Consensus

Chinese Consensus on Diagnosis and Treatment of Hepatic Encephalopathy

Chinese Expert Committee on Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complex, neuropsychiatric abnormality that occurs as a consequence of metabolic disorders in patients with hepatic insufficiency. The pathogenesis is complex with a strong prognosticator of death. To standardize the clinical management of HE, relevant new data were reviewed and assessed by Chinese Committee of Experts on Hepatic Encephalopathy in China and was discussed and debated extensively. Then the consensus on the management of HE was developed. The final recommendations are based on the data available at the time of production of the document and may be updated with pertinent scientific developments at a later time. All the discussion was organized by the editorial board of Chinese Journal of Experimental and Clinical Infectious Diseases (Electronic Edition), Chinese Journal of Liver Diseases (Electronic Edition) and Infection International (Electronic Edition). The evidence gradings in the consensus are listed in Table 1.

CONCEPT AND CLINICAL CLASSIFICATION OF HE

Definition

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with severe liver dysfunction (including acute or chronic liver failure) or portosystemic venous shunts after exclusion of other known brain diseases, which has potential reversibility. Its clinical features can be extensive and broad neuropsychiatric disorders, ranging from subtle deficits in central nervous system function (in mild cases) that can be detected only through intelligence or electrophysiological tests of personality changes, abnormal behavior, mental deterioration or even different levels of disturbance of consciousness or coma (in severe cases). The so-called hepatic coma is

just a serious phase of HE.

Clinical subtypes

According to the classification proposed in the World Congress of Gastroenterology 1998 in Vienna, hepatic encephalopathy is subdivided in type A, B and C.¹

Type A (acute) : HE associated with acute liver failure (fulminant hepatic failure, FHF) or subacute liver failure. After occurrence of HE, encephalopathic symptoms usually occurred within two weeks in the former case and 2-12 weeks in the later case.

Type B (bypass) : HE is caused by portal-systemic shunting without associated intrinsic liver disease, with normal liver histology. The clinical manifestation is the same as HE associated with liver cirrhosis. This portosystemic venous shunting can be spontaneous or caused by surgical or interventional operations, such as the portosystemic venous shunting caused by congenital vascular malformation, intrahepatic and extrahepatic portal vein obstructions (including the embolism or thrombosis of portal vein and its branches caused by trauma, carcinoid, myeloproliferative diseases and other diseases) and the portal hypertension resulting from lymphoma, metastatic tumor and cholangiocarcinoma oppression.

Type C (cirrhosis): HE occurs in patients with cirrhosis. It is the most common type of HE, often with portal hypertension and/or portosystemic venous shunting. Liver failure is the main cause of encephalopathy, followed by portosystemic venous shunting. According to the severity of clinical symptoms, type-C HE is subdivided into minimal HE (MHE) or subclinical encephalopathy and symptomatic HE (SHE) (Table 2).

In China, most HE patients are type-C, which occurred based on chronic liver disease and cirrhosis and often with portal hypertension and portosystemic venous shunting. HE of type A and type B are in relatively small number.

PATHOGENESIS

A number of theories have been proposed to explain the development of hepatic encephalopathy in patients

Correspondence: Jun Cheng, Institute of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University; 8 East Jingshun Street, Chaoyang District, Beijing 100015, China
Tel: +86-10-84322006; Fax: +86-10-84397196; E-mail: jun.cheng.ditan@gmail.com

Table 1. Grading of evidences

Levels of evidence	Descriptions
A	Data derived from multiple randomized clinical trials or meta-analysis
B	Data derived from a single randomized trial, or nonrandomized studies.
C	Only consensus opinion of experts, case studies

Table 2. Subtypes of type C HE

Subtypes	Definitions
MHE	No demonstrating clinically-overt cognitive dysfunction, mild cognitive abnormalities only recognizable with psychometric or neurophysiologic tests
SHE	Main abnormality is the cognitive, mental and movement disorders. It is subcategorized into two types: episodic and persistent
Episodic HE	Precipitated Excessive dietary protein, gastrointestinal bleeding, constipation, infection, paracentesis, hypokalemia (often as a result of large diuretic use) and transjugular intrahepatic portal-systemic shunt (TIPS)
	Spontaneous Occurring without obvious precipitating factors
	Recurrent Occurring more than 2 times within 1 year
Persistent HE	Mild HE Equal to West-Haven 1
	Severe HE Equal to West-Haven 2-3
	Treatment-dependent HE Quickly relieved through treatment, but soon recurrent after stopping treatment

with cirrhosis. But so far, the pathogenesis of HE has not yet been fully elucidated. Due to acute and chronic liver failure and/or porto-systemic venous shunting, the neurotoxic substances from intestinal veins will bypass the liver and directly enter the heart via another route without undergoing first-pass detoxification by the liver. Then the neurotoxic substances may gain entry into brain through the blood-brain barrier, and result in the dysfunction of the central nervous system. The hyperammonemia, a kind of neurotoxic substances, is recognized as one of the most critical factors,² especially in HE associated with chronic liver disease and cirrhosis (and/or with portosystemic venous shunting). All factors contributing to hyperammonemia include the increasing production of ammonia, the decreased mass of functioning hepatocytes, resulting in fewer opportunities for ammonia to be detoxified or portosystemic shunting diverting ammonia-containing blood away from the liver to systemic circulation. Ammonia has multiple neurotoxic effects, such as impairment of energy utilization in brain, impact of the balance between the central excitatory neurotransmitters (glutamate) and inhibitory neurotransmitters (such as glutamine, gamma-aminobutyric acid, GABA), which resulted in central inhibition. Other hypothesis has also been postulated. For instance, false neurotransmitters (octopamine and phenylethanolamine) replacing the normal neurotransmitters which results in neurotransmission disorder. Reduced concentrations of branched-chain amino acids (leucine, isoleucine and valine) and increased concentrations of aromatic amino acids (phenylalanine, tyrosine and tryptophan) may promote hepatic encephalopathy by causing the production of false neurotransmitters. Benzodiazepines exert their depressant effects on the central nervous

system by interacting with high-affinity binding sites on gamma-aminobutyric acid-benzodiazepine receptor complex. Swelling brain cells, dysfunctional astrocytes, neurotoxic effects of mercaptans, short-chain fatty acid and manganese deposition in the basal ganglia may contribute to the pathogenesis of hepatic encephalopathy.³

COMMON PRECIPITATING FACTORS

In HE cases with type-A, the basic liver injury was acute liver failure (fulminant hepatic failure, FHF) or subacute liver failure. A large number of liver cells were damaged and the gut-derived toxin could not be effectively removed, resulting in dysfunction of central nervous system. Type-A HE is a kind of endogenous HE, also known as non-ammonia encephalopathy, and often has no definite precipitating factors. Patients with simple type-B HE is rare in China. As for type-C HE, associated with chronic liver failure or portosystemic venous shunting, the detoxicating function of liver reduces. Once the production of toxicants increases and surpasses the compensatory liver detoxicating ability, then type-C HE occurs, which is largely related with the following precipitating factors.

Excessive intake of nitrogenous foods

Patients with chronic liver failure or portosystemic venous shunting have a poor tolerance with protein foods, especially animal protein. The overload of protein in intestinal tract will produce a large amount of ammonia and aromatic amino acid, which will cause HE. Oral ammonium salt, urea, methionine and other nitrogenous substances can increase the absorption

of nitrogen substances, which will result in hyperammonia and cause HE.

Gastrointestinal bleeding

Massive blood (every 100 ml blood is equivalent to an intake of 15-20 g protein) in gastrointestinal tract results in increased ammonia and nitrogen absorption from the gut. Meanwhile, the leucine and valine increase in blood, which will stimulate the increase of activity of branched chain amino acid dehydrogenase and enhance branched chain amino acid decomposition, aggregating the ratio imbalance between branched chain amino acid and aromatic amino acid. Hemorrhagic hypovolemia, cerebral ischemia and hypoxia can also increase the sensitivity of central nervous system to ammonia and other toxin.

Infection

Spontaneous bacterial peritonitis, pneumonia, urinary tract infection and bacteremia can enhance tissue catabolism and increase blood ammonia levels, which can further cause endotoxemia, aggravate liver damage and increase the blood-brain barrier permeability and precipitate HE.

Electrolyte imbalance

Hyponatremia can affect intracellular and extracellular osmolality and cause brain edema, thus inducing HE; hypokalemia is often associated with metabolic alkalosis. Diuretic therapy and abdominal paracentesis to remove a large volume of fluid can also cause alkalosis, which may facilitate the conversion of NH_4^+ to NH_3 . NH_3 is more easily absorbed from the intestine and passes through the blood-brain barrier and induces HE.

Azotemia

The hypovolemia caused by a variety of reasons, such as anorexia, diarrhea or liquid intake limitation, and large dosage of diuretics application or abdominal paracentesis can all induce pre-renal azotemia, hepatorenal syndrome or renal azotemia, which may also be caused by other reasons. All these factors contribute to elevated blood ammonia levels.

Constipation

Constipation can prolong the exposure of ammonia and other intestinal derived toxin to intestinal mucosa, which increases the absorption of these toxic substances.

Hypoglycemia

Hypoglycemia could decrease the capability of intracerebral detoxification for ammonia and other intestinal derived toxin.

Sedative

Sedative and hypnotic can directly combine with GABA-benzodiazepine receptor in brain, thus inhibiting the brain function and worsening hepatic encephalopathy.

CLINICAL MANIFESTATIONS AND STAGING

HE clinical manifestations vary significantly according to the nature of underlying diseases as well as the degree, speed and reason of liver cells damage. It has no significantly different features from other metabolic encephalopathies. The early manifestation is MHE, usually without clear clinical symptoms, which can be tested only by neuropsychological and intelligent test. MHE can further develop into SHE. Type-A HE generally occurs on the basis of acute liver failure, and patients often quickly occur a deep coma or even die from mild confusion in a few days after type-A HE, accompanied by such manifestations of acute liver failure as jaundice, bleeding, prothrombin time activity (PTA) reduction. Features of type-C HE are chronic recurrent episodes of altered mental state, such as behavior changes and even stupor and coma, often accompanied by increased muscle tone, tendon hyperreflexia, asterixis, positive ankle clonus, Babinski sign and other nerve system abnormalities. In the early days, the presentation of encephalopathy in most patients is recurrent and then becomes persistent, which is often accompanied by the manifestations of chronic liver damage and cirrhosis. Usually, excessive dietary protein is a provocative factor, but type-C HE may occur spontaneously or after stopping HE treatment.

According to the degree of consciousness disturbance, nervous system manifestations and EEG changes of the patients and reference to Practical Internal Medicine, HE can be divided into five stages (0-4), but each stage may overlap or transfer from one stage to the next stage (Table 3).⁴

Moreover, the extensively applied West-Haven Scale² (see Appendix 1) in foreign countries can be used to analyze patients' neuropsychiatric condition, and Glasgow Coma Scale² (see Appendix 2) to analyze the degree of patients' disturbance of consciousness and clinical hepatic encephalopathy staging scale (CHESS) (see Appendix 8) to analyze the severity of HE. But recently, Hassanein et al launched a more objective, accurate and operational method, hepatic encephalopathy scoring algorithm (HESA)⁵ (see Appendix 3) to reflect the neuropsychiatric status of patients.

Table 3. Clinical staging indicators of HE

Stages	Degrees of cognitive abnormalities and abnormal personality and behavior	Neurologic system signs	EEG abnormalities
Stage 0 (MHE/subclinical)	No personality or behavior abnormality; only mild cognitive abnormalities recognizable with psychometric or neurophysiologic tests	None	Normal wave α rhythm
Stage 1 (Prodromal stage)	Mild personality changes or abnormal behavior, such as euphoric excitement or depressed with few words; scruffy or defecating indiscriminately; unclear and slow talks but accurate response; inattentive, insomnia or inverted sleep pattern (sleeping in daytime and awake at night)	Asterixis can be detected	Irregular background activity (α and θ rhythms)
Stage 2 (Precoma stage)	Chiefly sleep disorders and mental confusion; obvious inversion of sleep pattern and drowsiness; slow response; intermittent disorientation, usually regarding time; gross deficits in ability to perform mental tasks; slurred speech; writing disorders; inappropriate behavior; even hallucinations, fear and rage; may have involuntary movements or ataxia	Sthenic tendon reflexes and muscle tone, positive asterixis and ankle clonus and Babinski signs	Continual θ rhythms, occasional with δ rhythms
Stage 3 (Lethargy stage)	Mainly lethargy or mental confusion, but can be aroused, often with confusion or hallucinations and gross disorientation	Sthenic tendon reflexes and muscle tone, asterixis and ankle clonus still may be positive. Positive Babinski signs	Ordinary θ rhythms with transient polyphase rhythms containing spike rhythms and slow rhythms
Stage 4 (Coma stage)	Coma (complete loss of consciousness, but can not be aroused) with or without reaction to painful stimuli; no reaction to various stimuli in time of deep coma	In time of light coma, sthenic tendon reflex and muscular tone and positive ankleclonus can be detected; in time of deep coma, no asterixis signs can be checked and various reflex disappears	Continual δ rhythms with occasional δ rhythms; a large amount of polyphase rhythms containing spike waves and slow rhythms

AUXILIARY EXAMINATION

Except for abnormal liver function, elevated serum bilirubin, separation of enzyme and bile (highly elevated serum bilirubin associated with liver enzymes reduced) and reduced prothrombin time activity, the examinations helpful to HE diagnosis are as following: blood ammonia

The fasting blood ammonia of normal people is 6-35 μ g/L (serum) or 47-65 μ g/L (whole blood). In patients with type-B and type-C HE, the blood ammonia rises, while in patients with type-A HE, the blood ammonia is often normal.

Plasma amino acids imbalance

Branched chain amino acids reduce and aromatic amino acids increase, resulting in the ratio of the two below 1 (> 3 in normal cases). But due to the requirement of special apparatus, no examination can be conducted at ordinary laboratory at present.

Neuropsychological and intelligence detection

It is significant to the diagnosis of MHE. At present, there are many methods for detection, but most of them are subject to age, gender and education level of the patients. Such methods are recommended as the Number Connection Test, part A (NCT-A, Appendix 4a-1) and part B (NCT-B, Appendix 4a-2); the Line-Tracing Test (LTT, Appendix 4b), the Brief Visuospatial

Memory Test-Revised (BVMT-R) (Appendix 5), the Clock Drawing Test (CDT, Appendix 6),⁶ the Digit-Symbol Test (DST, Appendix 4d) and the Serial Dotting Test (Appendix 4c), etc. These methods feature small correlation with the level of education, very simple and convenient operation (Evaluating criterion of these tests is given in Appendix 4f). Mini-Mental State Examination (MMSE, Appendix 7) can well reflect the situation of slight neuropsychiatric damage which take too much time (a check takes 5 to 10 minutes). They all can be conducted in clinical trials.

Neurophysiological tests

EEG

Generally, neurophysiological abnormality can be detected by EEG before biochemical or mental abnormalities. The main manifestation is slow rhythms, which usually appears on both sides of the forehead and the top and then gradually moves backward. EEG changes are not specific for HE, which can be detected in other metabolic encephalopathies such as uremic encephalopathy, but the severity of these changes is highly related to the clinical stage.

Evoked potentials (EPs)

There are many kinds of EPs, but endogenous event related EPs P300 with more sensitivity, is a better choice for the diagnosis of HE. However, due to the limitations of instrument, equipment and professionals, it is only applied in clinical trails.

Critical flicker frequency (CFF)

This method was originally applied for detection of the critical flicker frequency of warning disorders and can reflect the ability of central nervous system. In recent years, a compared study on 217 individuals (including cirrhosis patients and healthy population) in Spain showed that CFF can sensitively diagnose MHE (including minor HE and HE stage 1) and is reliable, simple, easy to apply. But as the application of CFF for diagnosis MHE is just on the start, further clinical application is required for its diagnostic value.⁷

Imaging examination

Cranial CT and MRI can detect cerebral edema. Manganese deposition can cause changes in structure of astrocytes. In examination of head MRI, frontal cortex brain atrophy and enhanced T1-weighted signal of globus pallidus and core-shell capsule can be detected. The main value of cranial CT and MRI is to exclude other causes of an abnormal mental state including cerebrovascular accident, intracranial tumor and other brain diseases.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis basis

Hepatic encephalopathy is a diagnosis of exclusion. Now, there are still no golden standards for HE diagnosis. As for HE diagnosis, considerations should be based on the following aspects.

- a. Different types of HE may occur in diverse clinical situations. Type-A HE occurs in patients with acute liver failure but without history of chronic liver disease; Type-B HE occurs in patients with portosystemic venous shunting but without liver disease basis; Type-C HE occurs in patients with severe liver disease and spontaneous or iatrogenic portosystemic venous shunting, such as cirrhosis, liver cancer, intrahepatic portosystemic shunt (TIPS).
- b. The patients may occur neuropsychiatric symptoms and signs, such as alteration of mood and personality, confusion and inappropriate behavioral, disorientation, alternate lethargy and excitement, hypermyotonia, positive of asterixis, ankle clonus and pathological reflex. In serious cases, such symptoms as lethargy, confusion and even coma may appear.
- c. Although the patients have no neuropsychiatric symptoms and signs, but their learning, understanding, attention, emergency and operating capacities defects. Through neuropsychological and intelligence test, there are at least two abnormalities. CFF anomalies can be taken as an important reference.
- d. Patients with precipitating factors of HE (type C and

type B), such as gastrointestinal bleeding, abdominal paracentesis to remove fluid, diuretic therapy, excessive protein dietary, taking tranquilizers and infection. The once-occurrence of HE is of great help to diagnosis. Type-A HE patients generally have no provocative factors.

e. To exclude other metabolic encephalopathies (such as the encephalopathies caused by ketoacidosis, hypoglycemia and uremia), toxic encephalopathies and nervous system diseases (such as intracranial hemorrhage, intracranial infections, psychosis and sedative overdose).

The patients with the conditions described as a., c., d. and e. above can be diagnosed as SHE patients; those who with the conditions of b., c., d. and e. above can be diagnosed as MHE patients.

HE is divided into different stages according to the severity of neuropsychiatric symptoms. Also, it can be graded according to West-Haven Scale, Glasgow Coma Scale or HESA.

Differential Diagnosis

Before diagnosis, HE should be discriminated with the following diseases:

Psychosis

HE, with psychiatric symptoms such as personality changes or abnormal behavior as the outstanding manifestations, can be easily misdiagnosed as psychosis. So, when the patients with serious liver diseases or portosystemic venous shunting history occurs neurological and psychiatric disorders, HE should be considered.

Other metabolic encephalopathies**Ketoacidosis**

These patients with a history of diabetes get ill usually caused by infection, emergency or overeating, alcoholism, etc. The manifestations include aggravated diabetes, loss of appetite, nausea, vomiting, abdominal pain, dizziness, headache, blurred consciousness and lethargy. The blood sugar is often greater than 16.7 mmol/L (300 mg/dl) with positive urine acetone bodies.

Hypoglycemia

Hypoglycemia may cause coma, often accompanied by sympathetic excitement, dizziness, palpitation, cold sweats, etc. Blood glucose concentration is often less than 2.8 mmol/L, and the symptoms may disappear after sugar supplement.

Renal encephalopathy

The manifestations also include mental retardation, delirium, hallucination, asterixis, lethargy and even coma, but these patients have a history of acute/chronic kidney disease and the evidence of azotemia, with reducing endogenous creatinine clearance rate, increasing blood urea nitrogen and creatinine or organic damage of kidney.

Pulmonary encephalopathy

The symptoms include headache, dizziness, memory loss, lack of energy and reduced ability. The more serious symptoms include drowsiness, lethargy, coma, positive asterixis and ankle clonus. However, the patients have a history of respiratory diseases, associated with hypoxia and carbon dioxide retention manifestation. The PaO_2 reduces and PaCO_2 increase in blood, carbon dioxide combining power rises and blood pH decreases.

Neurological diseases*Intracranial hemorrhage and intracranial tumor*

These patients generally have nervous systemic positioning signs. The patients with intracranial hemorrhage may have a history of high blood pressure. Cranial CT or MRI can detect the focus.

Intracranial infection

The symptoms include fever and infection poisoning. It has meningeal irritation signs. Cerebrospinal fluid examination can be helpful to diagnosis.

Reye syndrome

This is a group of syndromes featuring the cerebral edema and liver dysfunction caused by fat visceral organ infiltration. Its prominent clinical manifestations include liver dysfunction and cerebral edema. High blood ammonia, low blood sugar, prolonged prothrombin time, elevated serum transaminases and low serum bilirubin often occur too. So, it is easily misdiagnosed as acute HE. But Reye syndrome often occurs on children catching upper respiratory tract infection and taking salicylates (aspirin). A large amount of fat droplets in liver cells are helpful to diagnosis.

Toxic encephalopathy

Drugs and toxins such as carbon monoxide, alcohol, heavy metals like mercury and manganese can cause toxic encephalopathy. A thorough understanding of medical history will be helpful to its identification. Alcoholic liver disease can also result in HE, so it needs to be distinguished with the encephalopathy caused by ebrietas from HE.

Diagnosis process of HE (Figure 1)

TREATMENT PRINCIPLES AND MEASURES

HE is a complex metabolic disorder caused by a combination of factors, so comprehensive measures should be taken in many aspects. Different treatment schemes should be designed according to clinical types, different provocative factors and the severity of disease. Early recognition and prompt appropriate treatment is the key to improve HE prognosis, so aggressive treatment is necessary when determining the

existence of MHE.

Identification and removal of provocative factors

Type-C HE has a variety of provocative factors. Actively searching and immediate elimination may effectively inhibit the development of HE. For instance, esophageal variceal bleeding can induce the onset of HE. Active hemostasis, anemia correction and intestinal blood clearing are favorable for HE control; active infection control, correction of electrolyte disturbance, elimination of constipation and improvement of renal function are also the basic therapies to control HE.

Treatment of MHE

MHE patients mostly have no obvious symptoms and signs. But the patients may have weaker operating ability and sleep disorders. Treatment options: a. To adjust the diet structure and appropriately reduce protein intake (referring to enteral nutrition); b. Try nonabsorbable disaccharides such as lactulose or lactitol (referring to reducing intestinal pH and inhibiting the growth of intestinal bacteria); c. Patients with sleep disorder should not take benzodiazepine to avoid inducing clinical HE (C).

Symptomatic and supportive treatment

Patients with HE often lose appetite or in a coma and could not eat. So the active nutritional support is necessary.

Enteral nutrition

In the past, it was recognized that restricting protein diets may reduce intestinal ammonia production and prevent exacerbations of HE. However, recent research found that patients with cirrhosis often suffer from malnutrition. Although strict protein restriction can prevent elevated blood ammonia, it can further deteriorate the nutritional status of the patients and increase the risk of liver damage and death. Positive nitrogen balance is favorable for liver cell regeneration and the ammonia detoxification of muscle tissue. Recently, Cordoba et al conducted a clinical control study which randomized 30 patients with episodic HE to either low-protein diet group (protein intake rose from 0 g/d to 12 g/d on the third day and the figure doubled each three days till hitting 1.2 g/kg per day on the last two days) or normal protein diet group (1.2 g/kg per day).⁸ The results showed that there was no obvious difference in mental function improvement and the rate of protein synthesis between the two groups, but the protein catabolic rate of patients in the low-protein diet group is obviously higher during the 14-day observation period. ESPEN (European Society for Clinical Nutrition and Metabolism) Guidelines on Enteral Nutrition amended in 2006 suggests a patient with liver disease is supplied with 146-167 kJ/kg

Figure 1. Diagnosis process of HE.

Notes: Other metabolic encephalopathies include ketoacidosis, hypoglycemic coma, renal encephalopathy, pulmonary encephalopathy, etc.; intracranial organic diseases include intracranial hemorrhage, intracranial tumor, intracranial infection, etc.; toxic encephalopathies include the encephalopathies caused by drugs, toxins, heavy metals and alcoholism.

(35-40 kcal/kg) of non-protein calories and a protein intake of 1.2-1.5 g/kg per day.⁹

Recommendations

In patients with HE type-A or HE type-C in stage 3 or stage 4, protein feeding can be withdrawn for the few beginning days (C). After getting sober, the protein intake increases 10 g every 2-3 days gradually, aiming at 1.2 g protein·kg⁻¹·day⁻¹ (range 1-1.5 g) (A); As for

patients with HE type-C in stage 1 or stage 2, low-protein diets (20 g/d) should be provided in the few beginning days, then the amount will be increased every 2-3 days, also aiming at 1.2 g protein·kg⁻¹·day⁻¹ (range 1-1.5 g) if no HE occurs. Protein from vegetable and dairy sources are preferable to animal protein. In cases with vegetable protein, nonabsorbable fiber, less methionine and aromatic amino acids and more

branched-chain amino acids should be provided. The fiber is a substrate for colonic bacteria and subsequent colonic acidification, a natural cathartic, which can increase the discharge of fecal nitrogen. Animal protein (with the strongest encephalopathy-inducing effect) should be avoided as much as possible. Oral intake or intravenous supplement of necessary amino acid and branched-chain amino acids is favorable for the adjustment of amino acid proportion, promoting positive nitrogen balance and increasing the patients tolerance to protein. Meanwhile, the patients should be given sufficient calories (146 - 167 kJ/kg, 35 - 40 kcal/kg per day), mainly from carbohydrate. If patients are not able to maintain adequate oral intake from normal food, tube feeding or intravenous nutritional supplements should be given.

Zinc supplementation

Zinc is an important cofactor of urea cycle enzyme. Zinc deficiency is common in cirrhosis, especially if associated with malnutrition. Zinc supplementation can improve the activity of urea cycle and also has the potential to reduce the absorption of divalent cations like manganese. But, so far, there is no consensus on the results of some clinical studies in validating the therapeutic effect of zinc on HE yet.¹¹ Further clinical control study is still needed to explore its application value.

Water, electrolyte and acid-base balance

Hyponatremia, hypokalemia, hyperkalemia and alkalosis are all important precipitating factors to HE, and active corrections should be given according to the level of serum electrolytes and blood gas analysis results. The fluid volume of daily supplementation should be determined according to the urine volume of previous day (urine volume + 1000 ml) and the total volume should be controlled within 2,500 ml.

Treatment of basic diseases

Patients with hypoproteinemia may maintain colloid osmotic pressure by intravenous infusion of plasma and albumin. Albumin supplementation can also promote the repair of liver cells. As for patients with brain edema, alternate rapid infusion of 20% mannitol or 50% glucose should be adopted; moreover, adequate vitamin B, vitamin C, vitamin K, ATP and co-enzyme A should be added to improve the energy metabolism of brain.

Treatment targetting at the pathogenesis

Reduction in the production and absorption of ammonia and other harmful substances from the intestinal tract

Bowel cleansing

Because the toxins responsible for HE chiefly arise from the gut, bowel cleansing is a mainstay of therapy. Colonic cleansing can reduce the luminal production

and absorption of ammonia and other toxic substances, and could lower blood ammonia in cirrhotic patients. The retention of food, blood or other toxic substances in intestinal tract can be cleaned through catharsis or enema.

Recommendations

Twenty five percent magnesium sulfate (30-60 ml, ingested or via nasogastric tube p.o.) could be given for catharsis. Irrigation with non-absorbable disaccharides solution (such as lactulose, 300-500 ml in 500 ml water) can also be taken for enema, especially suitable for HE with portosystemic venous shunting.

Reducing intestinal pH and inhibiting the growth of intestinal bacteria

Application of non-absorbable disaccharides (lactulose and lactitol)¹²

Lactulose is a kind of disaccharide. As there is no lactulose enzyme in the human digestive tract, it is not broken down by intestinal disaccharidases and not absorbed in the stomach and small intestine. Thus, it could reach the colon, where bacteria will metabolize the disaccharidases to acetic acid and lactic acid. This could lower the colonic pH, inhibit intestinal ammonia production, and promote the conversion of luminal ammonia (NH₃) to ammonium (NH₄⁺), which should be less readily absorbed into the bloodstream from the bowel lumen. The production of organic acids by bacterial fermentation can also increase bowel lumen osmotic pressure, with the acidification of the colon, underlies its cathartic effect, which is helpful for the discharge of ammonia and other toxic substances in intestinal tract. Non-absorbable disaccharides, as prebiotics, are hostile to the survival of urease-producing intestinal bacteria and reduce the production of ammonia in colon. Abdominal discomfort, flatulence, and abdominal cramping, anorexia, nausea, vomiting and diarrhea are the most frequent subjective complaints with this drug. The miscellaneous sugar content of non-absorbable disaccharides is low (2%), so it is also applicable to patients with diabetic or lactase deficiency. However, they should be forbidden in patients with ileus. A number of randomized control studies showed that lactulose or lactitol can remarkably improve HE and the life quality of patients than placebo, but it still remains unknown whether it can improve the patients survival rate.^{12,13}

Recommendations

For patients with acute encephalopathy, lactulose (ingested or via nasogastric tube, 45 ml p.o.) is given every hour until evacuation occurs.² Then the dose is adjusted to an objective of two to three soft bowel movements per day (generally 15-45 ml every 8-12 hours) (A); Lactulose by enema (300 ml in 1 L water) is retained for 1 hour, with the patient in trendelenburg position (to increase the possibility of access to the

right colon). For patients with chronic encephalopathy, oral lactulose does not require the hourly initial administration. Lactitol, the lactulose derivative, has the same mechanism of action and effect as lactulose. But it is more palatable and better tolerated. The usual dose is 0.5 g/kg, bid, which can be adjusted to an objective of two to three soft bowel movements per day (A).

Application of probiotics

The probiotics (including bifidobacterium and lactobacillus) can restrict the growth of ammonia-producing and urease-producing intestinal bacteria by adjusting the structure of intestinal flora, resulting in reduced production and absorption of intestinal ammonia and other toxic substances. It can be applied together with prebiotics. In a recent open study, 190 patients with cirrhosis (55% with MHE) were randomly divided into 3 groups to respectively receive lactulose 30-60 ml/d or probiotic capsule (a quadrigeminus active bacterial agent including lactobacillus and streptococcus faecalis, etc.) or receive both kinds of treatment. After 1 month treatment, the patients achieved obvious improvement on neuropsychological test, P300 auditory evoked potential and the ammonia level in blood, but there was no significant difference among the efficacy of three groups.¹⁴

Recommendations

Live combined bifidobacterium, lactobacillus and enterococcus capsules, 2-3 tablets/time, tid, p.o.; Bacillus licheniformis capsules, 2 tablets /time, tid (B).

Application of antibiotics

Antibiotic is a therapeutic alternative to nonabsorbable disaccharides for treatment in acute and chronic HE.

In the past, it is recognized that oral intake of few-absorbable aminoglycoside antibiotics such as neomycin is beneficial to inhibit the overgrowth of colonic bacteria. However, the recent randomized placebo control study showed that neomycin is essentially contraindicated; it was found that a proportion of the ingested dose is indeed absorbed due to increased gut permeability, thus the risk of ototoxicity and renal toxicity and small intestine mucosa dysfunction may occur. Metronidazole can inhibit intestinal anaerobic bacteria and improve HE, but long-term use may result in the alteration of intestinal flora, gastrointestinal discomfort or neurotoxicity.¹⁵ Non-aminoglycoside antibiotics rifaximin is a derivative of rifampin and has a broad-spectrum and strong restriction on the growth of bacteria in intestinal tract. It is non-absorbable and only locally works in the gastrointestinal tract. It showed that 550 mg rifaximin in succession (bid), can remarkably prevent the occurrence of HE than placebo.^{16,17} In terms of chronic HE treatment, rifaximin has an effect equal to that of lactulose or neomycin and has no toxicity to

the auditory nerve and renal function.^{17,18}

Recommendations

Rifaximin 1,200 mg/d, tid (A).

The combination of antibiotics and non-absorbable disaccharides

Retrospective data analysis showed that the combination of two drugs can significantly lower the patients hospitalization rate and hospitalization time, but its potential therapeutic benefit remains to be further studied.¹⁹

Promote the metabolism of ammonia, antagonize false neurotransmitter and improve the balance of amino acids

Ammonia-lowering drugs

a. L-ornithine-L-aspartate (L-ornithine L-aspartate, LOLA, OA): OA is a stable salt of the 2 constituent amino acids. L-ornithine is the substrate of urea cycle (ornithine cycle). It can increase the activity of carbamoyl phosphate synthetase and ornithine carbamyl transferase and stimulates the synthesis of urea resulting in loss of blood ammonia. Both L-ornithine and L-aspartate are substrates for glutamate transaminase. With the administration of aspartate, ammonia is applied in the conversion of glutamate to glutamine and detoxification. Therefore, administration of OA can reduce the blood ammonia level. Aspartate is also involved in the synthesis of nucleic acids in the liver cells and indirectly promotes the metabolic process of Krebs cycle within the liver cells, thus facilitating the repair of stem cell. Clinical studies showed that compared with placebo control group, 20 g/d OA intravenous infusion can significantly reduce fasting blood ammonia and postprandial blood ammonia and improvement in the mental state grade of HE patients.²⁰ Oral administration of OA can improve the results of NCT-A, asterixis and EEG in patients with HE.²¹

Recommendations

For acute and chronic HE patients, OA (40 g) can be given within 24 hours. After patients getting sober, the dose of OA can be reduced to 20 g/d. For vein tolerability, the OA dose per 500 ml of solution should not exceed 30 g. The injection speed should not exceed 5 g/h. Thus such adverse reactions as nausea and vomiting could be avoided (A).

b. Arginine: As an intermediate metabolite ornithine cycle in the process of urea synthesis in liver, it can promote the synthesis of urea and lower blood ammonia. The clinical preparations are its hydrochloride salt. Being acidic, it can acidify blood and reduce the toxic effect of ammonia on the center.

Recommendations

Arginine hydrochloride (25%, 40-80 ml added to the glucose solution, i.v. q.d.) can be used (A). It can also correct alkalemia.

c. Glutamate: As the substrate of glutamine synthesis, sodium glutamate and potassium glutamate can reduce blood ammonia and adjust the balance between potassium and sodium. However, it is believed in recent years that glutamate can only temporarily reduce ammonia, and could not penetrate blood-brain barrier and reduce the ammonia in brain tissue, and may induce metabolic alkalosis and aggravate HE. In addition, the hypertonic effect caused by the excessive glutamine in brain is involved in the formation of brain edema, which is unfavorable to the recovery of HE. Therefore, it is no longer recommended for HE treatment.

The effect of antagonistic false neurotransmitters

Endogenous benzodiazepine analogues binding to the γ -aminobutyric acid receptor complex has been proposed as an important factor in the pathogenesis of HE. Theoretically, it is feasible to use flumazenil, the antagonist of the receptor for HE treatment. A large clinical trial of 560 cases showed that the improvement rate of brain function in patients treated with flumazenil or placebo is 15% and 3%, respectively.² The other 12 controlled studies on 765 patients showed that flumazenil can significantly improve HE, but did not show long-term benefits or improve the survival rate of patients. Therefore, its application is only considered for the patients who recently received benzodiazepines. Alterations of dopaminergic neurotransmission were initially postulated to contribute to the pathogens of HE. However, clinical controlled trials showed that the application of bromocriptine and levodopa could not give other benefits to HE patients in addition to partially improving the extrapyramidal symptoms of HE patients.

Recommendations

- Flumazenil (1 mg bolus i.v.) is indicated for patients who recently received benzodiazepines (B).
- Bromocriptine (30 mg p.o. b.i.d.) is indicated for patients with extrapyramidal symptoms and unresponsive to other therapies (C).

Correction of the imbalance between aromatic and branched-chain amino acids

Oral administration or intravenous infusion of branched-chain amino acid can correct amino acid metabolic imbalance and inhibit the formation of false neurotransmitters in brain. A meta analysis on five trials showed that the intravenous infusion of branched-chain amino acids can significantly improve the symptoms of HE. Although two of the five trials and another trial failed to reduce the mortality of HE patients by branched-chain amino acids,³ two large-scale trials in recent years (randomized control trials on 174 and 622 patients with cirrhosis, respectively) showed that the application of branched-chain amino acids not only reduce the incidence of HE, but also improve the

nutritional status of patients, improve liver function, decrease the incidence of liver failure and improve the survival rate of HE. Other trials showed that branched-chain amino acids can also stimulate liver cells regeneration. Adequate intake of branched chain amino acid mixture is effective to restore the patients' positive nitrogen balance, increase patients tolerance to protein food and improve their cerebral blood perfusion.¹¹ Its main side-effects include nausea, vomiting and allergic reactions, so the speed of infusion should be slow.

Recommendations

Branched chain amino acid mixture (250-500 ml q.d. i.v.) can be recommended (A).

Treatment of underlying diseases

Type A HE or type C HE occurs in patients with acute and chronic liver failure, respectively. Therefore, aggressive treatment of hepatic failure (referring to the Diagnostic and Treatment Guidelines for Liver Failure) is the fundamental prevention method to HE.

Liver function improvement

For chronic liver failure caused by viral hepatitis B, antiviral treatment with nucleoside or nucleotide analogues is indicated, which is helpful to mitigate or eliminate liver inflammation, necrosis and promote regeneration, helpful to restore liver's metabolism and detoxification function. For acute liver failure, due to the rapid progress of the disease, it may be hard to work on antiviral therapy, and the patients need to be transferred to ICU for comprehensive treatment.

Artificial liver support system

The system can be divided into non-biological type, biological type and mixed type. But only non-biological type is widely used in current clinical treatment, including hemodialysis, hemofiltration, plasmapheresis, hemoperfusion and plasma adsorption. Artificial liver support system can replace some functions of the liver to clear the accumulation of poisons in the body and provide conditions and times for the regeneration of liver cells. It is a transition therapy for patients waiting for liver transplantation and can be used in acute or chronic HE. But, in case of acute liver failure or end-stage liver disease, liver transplantation may be the only useful therapy.

Liver transplantation

For some severe HE, internal medicine therapy could not work well, then orthotopic liver transplantation may be the only effective treatment method.

Blocking portosystemic venous shunting

Theoretically, a permanency or temporary blocking of serious portosystemic venous shunting in patients with HE may be helpful to improving patients mental state. However, due to the existence of portal hypertension, the method could increase the risk of gastrointestinal bleeding, so it should be weighed thoroughly before

carrying out.

PREVENTION

Let patients know the precipitating factors and avoid their occurrence as much as possible by public health education.

Arrange the diet reasonably. The patients who catch cirrhosis or once caught HE should avoid high-protein diet and high-dose diuretics.

Guide the family members of the patients to observe the personality and behavior changes of the patients and recommend the family members to use "Clinical Hepatic Encephalopathy Staging Scale (CHESS) (Appendix 8)" to check the patient for early detection and treatment.

(Drafted by Hui-chun Xing)

(Committee of experts: Xin-yue Chen, Jun Cheng, Fang-ling Duan, Jian-gao Fan, Xiao-ling Fan, Li-min Guo, Ming-zhou Guo, Tao Han, Jing-yuan Liu, Xiong Ma, Wei Shen, Shi-guang Feng, Xian-bo Wang, Yun Wu, Wen Xie, Yao Xie, Hui-chun Xing, Ping-ge Yuan, Yong-ping Yang and Fu-kui Zhang)

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Appendix 1. West-Haven Scale¹

Grades	Distinguishing features
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition
Grade 2	Lethargy or apathy Minimal disorientation for time and place Subtle personality change Inappropriate behavior Impairment of subtraction
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation
Grade 4	Coma, unresponsive to verbal or noxious stimuli

Appendix 2. Glasgow Coma Scale²

Eyes open		Best motor responses		Best verbal responses	
Spontaneously	4	Obeys verbal orders	6	Oriented, conversant	5
To command	3	Localizes painful stimuli	5	Disoriented, conversant	4
To pain	2	Painful stimulus, flexion	3	Inappropriate words	3
No response	1	Painful stimulus, extension	2	Inappropriate sounds	2
		No response	1	No response	1

Notes: To obtain the score, the best ocular, verbal and motor responses are summed. The best score is 15 and the worst 3. Severe encephalopathy is defined as a score under 12.

Appendix 3. Hepatic Encephalopathy Scoring Algorithm (HESA)³

Grade 4	<ul style="list-style-type: none"> ○ No eyes opening ○ No verbal/voice response ○ No reaction to simple commands
All applicable = Grade 4 Otherwise continue examination	
Grade 3	<ul style="list-style-type: none"> ○ Somnolence ○ Confusion ○ Disoriented to place ○ Bizarre Behavior/Anger/Rage ○ Clonus/Rigidity/Nystagmus/Babinsky □ Mental Control = 0
3 or more applicable = Grade 3 Otherwise continue examination	
Grade 2	<ul style="list-style-type: none"> ○ Lethargy ○ Loss of time ○ Slurred speech ○ Hyperactive reflexes ○ Inappropriate Behavior □ Slow response □ Amnesia of recent events □ Anxiety □ Impaired simple computations
2 or more ○ and 3 or more □ applicable = Grade 2 Otherwise continue	
Grade 1	<ul style="list-style-type: none"> ○ Sleep disorder/impaired sleep pattern ○ Tremor □ Impaired complex computations □ Shortened attention span □ Impaired construction ability □ Euphoria or depression
4 or more applicable = Grade 1 Otherwise Grade 0	

Notes: ○ indicates symptoms assessed using clinical judgment and □ indicates symptoms assessed using neuropsychological measures.

Appendix 4a. NCT-A, B

Number connection test (NCT) is divided into part A (NCT-A) and part B (NCT-B).

NCT-A: Connect the 1 arbitrarily ordered figures together according to the numbers order. NCT-B: Connect the integers from 1 to 13 and the English letters from A to L according to 1-A, 2-B order, etc. In case that mistake is made in the process of connection, immediate correction should be made and the connection should continue from the correction point.

Record the spent time, including the time to correct mistakes.

NCT-A is widely applied, and NCT-B is being abandoned as it is subject to educational and cultural level and has low specificity in China. (Referring to evaluating criterion of 4a1, 4a2)

Appendix 4b. Line-tracing test (LTT)

Draw a line along the track established with the other two lines. The line could not be drawn cross or exposure to the track's lines. During the operation, the paper could not be moved and the pen could not leave the paper, and errors could be reduced as much as possible. The total time spent on it and accumulated score (1 point is deducted if the tracing line boundary connected but not crossed them; 2 points are deducted if the tracing line crossed the boundary line but not connected the paper edges; 3 points is deducted if the tracing line crossed over the edges of the paper. Besides, the number of total error could be calculated) could be evaluated. (Referring to evaluating criterion of 4b1, 4b2)

[illegible]

4a-1 NCT-A (Number connection test A)

ZVA

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
14	14	19	26	34	44
15	14	19	26	34	45
16	14	20	27	35	46
17	15	20	27	35	47
18	15	20	27	36	47
19	15	21	28	37	48
20	16	21	28	37	49
21	16	21	29	38	50
22	16	22	29	38	51
23	16	22	30	39	51
24	17	23	30	40	52
25	17	23	31	40	53
26	17	23	31	41	54
27	17	24	32	42	55
28	18	24	32	42	56
29	18	25	33	43	57
30	18	25	33	44	58
31	19	25	34	45	59
32	19	26	35	45	60
33	19	26	35	46	61
34	20	27	36	47	62
35	20	27	36	48	63
36	20	28	37	48	64
37	21	28	37	49	65
38	21	29	38	50	66
39	21	29	39	51	67
40	22	29	39	52	68
41	22	30	40	53	69
42	23	30	41	54	70
43	23	31	41	54	72
44	23	32	42	55	73
45	24	32	43	56	74
46	24	33	43	57	75
47	25	33	44	58	77
48	25	34	45	59	78
49	25	34	46	60	79
50	26	35	46	61	80
51	26	35	47	62	82
52	27	36	48	63	83
53	27	37	49	64	85
54	28	37	50	65	86
55	28	38	50	66	87
56	29	39	51	68	89
57	29	39	52	69	90
58	30	40	53	70	92
59	30	40	54	71	93
60	31	41	55	72	95
61	31	42	56	73	97
62	32	43	57	75	98
63	32	43	58	76	100
64	33	44	59	77	102
65	33	45	60	78	103
66	34	46	61	80	105
67	35	46	62	81	107
68	35	47	63	82	109
69	36	48	64	84	110
70	36	49	65	85	112
71	37	49	66	87	114
72	38	50	67	88	116
73	38	51	68	90	118
74	39	52	69	91	120

To be continued

ZVA

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
75	40	53	70	93	122
76	40	54	71	94	124
77	41	55	73	96	126
78	42	56	74	97	128
79	42	57	75	99	130
80	43	57	76	101	133

4a-2. Number connection test B, NCT- B

ZVB

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
14	33	45	60	80	106
15	34	46	61	82	108
16	35	47	63	83	110
17	35	48	64	85	112
18	36	48	65	86	115
19	37	49	66	88	117
20	37	50	67	89	119
21	38	51	69	91	121
22	39	52	70	93	123
23	39	53	71	94	125
24	40	54	72	96	128
25	41	55	74	98	130
26	42	56	75	100	133
27	42	57	76	102	135
28	43	58	78	103	137
29	44	59	79	105	140
30	45	60	81	107	143
31	46	61	82	109	145
32	47	63	84	111	148
33	47	64	85	113	151
34	48	65	87	115	153
35	49	66	88	117	156
36	50	67	90	120	159
37	51	69	92	122	162
38	52	70	93	124	165
39	53	71	95	126	168
40	54	72	97	129	171
41	55	74	99	131	174
42	56	75	100	133	177
43	57	76	102	136	181
44	58	78	104	138	184
45	59	79	106	141	188
46	60	81	108	144	191
47	61	82	110	146	194
48	62	84	112	149	198
49	64	85	114	152	202
50	65	87	116	154	205
51	66	89	118	157	209
52	67	90	121	160	213
53	69	92	123	163	217
54	70	94	125	166	221

To be continued

ZVB

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
55	71	95	127	169	225
56	72	97	130	172	229
57	74	99	132	175	233
58	75	101	134	179	238
59	77	103	137	182	242
60	78	104	139	185	246
61	79	106	142	189	251
62	81	108	145	192	256
63	82	110	147	196	260
64	84	112	150	199	265
65	85	114	153	203	270
66	87	117	156	207	275
67	89	119	158	211	280
68	90	121	161	214	285
69	92	123	164	218	290
70	94	125	167	222	296
71	95	128	170	227	301
72	97	130	174	231	307
73	99	132	177	235	312
74	101	135	180	239	318
75	103	137	183	244	324
76	105	140	187	248	330
77	107	143	190	253	336
78	109	145	194	257	342
79	111	148	197	262	349
80	113	151	201	267	355

4b-1. Line-tracing test, LTT (time, s)

LNZ

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
15	37	49	66	89	119
16	37	50	67	89	120
17	37	50	67	90	121
18	38	50	67	90	121
19	38	51	68	91	122
20	38	51	68	92	123

To be continued

LNZ

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
21	38	51	69	92	124
22	39	52	69	93	125
23	39	52	70	94	125
24	39	52	70	94	126
25	39	53	71	95	127
26	40	53	71	95	128
27	40	53	72	96	129
28	40	54	72	97	130
29	40	54	73	97	131
30	41	55	73	98	131
31	41	55	74	99	132
32	41	55	74	99	133
33	42	56	75	100	134
34	42	56	75	101	135
35	42	56	76	101	136
36	42	57	76	102	137
37	43	57	77	103	138
38	43	58	77	103	139
39	43	58	78	104	140
40	43	58	78	105	141
41	44	59	79	106	142
42	44	59	79	106	142
43	44	60	80	107	143
44	45	60	80	108	144
45	45	60	81	108	145
46	45	61	81	109	146
47	46	61	82	110	147
48	46	62	83	111	148
49	46	62	83	111	149
50	47	62	84	112	150
51	47	63	84	113	151
52	47	63	85	114	152
53	47	64	85	114	153
54	48	64	86	115	154
55	48	64	86	116	155
56	48	65	87	117	156
57	49	65	88	117	158
58	49	66	88	118	159
59	49	66	89	119	160
60	50	67	89	120	161
61	50	67	90	121	162
62	50	68	91	122	163
63	51	68	91	122	167
64	51	68	92	123	165
65	51	69	92	124	166
66	52	69	93	125	167
67	52	70	94	126	168
68	52	70	94	126	170

To be continued

LNZ

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
69	53	71	95	127	171
70	53	71	96	128	172
71	54	72	96	129	173
72	54	72	97	130	174
73	54	73	98	131	175
74	55	73	98	132	177
75	55	74	99	133	178
76	55	74	100	133	179
77	56	75	100	134	180
78	56	75	101	135	181
79	56	76	102	136	183
80	57	76	102	137	184

4b-2. Line-tracing test, LTT (accumulating error score)

LNF

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
15	12	29	54	87	128
16	12	29	54	87	128
17	12	30	55	88	129
18	12	30	55	88	129
19	12	30	56	89	130
20	13	30	56	90	131
21	13	31	57	90	131
22	13	31	57	91	132
23	13	31	57	91	133
24	13	32	58	92	133
25	14	32	58	92	134
26	14	32	59	93	135
27	14	33	59	93	135
28	14	33	60	94	136
29	14	33	60	94	137
30	15	34	60	95	137
31	15	34	61	95	138
32	15	34	61	96	138
33	15	35	62	97	139
34	16	35	62	97	140
35	16	35	63	98	140
36	16	36	63	98	141
37	16	36	63	99	142
38	16	36	64	99	142
39	17	37	64	100	143
40	17	37	65	100	144
41	17	37	65	101	144
42	17	38	66	102	145
43	18	38	66	102	146

To be continued

LNF

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
44	18	38	67	103	147
45	18	39	67	103	147
46	18	39	68	104	148
47	19	39	68	104	149
48	19	40	68	105	149
49	19	40	69	106	150
50	19	40	69	106	151
51	20	41	70	107	151
52	20	41	70	107	152
53	20	42	71	108	153
54	20	42	71	108	153
55	21	42	72	109	154
56	21	43	72	110	155
57	21	43	73	110	155
58	21	43	73	111	156
59	22	44	74	111	157
60	22	44	74	112	158
61	22	44	75	113	158
62	22	45	75	113	159
63	23	45	76	114	160
64	23	46	76	114	160
65	23	46	77	115	161
66	23	46	77	116	162
67	24	47	78	116	163
68	24	47	78	117	163
69	24	48	79	117	164
70	25	48	79	118	165
71	25	48	80	119	165
72	25	49	80	119	166
73	25	49	81	120	167
74	26	49	81	120	168
75	26	50	82	121	168
76	26	50	82	122	169
77	27	51	83	122	170
78	27	51	83	123	170
79	27	51	84	124	171
80	27	52	84	124	172

4c. Serial dotting test, SDT

KP

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
15	31	36	43	50	59
16	31	36	43	50	59
17	31	37	43	51	59
18	31	37	43	51	60
19	32	37	43	51	60
20	32	37	44	51	60
21	32	37	44	52	61
22	32	38	44	52	61
23	32	38	44	52	61
24	32	38	45	52	61
25	32	38	45	53	62
26	33	38	45	53	62
27	33	38	45	53	62
28	33	39	45	53	63
29	33	39	46	54	63
30	33	39	46	54	63
31	33	39	46	54	64
32	33	39	46	54	64
33	34	40	46	55	64
34	34	40	47	55	64
35	34	40	47	55	65
36	34	40	47	55	65
37	34	40	47	56	65
38	34	40	48	56	66
39	35	41	48	56	66
40	35	41	48	56	66
41	35	41	48	57	67
42	35	41	48	57	67
43	35	42	49	57	67
44	35	42	49	57	68
45	36	42	49	58	68
46	36	42	49	58	68
47	36	42	50	58	68
48	36	42	50	59	69
49	36	43	50	59	69
50	36	43	50	59	69
51	37	43	51	59	70
52	37	43	51	60	70
53	37	43	51	60	70
54	37	44	51	60	71
55	37	44	52	61	71
56	37	44	52	61	71
57	38	44	52	61	72
58	38	44	52	61	72
59	38	45	52	62	72
60	38	45	53	62	73
61	38	45	53	62	73
62	39	45	53	63	73
63	39	46	53	63	74
64	39	46	54	63	74

To be continued

ZVA

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
65	39	46	54	63	75
66	39	46	54	64	75
67	39	46	54	64	75
68	40	47	55	64	76
69	40	47	55	65	76
70	40	47	55	65	76
71	40	47	56	65	77
72	40	47	56	66	77
73	41	48	56	66	77
74	41	48	56	66	78
75	41	48	57	66	78
76	41	48	57	67	78
77	41	49	57	67	79
78	42	49	57	67	79
79	42	49	58	68	80
80	42	49	58	68	80

4d. Digit-symbol test (DST)

ZS

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
15	80	66	55	45	37
16	79	65	54	45	37
17	78	65	54	44	37
18	77	64	53	44	36
19	77	63	52	43	36
20	76	63	52	43	36
21	75	62	51	43	35
22	74	62	51	42	35
23	74	61	50	42	34
24	73	60	50	41	34
25	72	60	49	41	34
26	72	59	49	40	33
27	71	59	48	40	33
28	70	58	48	40	33
29	69	57	47	39	32
30	69	57	47	39	32
31	68	56	47	38	32
32	67	56	46	38	32
33	67	55	46	38	31
34	66	55	45	37	31
35	65	54	45	37	31
36	65	54	44	37	30
37	64	53	44	36	30
38	63	52	43	36	30
39	63	52	43	36	29

To be continued

ZS

	+1WP	0WP	-1WP	-2WP	-3WP
Alter (Jahre)	+1SD	Norm	-1SD	-2SD	-3SD
40	62	51	43	35	29
41	62	51	42	35	29
42	61	50	42	34	29
43	60	50	41	34	28
44	60	49	41	34	28
45	59	49	40	33	28
46	59	48	40	33	27
47	58	48	40	33	27
48	57	47	39	32	27
49	57	47	39	32	27
50	56	47	38	32	26
51	56	46	38	32	26
52	55	46	38	31	26
53	55	45	37	31	26
54	54	45	37	31	25
55	54	44	37	30	25
56	53	44	36	30	25
57	52	43	36	30	25
58	52	43	36	29	24
59	51	43	35	29	24
60	51	42	35	29	24
61	59	42	34	29	24
62	50	41	34	28	23
63	49	41	34	28	23
64	49	40	33	28	23
65	48	40	33	27	23
66	48	40	33	27	22
67	47	39	32	27	22
68	47	39	32	27	22
69	47	38	32	26	22
70	46	38	32	26	22
71	46	38	31	26	21
72	45	37	31	26	21
73	45	37	31	25	21
74	44	37	30	25	21
75	44	36	30	25	21
76	43	36	30	25	20
77	43	36	29	25	20
78	43	35	29	24	20
79	42	35	29	24	20
80	42	34	29	24	20

Appendix 5. Brief visuospatial memory test-revised (BVMT-R)

Brief Visuospatial Memory Test-Revised (BVMT-R): It contains 6 tests, each 2 points and totally 12 points. When the point is less than 6 points, it represents that the patient's construction ability is impaired.

Appendix 6. Clock Drawing Test (CDT)

The patient is asked to draw a watch dial on white paper and mark the figures on corresponding positions and then point the watch hands to 8:20. Result judgment: 1 point for a closed circle; 1 point for marking figures on the proper positions; 1 point for marking all the 12 figures correctly; 1 point for pointing the watch hands to the proper position. The patient getting 0-1 points has severe HE, 2 points moderate HE and 3 points mild HE.

Appendix 7. Mini-mental state examination (MMSE)

Name: Gender: Endemic Area: Bed Number: In-patient Number:
 History of Smoking and Drinking _____ Other diseases: Diabetes ____ Years, Hypertension ____ years
 History of operation: _____ History of other diseases _____
 Education: University (and above), high school, junior school, elementary school and illiteracy
 Dementia: No/Yes (mild, medium and heavy)
 Clinical laboratory and examination:
 Diagnosis:
 Proposed surgery: Other:
 Note:
 Total Score: _____ (Totally 30 points) Examiner: _____ Date: _____

Serial No. Evaluated Items Correct Incorrect
 * 1. Now, I am to ask some questions to check your memory and calculation ability and most of them are very simple.

(1)	What year is it?	1	0
(2)	What season is it?	1	0
(3)	What month is it?	1	0
(4)	What date is it?	1	0
(5)	What day is today?	1	0
(6)	What city is it?	1	0
(7)	What district is it?	1	0
(8)	What hospital is it?	1	0
(9)	What floor is it?	1	0
(10)	Where is it and what department is it?	1	0

* 2. Now I tell you the names of three things, and please repeat them after I finish. Please remember these three things, then, I would like to ask you to repeat (carefully make it clear that everything, each a second). (Tell) These three things are: tree, bell and car. Repeat:

Tree	1	0
Bell	1	0
Car	1	0

* 3. Please calculate what 100 minus 7 is ? Then continue the calculation by subtracting 7 each time and tell me

each answer until I say “stop”.

100 -7 =93	1	0
93 -7 =86	1	0
86 -7 =79	1	0
79 -7 =72	1	0
72 -7 =65	1	0

4. Now, please speak out the three things that I just let you remember.

Tree	1	0
Clock	1	0
Car	1	0

5. (The examiner show his own watch)

Please tell me what it is? 1 0

(The examiner show his pencil)

Please tell me what it is? 1 0

*6. Please follow me: “Si Shi Si Zhi Shi Zi” 1 0

7. (The examiner gives the test receiver a card with a sentence of “Please close your eyes!” on it)

Please read the sentence and do as required: 1 0

8. I give you a piece of paper, and please do like I have told you. Now, begin!

Please hold the paper with your right hand 1 0

Fold it with two hands 1 0

Put the paper on your left leg 1 0

*9. Please write what you want to say to the doctor in a whole sentence: 1 0

* 10. Please draw the following figure: 1 0

Notes:

*1. The total score ranges from 0 to 30 points and the normal and abnormal cutoff value is related to the level of education: illiterate group (uneducated) 17 points, primary school group (less than 6 years of education) 20 points, and middle school group and above (over 6 years of education) 24 points. If the points are below the cut-off value, cognitive dysfunctions can be confirmed, and above the cut-off value normal. In time of examination, the external interference should be avoided as much as possible. The elderly easily get discouraged and frustrated or give up, so more encouragement should be given to them. An examination generally needs 5 to 10 minutes.

*2. The examiner is only allowed to say once. The test receiver is not allowed make response according to the order of the articles. If there is error in the first time, score first. Tell the patient the error and to do once more, till he/she getting the right answer. But, the highest times should not exceed 5.

*3. This is the “sequential seven-subtraction” test in clinical treatment. Meanwhile, It can check the test receiver’s attention. Do not repeat the answers for test and do not use pen for calculation. If one calculation is incorrect, the point for the calculation will be deducted. If the latter is correct, the point for it will be given. For instance: 100 - 7 = 93 (correct, points given), 93-7 = 88 (incorrect, no points) and 88-7 = 81 (correct, points given).

* 6. Only 1 time is allowed, and only correct and clear pronunciation can get 1 point.

* 9. Sentence must have subject, predicate and meaning.

*10. One point is given only after two pentagon patterns and a quadrangle formed by the two pentagon patterns are drawn.

Appendix 8. Clinical hepatic encephalopathy staging scale (CHES)

This is a simple assessment method of the severity of HE. The total score is the sum of the answers to the nine items. Minimal score = 0; maximal score = 9.

Items		Scores	
		0	1
1	Does the patient know which month he/she is in (i.e. January, February)?	Yes	No, or he/she does not talk
2	Does the patient know which day of the week he/she is in (i.e., Thursday, Friday, Sunday, etc.)?	Yes	No, or he/she does not talk
3	Can he/she count backward from 10 to 1 without making mistakes or stopping?	Yes	No, or he/she does not talk
4	If asked to do so, does he/she raise his/her arms?	Yes	No
5	Does he/she understand what you are saying to him/her? (based on the answers to question 1 to 4)	Yes	No, or he/she does not talk
6	Is the patient awake and alert?	Yes	No, he/she is sleepy or fast asleep
7	Is the patient fast asleep, and is it difficult to wake him/her up?	No	Yes
8	Can he/she talk?	Yes	He/she does not talk
9	Can he/she talk correctly? In other words, can you understand everything he/she says, and he/she doesn't stammer?	Yes	No, he/she does not talk or does not talk correctly
Total CHES score:			