Nutritional Support in Hepatic Encephalopathy

BARRY A. MIZOCK, MD, FACP

From the Division of Critical Care Medicine and Department of Medicine, Cook County Hospital and The Chicago Medical School, Chicago, Illinois, USA

Date accepted: 20 March 1998

ABSTRACT

Hepatic encephalopathy (HE) is a syndrome of global cerebral dysfunction resulting from underlying liver disease or portal-systemic shunting. HE can present as one of four syndromes, depending on the rapidity of onset of hepatic failure and the presence or absence of preexisting liver disease. The precise pathogenesis is unknown but likely involves impaired hepatic detoxification of ammonia as well as alterations in brain transport and metabolism of amino acids and amines. The etiology of malnutrition in hepatic failure is multifactorial. Nutritional deficits may be clinically manifest as marasmus or kwashiorkor, or both. Nutritional support in HE is directed toward reducing morbidity related to underlying malnutrition and concurrent disease. However, reaching nutritional goals is often complicated by protein and carbohydrate intolerance. The use of protein restriction in HE is controversial. Modified formulas that are supplemented in branched chain amino acids may be of value in patients who exhibit protein intolerance with standard feeding solutions or in patients who present with advanced degrees of encephalopathy.


Key words: hepatic encephalopathy, liver disease, nutritional support, branched chain amino acids

INTRODUCTION

Hepatic encephalopathy (HE) is a cardinal manifestation of hepatic failure that may result from an acute insult or from chronic damage such as alcohol abuse. Severe liver disease often manifests as a syndrome characterized by hyperbilirubinemia, coagulopathy, vasodilation, and alterations in mental status ranging from subtle changes to deep coma. Many patients hospitalized with hepatic failure are critically ill, often with concurrent conditions that are potentially life threatening and that require treatment in an intensive care unit.

Patients with liver disease who develop HE have a poor prognosis. Impaired hepatic immune clearance is one of the more important factors that cause clinical deterioration in these patients. Hepatic Kupffer cells normally take up and detoxify bacteria and endotoxin of intestinal origin, thereby limiting the magnitude and duration of their effects in the bloodstream. The liver also clears activated inflammatory mediators such as leukotrienes and cytokines. The inability of the damaged liver to adequately perform these functions promotes development of an inflammatory response that has adverse effects on metabolism (e.g., increased energy expenditure, protein catabolism) and organ function. This, in turn, predisposes toward the development of multiple system organ failure and death.

Correspondence to: Barry A. Mizock, MD, Department of Medicine, Cook County Hospital, 1835 West Harrison Street, Chicago, Illinois 60612, USA.
TABLE I.

SYNDROMES OF HE

Acute hepatic encephalopathy
Acute episodic hepatic encephalopathy
Chronic portosystemic encephalopathy
Subclinical or latent hepatic encephalopathy

HE) or may be unresponsive to treatment, producing dementia-like symptoms (chronic permanent HE). Finally, HE may present in a subclinical or latent form in which abnormalities without clinical evidence of encephalopathy have latent HE. The diagnosis of HE is clinical. It is important to exclude alternate diagnoses (e.g., other metabolic or toxic encephalopathies, intracranial lesions) because the manifestations of HE are non-specific. The clinical presentation of acute and chronic HE differs in some respects; agitation and restlessness are more common in the acute form, whereas alterations in the level of consciousness and intellectual changes typically occur in the chronic forms. HE may occasionally present with atypical manifestations such as seizures, hallucinations, and sensory nervous system symptoms. There are several grading systems for HE (the same system is often used for both acute and chronic HE). The modified Parson-Smith scale divides encephalopathy into five grades (Table II). Neuropsychologic testing is often required to diagnose HE in its earliest stages. Abnormalities in liver function tests are common but are non-specific; increased serum globulins, hypoalbuminemia, and increased transaminases are typically seen. Blood ammonia levels are elevated in 90% of patients with HE but correlate poorly with the grade of encephalopathy. In addition, hyperammonemia is not specific for HE because increased levels may also be seen in severe sepsis. Cerebrospinal fluid (CSF) glutamine is probably the most specific test for HE; nonetheless, elevated levels may also be found in septic and hypercapnic encephalopathy. Blood ammonia levels are elevated in 90% of patients with HE but correlate poorly with the grade of encephalopathy. In addition, hyperammonemia is not specific for HE because increased levels may also be seen in severe sepsis. Cerebrospinal fluid (CSF) glutamine is probably the most specific test for HE; nonetheless, elevated levels may also be found in septic and hypercapnic encephalopathy. The electronencephalogram (EEG) in HE is non-specific; typical patterns include slow and triphasic waves. Visual evoked responses (VER) have also been used to confirm the diagnosis. EEG and VER are of greatest value in patients with suspected subclinical HE because abnormalities in these tests may prompt the clinician to initiate treatment.

PATHOGENESIS OF HE

The pathogenesis of HE is unknown but is likely to be multifactorial. In addition, several pathogenic features differ between acute and chronic forms of HE. Cerebral edema is seen only in acute HE (e.g., fulminant hepatitis). Neuropathologic studies indicate that astrocyte swelling is characteristic of the acute form whereas Alzheimer type II astrocytosis is typical of chronic HE. Nevertheless, the encephalopathy that occurs in both acute and chronic liver failure is reversible, which suggests a metabolic etiology. Cerebral metabolic rates for oxygen and glucose are reduced in HE. This rate reduction is thought to result from reduced energy demand (as a consequence of lowered neuronal activity) rather than decreased respiratory metabolism because encephalopathy precedes a decrease in brain levels of high energy phosphates. There is considerable evidence that suggests the astrocyte plays a role in the pathogenesis of HE. As mentioned previously, most pathologic changes occur in astrocytic rather than neuronal cells (hence the speculation that HE may represent a primary "gliopathy"). The astrocyte normally performs a variety of functions in the central nervous system such as maintenance of the ionic environment and pH of the extracellular space. Astrocytic end feet induce brain capillaries to form tight junctions, which, in turn, establish the blood-brain barrier. Water, gases, ammonia, and lipid-soluble molecules can diffuse across the endothelial cell whereas other substances such as amino acids must be carried across by transport systems. Astrocytic uptake systems terminate the effect of some neurotransmitters by removing them from the synaptitic cleft; for example, glutamate is taken up and inactivated by metabolism to glutamine (see later).

There are two basic processes that must be accounted for by any theory of HE: 1) failure of hepatic clearance of gut-derived substances (e.g., ammonia, gamma-aminobutyric acid [GABA]) either through portosystemic shunting or severe hepatocellular failure; and 2) altered amino acid metabolism that results in changes in neurotransmitters. In 1982, Schafer and Jones proposed that GABA could play a role in the pathogenesis of HE. They hypothesized that HE was caused by defective hepatic clearance of gut-derived GABA in the setting of increased blood-brain barrier (BBB) permeability. However, subsequent studies failed to support a pathogenetic role for GABA. Endogenous benzodiazepine-like substances were also implicated in HE. Anecdotal reports of improvement in encephalopathy with administration of flumazenil, a benzodiazepine receptor antagonist, lent credence to this theory. Nonetheless, efforts to accurately identify these substances have not been successful, and the response of HE to benzodiazepine receptor antagonists has been inconsistent. In addition, these theories do not account for the pathogenic role of ammonia or the favorable effects of branched chain amino acids on HE.

Ammonia is the substance most consistently linked with HE. The primary source of portal blood ammonia has been attributed to bacterial degradation of protein and urea in the intestine. However, it now appears that the majority of ammonia production results from glutamine oxidation by the small intestine, with bacterial degradation making a smaller contribution. In this regard, neomycin has been demonstrated to lower ammonia by reducing intestinal mucosal glutaminase activity rather than by an antibacterial action. Liver is the main site of ammonia metabolism (to urea and glutamine); muscle also takes up ammonia to form glutamine. Hyperammonemia is promoted by decreased hepatic function (secondary to depressed ureagenesis or shunting). Skeletal muscle wasting is common in malnourished cirrhotics; this, in turn, reduces the body's ability to metabolize ammonia. Ammonia crosses the BBB by simple diffusion across the endothelial cell. Brain uptake of ammonia is enhanced in liver failure due to increased BBB permeability; this could account for HE in patients with normal arterial ammonia levels, as well as the increased sensitivity of cirrhotics to high protein diets. Because there is no urea cycle in the brain, ammonia metabolism must take place by alternate routes. The major pathway is regulated by glutamine synthetase in which ammonia combines with glutamate.

TABLE II.

MODIFIED PARSON-SMITH SCALE OF ENCEPHALOPATHY

Grade 0: Subclinical encephalopathy; abnormalities only on psychometric testing
Grade 1: Trivial lack of awareness; shortened attention span
Grade 2: Lethargy, disorientation, personality change
Grade 3: Somnolence to semistupor; responsive to stimuli
Grade 4: Coma
to form glutamine. The role of ammonia in HE is supported by studies that show that elevations in CSF glutamine (and its metabolite alpha ketoglutarate) are sensitive and specific indices to form glutamine. The role of ammonia in HE is supported by transmission by a postsynaptic action. Nonetheless, certain evidence contradicts the concept that ammonia functions as a direct neurotoxin. Serum ammonia levels correlate poorly with the degree of HE, and ammonia is a neuroexcitatory proconvulsant compound that, when infused, produces a picture dissimilar to HE. Also, ammonia infusion does not produce encephalopathy when glutamine synthesis is blocked. It is, therefore, more likely that toxicity results from an indirect effect that may be mediated by stimulation of glutamine synthesis. In acute HE, augmented glutamine synthesis is pathogenic by promoting cerebral edema. In chronic encephalopathy, high rates of astrocytic glutamine synthesis may disrupt neurotransmitter uptake. In addition, blood-brain uptake of aromatic amino acids and resultant production of pathogenic neuroamines appears to be linked to glutamine synthesis (see later). The hypothesis that glutamine formation constitutes a means to "detoxify" ammonia may, therefore, be incorrect.

Glutamine is an excitatory neurotransmitter that is released from the presynaptic neuron. It is inactivated by re-uptake into the pericapillary astrocyte where it is transformed into glutamine via glutamine synthetase. It has been suggested that hyperammonemia promotes encephalopathy by enhancing glutamine synthesis, which, in turn, depletes brain glutamate. This may be an oversimplification, because although total brain glutamate levels are decreased in HE, extracellular glutamate is increased. Alternately, disrupted neurotransmission may result from a failure of astrocytic glutamate uptake. This claim is supported by evidence that indicates that expression of the astrocytic glutamate transporter (GLUT-1) is reduced during experimental liver failure. A reduction in glutamate binding sites may also play a role.

In 1971, Fischer and Baldessarini published the False Neurotransmitter Theory that implicated altered metabolism of aromatic amino acids (AAA) in the pathogenesis of HE. Aromatics (phenylalanine, tyrosine, tryptophan) and their amines (e.g., phenylethylamine, octopamine, tryptamine) are produced in gut during digestion and are normally hepatically cleared. In the setting of hepatic dysfunction, these monamine "false neurotransmitters" are shunted around the liver and flood the brain, thereby causing HE. One of the major weaknesses of this theory is that it failed to account for the role of ammonia in HE. In 1979, Fischer's group published the Unified Theory of Portal Systemic Encephalopathy that accounted for the role of ammonia in HE, and explained the significance of alterations in the plasma concentrations and brain uptake of neutral amino acids. The Unified Theory has several key elements. First, liver failure is associated with alterations in the plasma concentration of branched chain amino acids (BCAA), AAA, and methionine. BCAA are reduced due to peripheral catabolism, whereas aromatics are increased secondary to impaired hepatic clearance. A reduction in the plasma BCAA/AAA ratio would favor brain uptake of aromatics because they compete for transport across the BBB. Second, the activity of the neutral AA transport carrier (System L) is selectively stimulated by enhanced synthesis of brain glutamine resulting from hyperammonemia. This mechanism was proposed based on data that suggested that glutamine efflux from the brain is coupled with AAA influx via System L. Third, elevated brain concentration of AAA stimulate the production of inhibitory neuroamines. Although the unified theory represented a major step in the understanding of HE, it had several weaknesses. First, it failed to account for data that demonstrated that the transport of different neutral amino acids is increased to different degrees under conditions of HE. Tryptophan appears to be preferentially taken up because it is transported by both saturable and non-saturable systems in the BBB; the non-saturable component (which is not expected to be affected by competition) accounts for the larger fraction of tryptophan entry. This suggests that simple stimulation of neutral amino acid transport is inadequate to explain what was observed experimentally. Second, the role of glutamine in promoting neutral AA uptake by virtue of a simple exchange is questionable based on studies that show that glutamine is poorly transported by the neutral AA transporter. Recent data demonstrate that amino acid transport is more complex than initially thought; it appears that separate sodium-dependent transport systems exist for export of neutral amino acids and glutamine out of brain. Apparent alterations in BBB permeability in HE may result from diminished blood flow rather than enhanced inflow. The role of glutamine in this process remains to be clarified. It is possible that increased astrocytic synthesis of glutamine influences membrane permeability by repressing transport activity (analogous to an enzyme), thereby decreasing efflux of AAA.

Despite its shortcomings, the Unified Theory was important because it implicated neuroamines as pathogenic in HE. Phenylethylamine, tyramine, phenylethanolamine, octopamine) have been found to be elevated in blood and CSF in humans and animals with HE; data exist that both support and refute the role of these substances. Recent research has focused on tryptophan-derived monooamines (e.g., serotonin [5-hydroxytryptamine] and tryptamine). Increased concentration of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) has been found in CSF and brain in HE. However, the correlation between levels of 5-HIAA in CSF and the degree of neurologic impairment in humans is poor. In contrast, tryptamine and its metabolite, indole acetic acid, appear to be more closely correlated with the degree of encephalopathy. A pathogenic role for tryptamine is supported by a recent study that demonstrated decreased tryptamine binding sites in the brains of patients with AAA.

In summary, although the precise pathogenesis of HE is unknown, alterations in astrocytic uptake and metabolism of ammonia and amino acids are likely to be important.

**METABOLIC ALTERATIONS IN LIVER FAILURE**

Hepatic failure is associated with alterations in carbohydrate, lipid, and protein metabolism, which reflect the influence of neuroendocrine and cytokine mediators (Table III). Hyperinsulinemia and hyperglucagonemia are typically present in patients with liver failure; glucagon is disproportionately increased, resulting in an elevated glucagon/insulin ratio. Increased circulating insulin levels may result from either decreased hepatic clearance (e.g., secondary to hepatic dysfunction or portosystemic shunting) or increased pancreatic synthesis. A number of studies have attempted to define the primary process; however, no clear consensus exists and it is likely that hyperinsulinemia results from a combination of both mechanisms. Sustained hyperinsulinemia promotes peripheral insulin resistance; this results in hyperglycemia, which in turn further stimulates insulin secretion. This sequence ultimately leads to beta cell exhaustion and diabetes mellitus (see later). Hyperglucagonemia in cirrhosis has likewise been attributed to both diminished hepatic clearance and increased pancreatic secretion. Plasma glucagon levels increase in relation to the severity of liver disease. It has been postulated that depletion of hepatic glycogen stores (which typically occur in cirrhosis) mediates the increase in glucagon secretion. Cytoxines have also been shown to directly stimulate pancreatic alpha
NUTRITIONAL SUPPORT IN HEPATIC ENCEPHALOPATHY

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Decreased hepatic and skeletal muscle glycogen synthesis</th>
<th>Increased gluconeogenesis</th>
<th>Glucose intolerance and insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>Increased lipolysis</td>
<td>Enhanced turnover and oxidation of non-esterified fatty acids</td>
<td>Normal or increased ketogenesis</td>
</tr>
<tr>
<td>Protein</td>
<td>Increased catabolism</td>
<td>Enhanced peripheral utilization of branched chain amino acids</td>
<td>Decreased ureagenesis</td>
</tr>
</tbody>
</table>

The liver and negatively feeds back on the pituitary to inhibit IGF-1 is a polypeptide that is mainly synthesized in the liver and negatively feeds back on the pituitary to inhibit growth hormone secretion. IGF-1 also has a number of effects on cell function. Growth hormone is increased in cirrhosis whereas the plasma concentration of insulin-like growth factor-1 (IGF-1) is decreased. IGF-1 is a polypeptide that is mainly synthesized in the liver and negatively feeds back on the pituitary to inhibit growth hormone secretion. IGF-1 also has a number of effects on substrate metabolism, including augmentation of protein synthesis and glycogen formation. Liver failure results in decreased production of IGF-1; low levels may contribute to protein catabolism and decreased glycogen formation, which characteristically accompany hepatic failure.

The major alterations in carbohydrate metabolism in cirrhosis include: decreased hepatic and skeletal muscle glycogen synthesis and storage, increased gluconeogenesis, and glucose intolerance with insulin resistance. Decreased hepatic glycogenosis promotes hypoglycemia and ketosis during fasting; reduced glycogen formation in muscle has been implicated in the pathogenesis of glucose intolerance and insulin resistance (see later). Impaired hepatic glycogenosis may result, in part, from reduced storage secondary to hepatic fibrosis; hyperglucagonemia and low levels of IGF-1 also inhibit glycogen formation. Gluconeogenesis is increased during hepatic failure as a mechanism to compensate for reduced glucose production from glycogen.

The major alterations of lipid metabolism include increased lipolysis and enhanced turnover and oxidation of non-esterified fatty acids. The pathogenesis of altered lipid metabolism is unclear. There is a dissociation between the rate of lipolysis and fatty acid oxidation that suggests an increased rate of reesterification. Most studies indicate that cirrhotics have normal or increased rates of appearance of acetocetate and beta-hydroxybutyrate. Transport of ketones across the BBB is reduced by 60% during HE; this may compromise cerebral energy supply in conditions where oxidative demand is high. Lipid metabolism in the cirrhotic resembles a state of accelerated starvation where lipids are preferentially oxidized. Fatty acid deficiency and depleted fat stores commonly result; the decrement correlates with nutritional status and the severity of liver disease. Although mild to moderate hypertriglyceridemia can occur as the result of increased lipolysis and decreased activity of lipoprotein lipase, high levels of triacylglycerols are unusual unless there is superimposed sepsis. Administration of intravenous lipids is generally safe; although the maximal clearing capacity of an exogenous fat load is decreased, a moderate fat load (e.g., < 1 g • kg⁻¹ • d⁻¹) is adequately cleared.

Many, but not all, authors have found that protein catabolism is increased in cirrhosis. Augmented protein breakdown is more common in patients with concurrent stress such as sepsis or gastrointestinal hemorrhage. Protein catabolism during liver failure promotes HE because ammonia production and peripheral release of AAA is increased. The etiology of the catabolic state is probably multifactorial with hormones (e.g., glucagon) and cytokines (e.g., TNF, IGF-1) playing major roles. The status of protein synthesis in cirrhosis is heterogeneous because decreased, increased, and unchanged synthetic rates have been reported. Enhanced utilization of branched chain amino acids as an energy source by muscle occurs during hepatic failure. This may account for the low plasma BCAA levels typically seen in chronic liver disease.

MALNUTRITION IN LIVER FAILURE

Protein-calorie malnutrition (PCM) is common in patients with cirrhosis. In fact, it has been suggested that PCM can be considered the most common complication of chronic liver disease. However, quantifying the incidence of PCM is problematic because there is no standardized approach to the diagnosis and classification of malnutrition in these patients. In addition, the prevalence of PCM varies based on the etiology of liver disease. In patients hospitalized with alcoholic liver disease, the rate may approach 100% (with one-third classified as severe); the incidence in non-alcoholic cirrhosis ranges from 12 to 40%. Lautz et al. performed detailed nutritional assessment in 123 patients with different etiologies of liver cirrhosis. Eighty patients (65%) showed evidence of PCM; of these, 34% were considered kwashiorkor-like, 18% were marasmic, and 49% mixed marasmus/kwashiorkor. Malnutrition was found more frequently at the advanced stages of liver disease; furthermore, the type of malnutrition did not correlate with the etiology of cirrhosis.

Mortality was doubled in patients who were malnourished, with the increase in mortality being similar among the groups. Shaw et al. also found that malnutrition had the strongest correlation (inverse) with survival in patients who had undergone transplant. However, confirming malnutrition as an independent risk factor for mortality may be difficult because the incidence of both factors correlates with the severity of liver disease. Merli et al. performed a prospective study in 1053 patients with chronic liver disease to attempt to clarify whether malnutrition represented an independent risk factor for survival. Patients were stratified for severity of liver disease using the Child-Pugh classification and were defined as malnourished based on midarm muscle area and midarm fat area below the fifth percentile. Cumulative survival was lower in patients with a reduction in muscle mass in Child-Pugh classes A and B, but not in C. Although their data indicated that malnutrition was associated with deterioration of liver function, multivariate analysis failed to demonstrate that malnutrition was an independent risk factor for mortality.

Malnutrition has been shown to be an independent predictor of certain complications of chronic liver disease such as encephalopathy or ascites bleeding. Refractory or persistent ascites and spontaneous bacterial peritonitis may also be linked with poor nutritional status. Whether or not malnourished patients are more prone to develop HE has not been clearly established, but could be expected based on several factors. First, malnutrition tends to be more common in patients with advanced liver disease, and HE is more likely in this group. Second, nutritional deficits such as...
decreased lean body mass (muscle is important in ammonia uptake) and hypoalbuminemia (which increases free tryptophan levels) could theoretically promote HE.\textsuperscript{81} Beneficial effects of nutritional intervention on the course of HE have been observed. Kearns et al.\textsuperscript{82} found that median encephalopathy scores improved more rapidly in patients with alcoholic liver disease who were tube fed relative to those on a regular diet. Cabre et al.\textsuperscript{83} demonstrated improvement in Child's score and a reduction in the in-hospital mortality rate in malnourished cirrhotics who received tube feeding in comparison to those on an oral diet. However, other studies failed to confirm a beneficial effect of supplemental nutrition on HE.\textsuperscript{84,85} BCAA-enriched solutions have been shown to be of variable benefit in patients with HE. The inability of various investigators to consistently demonstrate favorable effects with modified solutions, led to detection of edema and ascites, obvious muscle wasting, loss of subcutaneous fat, easily pluckable hair, and dry skin. Manifestations of vitamin and trace element deficiency should also be sought. In clinical practice, body composition of cirrhotic patients is assessed by indirect techniques such as anthropometry, the creatinine-height index, or bioelectric impedance. Anthropometric measurements, such as the midarm circumference or triceps skinfold thickness, are used to assess the somatic protein compartment, and body fat reserves. In patients with ascites or edema, or both, the creatinine-height index is a more reliable index of lean body mass than midarm circumference, although it is less useful in the presence of renal insufficiency. The utility of bioelectric impedance analysis is limited in patients with ascites or edema.\textsuperscript{86} Measurements of albumin, transferrin, and other circulating proteins are used to assess the visceral protein compartment. However, these proteins lose their specificity as an index of nutritional status in patients with critical illness. In this setting, levels tend to correlate more with the extent of stress or liver injury than with the degree of malnutrition. Urinary urea nitrogen excretion is used to evaluate the severity of protein catabolism. However, liver failure is associated with impaired urea synthesis and measurement of urine urea nitrogen may underestimate the degree of negative nitrogen balance.

**General Comments**

The nutritional support of the hospitalized patient with HE has traditionally focused on protein restriction. However, administration of a low-protein diet to patients with liver disease paradoxically produces a plasma amino acid profile that mimics that seen with a high-protein diet.\textsuperscript{90} This occurs because these patients exhibit a more rapid than normal transition to gluconeogenesis when starved (due to diminished hepatic glycogen stores), which in turn promotes skeletal muscle catabolism.\textsuperscript{28,92} O’Keeffe et al.\textsuperscript{93} noted that the input of amino acids into the blood during fasting was 5 times higher in cirrhotics and 12 times higher in patients with fulminant hepatic failure than the normal input from dietary protein. Provision of adequate protein is, therefore, preferable to protein restriction due to beneficial effects in suppressing skeletal muscle catabolism. Nevertheless, there is a lack of benefit to the specific route of administration of nutrition in patients with HE. Those who believe that the gastrointestinal tract plays a central role in the pathogenesis of HE argue for the use of intravenous nutrition on the basis of improved protein tolerance.\textsuperscript{94} Nevertheless, total parenteral nutrition carries significant risks including worsening of liver function due to fatty infiltration or cholestasis. Feeding by the enteral route was therefore preferred whenever possible. Benefits of enteral nutrition include lower cost, better preservation of intestinal villus architecture, and reduced bacterial translocation. Tube feeding may be preferable to a hospital diet because nutritional goals are more reliably met, and the risk of aspiration is lower. Irritation or pressure on esophageal varices from nasogastric tubes can potentially result in bleeding;\textsuperscript{95} however, this complication is poorly documented and probably rare. Controversies regarding enteral feeding include significant gastrointestinal bleeding, intestinal obstruction, and concomitant pancreatitis. Patients with tense ascites may not be able to tolerate complete feeding by the enteral route; nevertheless, they may tolerate enough enteral nutrition to confer beneficial effects on gastrointestinal integrity. In patients who are able to eat, the use of smaller, more frequent meals may improve feeding tolerance, particularly in the presence of fat malabsorption where large fat boluses may produce diarrhea. Patients with hepatic failure commonly have reduced gastric emptying and slow intestinal transit times;\textsuperscript{96} it has been suggested that this might promote absorption of intestinal toxins.\textsuperscript{97} The use of agents that increase gastrointestinal motility might be useful in this regard.\textsuperscript{98} Insertion of a postpyloric feeding tube may enable enteral feeding in patients with prolonged gastric ileus because small bowel motility is often preserved despite impaired gastric emptying. Vegetable protein diets have been promoted in patients with low-grade HE on the basis of improved tolerance relative to animal protein. Two studies supported this concept;\textsuperscript{99,100} however, no difference was found in a third.\textsuperscript{101} Potential mechanisms for the efficacy of vegetable protein include: lower aromatic and methionine content, increased fiber content that promotes excretion of nitrogen or bacteria in the fecal mass, and a more effective use of dietary nitrogen for protein synthesis. However, diets containing more than 50 g/d of vegetable protein are poorly tolerated (due to bloating, flatulence, early satiety) when administered to individuals from developed countries where dietary fiber content is normally low.

The concept of using BCAA-supplemented solutions in encephalopathic patients emerged from the false neurotransmitter and Unified Theories of HE. Initial animal studies were performed in the 1970s with extensive human trials following in the 1980s. BCAA-supplemented formulas have been shown to have a number of beneficial effects in liver failure. In the patient with HE who is protein-intolerant, a modified formula permits greater protein intake without inducing encephalopathy than do standard protein formulas.\textsuperscript{102,103} BCAA-supplemented solutions are anticonvulsant.
NUTRITIONAL SUPPORT IN HEPATIC ENCEPHALOPATHY

and have a stimulatory effect on hepatic protein synthesis.\textsuperscript{104} It should be noted, however, that this effect requires the presence of a significant level of stress (e.g., urine urea nitrogen excretion \textgtr 8–10 g/d).\textsuperscript{105} Studies failing to demonstrate positive effects of BCAA on protein metabolism often included patients who were not critically ill. As previously mentioned, BCAA appear to ameliorate encephalopathy;\textsuperscript{86} it was initially proposed that this effect resulted from normalization of the plasma BCAA/AAA ratio.\textsuperscript{43} However, BCAA infusions were subsequently shown to reduce brain tryptophan despite unaltered competition for transport.\textsuperscript{106} It is possible that modified solutions ameliorate HE as the result of reduced ammonia production and decreased peripheral release of AAA.\textsuperscript{106,107} Finally, modified solutions may reduce mortality in patients with HE.\textsuperscript{86,108} Although certain purported benefits of modified solutions remain controversial, most authorities agree that BCAA facilitate nutritional support in patients who exhibit protein intolerance with standard solutions. The reader is referred to several reviews for a more comprehensive discussion of this topic.\textsuperscript{102,103,109–111}

Enteral hepatic formulas are available in the USA as NutriHep (Nestle Clinical Nutrition, Deerfield, IL) or Hepatic Aid II (McGaw, Santa Anna, CA). NutriHep contains 50% BCAA, 2.4% AAA, and 1.5 cal/mL; with supplemented vitamins and electrolytes. Hepatic Aid contains 46% BCAA, 1.87% AAA, and 1.2 cal/mL; it is vitamin and electrolyte free. Hepatamine is the only parenteral hepatic solution available in the USA; it contains 36% BCAA, 3% AAA, and 56% essential amino acids. Hepatic solutions are approximately six times more expensive than standard formulas.

Specific Recommendations

Guidelines for nutritional support of patients with liver disease were recently provided by the European Society for Parenteral and Enteral Nutrition (ESPEN).\textsuperscript{112} Caloric requirements for patients with HE approximate 25-30 non-protein kcal • kg\textsuperscript{-1} • IBW\textsuperscript{-1} • d\textsuperscript{-1}. The Harris-Benedict equation may also be used to estimate energy requirements; stress factors of 1.2–1.4 have been advocated to obtain an estimate of the resting energy expenditure. However, a significant variation in energy expenditure is found among patients with liver failure.\textsuperscript{113,114} Muller et al. observed that 18% of the cirrhotic patients they studied were hypermetabolic whereas 31% were hypometabolic; a greater loss of muscle and body cell mass was noted in those who were hypermetabolic. This wide variance in energy expenditure makes the use of stress factors unreliable in predicting caloric requirements. A more accurate determination may be obtained using indirect calorimetry; resting energy expenditure X 1.3 is recommended as an estimate of total energy expenditure.\textsuperscript{112} Non-protein calories in parenteral nutrition may be apportioned as 65-50% carbohydrate and 35-50% fat. Intravenous lipid should not be infused at rates greater than 1 g • kg\textsuperscript{-1} • d\textsuperscript{-1} because hypertriglyceridemia and immunosuppression may ensue.\textsuperscript{115,116} Triacylglycerol levels should be monitored routinely in patients receiving parenteral nutrition; levels less than 350 mg/dL (3.95 mmol/L) are acceptable.\textsuperscript{117} Although it is theoretically possible that lipid solutions can worsen HE by virtue of displacing tryptophan from binding sites on albumin,\textsuperscript{118} an adverse effect has not been confirmed.\textsuperscript{119} Fat malabsorption of 10-30 g/d may be seen in approximately 50% of cirrhotics;\textsuperscript{120} provision of lipid as medium chain triacylglycerols may decrease steatorrhea.\textsuperscript{121}

Patients with hepatic failure have increased protein requirements.\textsuperscript{69–71} However, the amount of exogenous protein necessary to maintain positive nitrogen balance varies depending on the severity of underlying stress. The approach of limiting protein in patients with low-grade HE can be criticized based on absence of controlled studies of protein restriction, as well as improvement in mental status in some patients with tube feeding.\textsuperscript{122,123} Patients with grade 1-2 HE can initially receive 20-30 g (or vegetable protein) diets or tube feeding using standard enteral formulas. Central or peripheral parenteral nutrition can be used to completely support patients in whom enteral feeding is contraindicated, or to supplement enteral nutrition in those with mild-to-moderate gastrointestinal dysfunction. Protein may be initiated at 0.5–0.6 g • kg\textsuperscript{-1} • d\textsuperscript{-1} and then advanced by 0.25–0.50 g • kg\textsuperscript{-1} • d\textsuperscript{-1} until the target level is reached; progression to grade 2 HE occurs. Target doses of 1.0–1.5 g • kg\textsuperscript{-1} • d\textsuperscript{-1} are reasonable, with the higher values intended for the more hypercatabolic patient.\textsuperscript{112} In the protein intolerant patient, a modified high BCAA solution can be substituted or added as a supplement (other precipitating events such as infection should be excluded before the patient is deemed protein intolerant). Alternatively, some clinicians reduce the protein dose, continue lactulose and other supportive measures, and subsequently rechallenge the patient after several days. In patients who present with grade 3-4 HE, the author’s preference is to initiate feeding with a modified solution rather than restricting protein; dosing of protein is similar to grade 1-2 HE. Although there is not a clear consensus that modified solutions improve HE, there is little evidence to suggest that it is worsened. In addition, the ability to provide needed protein is of obvious benefit. Many encephalopathic patients receiving hepatic formulas improve by one grade within 48–72 h of beginning the infusion.\textsuperscript{123}

Micronutrient deficiency occurs in 10–50% of cirrhotics.\textsuperscript{120,124} It is more commonly seen in those with alcoholic liver disease. The major etiologies include: poor dietary intake, malabsorption, reduced metabolism of certain vitamins by the cirrhotic liver, increased requirements, and renal losses of trace elements. Deficiencies in fat soluble vitamins (A, D, E, and K) should be considered in patients with cholestatic liver disease, fat malabsorption, chronic alcoholism, or in patients taking certain drugs (e.g., neomycin, cholestyramine). Measurement of levels of vitamin A and D has been recommended before supplementation.\textsuperscript{125} Requirements for vitamin K can be indirectly assessed by measuring the prothrombin time. Deficiencies in water-soluble vitamins may also occur, particularly in the alcoholic. Thiamine, folate, and cyanocobalamin are most often involved.\textsuperscript{126} Administration of a multivitamin preparation plus additional thiamine in the alcoholic is reasonable.

Zinc deficiency is the most common trace element abnormality in patients with liver failure.\textsuperscript{127,128} Zinc may have an important role in cerebral function; it is released with membrane depolarization and modulates a variety of receptors (e.g., glutamate, GABA, benzodiazepine).\textsuperscript{127} Synthesis of urea is also felt to be reduced by zinc deficiency.\textsuperscript{129} Cirrhotics exhibit excessive urinary zinc losses that may predispose to deficiency. Several studies have demonstrated benefit of zinc supplementation on HE;\textsuperscript{127,128} however, others have failed to show benefit.\textsuperscript{128,130} Zinc supplementation in HE is typically dosed at 600 mg/d orally (as zinc acetate or zinc sulfate). Both zinc and vitamin A supplementation may indirectly influence nutritional status by improving the sense of taste. Deficiencies of selenium and chromium have also been described during liver failure, but the clinical implications and efficacy of supplementation requires further investigation.\textsuperscript{127,131}

Nutritional Considerations in Fulminant Hepatic Failure

Patients with fulminant hepatic failure exhibit impaired gluconeogenesis and depleted glycogen stores with a tendency to develop hypoglycemia. These patients are often markedly catabolic and are at high risk for developing malnutrition. Urinary amino acid losses may be profound; deficits may be further exacerbated by artificial liver support systems.\textsuperscript{123} Cerebral edema is usually present in patients with grade 3-4 HE that places...
NUTRITIONAL SUPPORT IN HEPATIC ENCEPHALOPATHY

Patients with fulminant liver failure appear to be able to adequately clear parenteral lipid emulsions.13

ACKNOWLEDGMENT

The author would like to acknowledge Dr. Richard A. Hawkins for his assistance in preparing the manuscript.

REFERENCES

acid in CSF of man: effects of cirrhosis of the liver and propranolol administration. J Neurol Neurosurg Psychiatry 1975;38:222
55. Kabudi UM. Is hepatocyte glycogen content a regulator of glucagon secretion? Metabolism 1992;41:113
75. Marsano L, McClain CJ. Nutrition and alcoholic liver disease. JPN 1991;15:337
228


103. Fischer JE. Branched-chain-enriched amino acid solutions in patients with liver failure: an early example of nutritional pharmacology. JPEN 1990;14(suppl):249S


120. Muller MJ. Malnutrition in cirrhosis. J Hepatol 1995;23(suppl 1):31


NUTRITIONAL SUPPORT IN HEPATIC ENCEPHALOPATHY