HE.[128] However, the morbidity and mortality are very high and liver transplantation should be preferred in such patients.

T1-weighted NMR reveals signal hyperintensity in basal ganglia associated with manganese deposits. Similarities exist between aspects of chronic HE and manganese intoxication.[129] Liver transplantation is followed by regression of NMR basal ganglia changes and HE.[130] Longitudinal studies with chelating agents should be performed to demonstrate a possible therapeutic effect.

After TIPS placement, a large portosystemic shunt is present which can trigger HE. The usual conservative therapeutic procedures are performed. If these are unsuccessful in chronic forms of encephalopathy, cerebral function can be improved by reducing the shunt diameter.[39,131]

Modification of intestinal flora has also been examined as a possible therapeutic option. Supplementation of specific intestinal bacteria was hoped to induce colonisation of the colon with non-urea producing bacteria. *Lactobacillus acidophilus*[132,133] and *Enterococcus faeciuim*[134] were used for this purpose. However, results have been inconsistent

and so no recommendations can be expressed for this therapy.

6. Recommendations

A summary of recommendations for therapy are presented in table V.

In acute HE precipitating factors are usually present. These should first be ruled out or, if found to be present, treated. At the same time, lactulose should be administered as an enema, orally or in combination. Oral administration is contraindicated in patients with impaired consciousness because of the risk of aspiration, and rectal administration should be carried in parallel with an intravenous glucose infusion. In the presence of suspected benzodiazepine-induced HE, trial administration of a benzodiazepine receptor antagonist may be useful. As soon as oral nutrition can be resumed, a low-protein diet (e.g. 20 to 30 g/day) should be initiated. Protein tolerance should be determined by titration in small steps. Lactulose treatment should be continued orally. If no improvement is observed, a modified amino acid solution can be given parenterally.

There is no clear-cut database relating to the long term treatment of acute HE, and in most cases lactulose is administered empirically. When the symptoms have subsided, a treatment-free interval may be attempted after several months or alternatively long term therapy with lactulose can be continued. In protein intolerant patients, branched-chain amino acids should be given in addition.

Among the forms of therapy universally accepted as effective, lactulose treatment has the major advantage of causing the fewest serious adverse effects and therefore also being suitable for long term therapy. Lactitol can also be used for long term therapy.

For chronic HE all forms of therapy are applicable and should be attempted. In therapy-refractive HE, liver transplantation should be considered as an alternative.

Treatment for minimal HE is not mandatory. Therapy decisions in these cases should be made on a patient by patient basis according to each individual's condition. If treatment appears indicated, it should take the form of oral lactulose and/or branched-chain amino acids.

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