CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will be alert for hepatic encephalopathy early in the course of cirrhosis

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Hepatic encephalopathy: Suspect it early in patients with cirrhosis

ABSTRACT

As viral hepatitis and nonalcoholic fatty liver disease continue to increase in prevalence, we will see more cases of hepatic encephalopathy. Primary care physicians are often the first to suspect it, as they are familiar with the patient's usual mental and physical status. This serious complication typically occurs in patients with severe comorbidities and requires multidisciplinary evaluation and care.

KEY POINTS

Hepatic encephalopathy should be considered in any patient with cirrhosis who presents with neuropsychiatric manifestations in the absence of another brain disorder, such as stroke or brain tumor.

"Minimal" hepatic encephalopathy may not be obvious on clinical examination but can be detected with neurophysiologic and neuropsychiatric testing.

Every cirrhotic patient is at risk; potential precipitating factors should be addressed during regular clinic visits.

Management requires prompt identification of precipitating factors and initiation of empiric medical therapy. Current treatments include drugs to prevent ammonia generation in the colon.

Long-acting benzodiazepines should not be used to treat sleep disorders in patients with cirrhosis, as they may precipitate encephalopathy.

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Hepatic encephalopathy is a serious but often reversible complication that arises when the liver cannot detoxify the portal venous blood (**TABLE 1**).[1]

Prompt identification and treatment are essential, because once overt encephalopathy develops the prognosis worsens rapidly. Thus, internists and other primary care physicians who care for patients with severe liver disease play a key role in identifying the condition. They will often see the patients when hepatic encephalopathy is in its early stages and its neuropsychiatric manifestations—reduced attention, diminishing fine motor skills, or impaired communication—are subtle. Since primary care physicians see patients over a longer span of time, they are more likely to recognize these subtle changes.

PROPOSED PATHOGENETIC FACTORS

About 5.5 million cases of chronic liver disease and cirrhosis were reported in the United States in 2001. Hepatic encephalopathy is becoming more common as the prevalence of cirrhosis increases,[2] and this will have important economic repercussions; in 2001, charges from hospitalizations because of hepatic encephalopathy were estimated at $932 million.[3]

Hepatic encephalopathy develops as cirrhosis progresses or as a result of portosystemic shunting, so that the liver cannot detoxify the portal venous blood. Several neurotoxins (notably ammonia) and inflammatory mediators play key roles in its pathogenesis, inducing low-grade brain edema and producing a wide

TABLE 1

Classification of hepatic encephalopathy

Type A
Encephalopathy associated with acute liver failure

Type B
Encephalopathy with portosystemic bypass and no intrinsic hepatocellular disease

Type C
Encephalopathy associated with cirrhosis

Type D
Encephalopathy associated with disorders of the urea cycle

spectrum of neuropsychiatric manifestations.[4] Yet its pathogenesis is not entirely understood, impeding advances in its diagnosis and therapy.

Several hypotheses about the pathogenesis of hepatic encephalopathy have emerged in the last few years, and a number of factors are reported to directly or indirectly affect brain function in this condition. Ammonia and glutamine are the neurotoxins most often implicated in this syndrome[5]; others include inflammatory mediators, certain amino acids, and manganese.[5,6]

In cirrhosis, the prognosis worsens rapidly once encephalopathy develops

Ammonia causes brain swelling

Ammonia is primarily the byproduct of bacterial metabolism of protein and nitrogenous compounds in the colon and of glutamine metabolism in enterocytes.[7]

Normally, gut-absorbed ammonia is delivered via the portal vein to the liver, where most of it is metabolized into urea, leaving a small amount to be metabolized in the muscles, heart, brain, and kidneys. In cirrhosis and other conditions associated with hepatic encephalopathy, less ammonia is metabolized into urea and more of it reaches the astrocytes in the brain. The brain lacks a urea cycle but metabolizes ammonia to glutamine via glutamine synthase, an enzyme unique to astrocytes.

Ammonia causes swelling of astrocytes and brain edema via generation of glutamine, an osmotically active substance.

Glutamine causes swelling, oxidative stress

Glutamine draws water into astrocytes and induces changes of type II astrocytosis (also called Alzheimer type II astrocytosis)[5] characterized by swelling, enlarged and pale nuclei, and displacement of chromatin to the periphery of the cell. Inhibition of glutamine synthase prevents astrocyte swelling in animals.[8]

Glutamine also enhances the activation of several receptors, including *N*-methyl-D-aspartate (NMDA) receptors,[9,10] gamma-aminobutyric acid (GABA) receptors, and peripheral-type benzodiazepine receptors on the mitochondrial membrane.[10–12] A state of oxidative stress ensues, and this affects oxidation of protein and RNA, neurotransmitter synthesis, and neurotransmission at the neuronal junction.[13] Reactive nitrogen and oxide radicals induce the release of inflammatory mediators such as interleukins 1 and 6, tumor necrosis factor, interferons, and neurosteroids, and contribute to edema and neurotoxicity.[6,10] Neurosteroids are byproducts of mitochondrial metabolism of steroid hormones in the astrocyte.

Manganese enhances neurosteroid synthesis

Manganese enhances neurosteroid synthesis via activation of translocator proteins on the astrocyte membrane. It was first recognized as a factor in hepatic encephalopathy when cirrhotic patients experiencing extrapyramidal symptoms were found to have deposits of manganese in the caudate nucleus and in the globus pallidus on magnetic resonance imaging (MRI). Such deposits were also seen in specimens of brain tissue on autopsy of these patients. When the encephalopathy resolved, so did the abnormalities on MRI.[14,15]

Changes in the blood-brain barrier

Astrocytes contribute to the selective permeability of the blood-brain barrier. Disruptions in the permeability of the blood-brain barrier underlie hepatic encephalopathy, with poor diffusion of molecules out of astrocytes.

For instance, zinc, which plays a regulatory role in gene transcription and synaptic plasticity, accumulates in the astrocytes, causing relative zinc deficiency and further affecting neurotransmitter synthesis and neurotransmission at the neuronal synapse.[6,16]

Hyponatremia

Hyponatremia (a serum sodium concentration < 130 mmol/L) is increasingly being recognized as an independent predictor of overt hepatic encephalopathy and is reported to increase the risk by a factor of eight.[17]

Neuronal dysfunction

Astrocytes are integral to the physiologic functioning of the neurons, and it is becoming clear that both neurons and astrocytes are affected in hepatic encephalopathy.

Additionally, neuroinflammation and a decrease in energy metabolism by the brain are described during episodes of hepatic encephalopathy.[18]

Amino acid imbalance

An imbalance between aromatic amino acids (ie, high levels of tyrosine and phenylalanine) and branched-chain amino acids (leucine, isoleucine, and valine) has been linked with encephalopathy in patients with liver disease,[19–21] but it is not totally clear whether this imbalance contributes to hepatic encephalopathy or is a consequence of it.

Low-grade brain edema

Edema of the brain occurs in all forms of hepatic encephalopathy, but in cirrhosis it is characteristically of low grade. The mechanism behind this low-grade edema is not clear. Studies have shown that swelling of astrocytes is not global but involves certain areas of the brain and is associated with compensatory extrusion of intracellular myoinositol.[22] This, in combination with a mild degree of brain atrophy[23] observed in patients with chronic liver disease, is thought to keep the brain from extreme swelling and herniation, a phenomenon usually seen in acute hepatic failure.[24,25]

Transjugular intrahepatic portosystemic shunting and encephalopathy

The incidence rate of hepatic encephalopathy after placement of a portosystemic shunt to treat portal hypertension ranges from 30% to 55% and is similar to the rate in cirrhotic patients without a shunt.[26] In 5% to 8% of patients, the hepatic encephalopathy is refractory and requires intentional occlusion of the shunt.[26,27] An elevated serum creatinine level appears to be a risk factor for refractory hepatic encephalopathy in patients with a portosystemic shunt.[26]

In one study,[28] when transjugular intrahepatic portosystemic shunting was done early in the treatment of cirrhotic patients with acute variceal bleeding, the rates of treatment failure and death were significantly less than in a control group that received endoscopic therapy, and no significant difference was noted in the rate of encephalopathy or of serious adverse effects between the groups.

Whether to place a portosystemic shunt in a patient with cirrhosis and a history of hepatic encephalopathy depends on the possible underlying causes of the encephalopathy. For example, if encephalopathy was precipitated by variceal bleeding, shunt placement will prevent further bleeding and will make a recurrence of encephalopathy less likely. However, if the encephalopathy is persistent and uncontrollable, then shunt placement is contraindicated.[27]

A SPECTRUM OF SYMPTOMS

The spectrum of symptoms extends from a subclinical syndrome that may not be clinically apparent (early-stage or "minimal" hepatic encephalopathy) to full-blown neuropsychiatric manifestations such as cognitive impairment, confusion, slow speech, loss of fine motor skills, asterixis, peripheral neuropathy, clonus, the Babinski sign, decerebrate and decorticate posturing, seizures, extrapyramidal symptoms, and coma.[4] The clinical manifestations are usually reversible with prompt treatment, but recurrence is common, typically induced by an event such as gastrointestinal bleeding or an infection.

Neuroinflammation and decreased energy metabolism in the brain have been noted in hepatic encephalopathy

Minimal hepatic encephalopathy is important to recognize

Although this subclinical syndrome is a very early stage, it is nevertheless associated with higher rates of morbidity and can affect quality of life, including the patient's ability to drive a car.[29,30]

Abnormal changes in the brain begin at this stage and eventually progress to more damage and to the development of overt clinical symptoms.

TABLE 2

West Haven Grading System

Grade 0
Minimal hepatic encephalopathy, no asterixis, no detectable change in behavior or in mental status

Grade 1
Decreased attention span, altered mood, and sleep disturbance

Grade 2
Lethargy, confusion, slurred speech, asterixis

Grade 3
Somnolence and stupor but arousable, confusion, disorientation to time and place, clonus, nystagmus, positive Babinski sign

Grade 4
Coma

FROM FERENCI P, LOCKWOOD A, MULLEN K, TARTER R, WEISSENBORN K, BLEI AT. HEPATIC ENCEPHALOPATHY—DEFINITION, NOMENCLATURE, DIAGNOSIS, AND QUANTIFICATION. FINAL REPORT OF THE WORKING PARTY AT THE 11TH WORLD CONGRESSES OF GASTROENTEROLOGY, VIENNA, 1998. WITH PERMISSION FROM JOHN WILEY AND SONS, PUBLISHERS.

TABLE 3

Glasgow Coma Scale

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

ADAPTED FROM INFORMATION IN TEASDALE G, JENNETT B. ASSESSMENT OF COMA AND IMPAIRED CONSCIOUSNESS. A PRACTICAL SCALE. LANCET 1974; 2:81–84.

The PSE test is validated in Europe for the diagnosis of minimal hepatic encephalopathy, but not in the United States

The exact prevalence of minimal hepatic encephalopathy is not known because it is difficult to diagnose, but reported rates range between 30% and 84% of patients with cirrhosis.[31] Progression from minimal to overt hepatic encephalopathy is 3.7 times more likely than in patients without the diagnosis of minimal hepatic encephalopathy.[32]

Thus, minimal hepatic encephalopathy is important to identify,[29] so that treatment can be started.

Overt encephalopathy and survival

The prevalence of overt encephalopathy in cirrhosis ranges from 30% to 40% and is even higher in the advanced stages. Once encephalopathy develops, the prognosis worsens rapidly. In patients who do not undergo liver transplantation, the survival rate at 1 year is 42%, and the survival rate at 3 years is 23%.[33]

These rates are worse than those after liver transplantation, and the American Association for the Study of Liver Diseases recommends that patients with cirrhosis who develop a first episode of encephalopathy be considered for liver transplantation and be referred to a transplantation center.[34]

CHALLENGES IN DIAGNOSIS

Since the symptoms of hepatic encephalopathy are not specific and can be subtle in the early stage, its diagnosis may be a challenge. It is important to recognize that this neuropsychiatric complication occurs in people with severe comorbidities and requires dedicated time for evaluation and management.

Special tests may be needed to detect subclinical hepatic encephalopathy

In subclinical hepatic encephalopathy, the apparent lack of manifestations poses a great diagnostic challenge, but a thorough history may uncover poor social interaction, personality changes, poor performance at work, and recent traffic violations or motor vehicle accidents. Primary care physicians are usually the first to suspect the condition because they are familiar with the patient's baseline mental and physical conditions.

For example, the primary care physician may notice decreased attention and worsening memory during a follow-up visit, or the physician may ask whether the patient has difficulty with work performance and handwork (psychomotor

and fine motor skills), and whether there have been traffic violations or car accidents (visuospatial skills). Such clues, although not restrictive, may help identify patients with minimal hepatic encephalopathy and prompt referral for neuropsychiatric testing.

Neurologic deficits described in the subclinical form are in the domains of attention and concentration, working memory, visuospatial ability, and fine motor skills; communication skills remain intact.[35] These deficits are not reliably detected on standard clinical evaluation but can be detected by neuropsychiatric and neurophysiologic testing.

While several tests for minimal hepatic encephalopathy have been developed, they need to be validated in large trials in the United States.

Neurophysiologic tests include electroencephalography and auditory or visual event-related P300 (evoked potential) testing.

Neuropsychiatric tests traditionally involved several batteries administered and interpreted by specialized personnel. They were time-consuming and were not practical in a typical office setting. They were later refined into the Psychometric Hepatic Encephalopathy Score test (ie, the PSE syndrome test).[36] This combines a digit symbol test, a serial dotting test, a line-tracing test, and a number-connection or figure-connection test. An abnormal result in at least three of the four subtests constitutes an overall abnormal PSE syndrome test.

The PSE syndrome test has been validated for standard use in Germany, Spain, Italy, the United Kingdom, and India.[35] In 1999, the Working Group on Hepatic Encephalopathy designated it as the official test for minimal hepatic encephalopathy.[1] But the test has not been validated for use in the United States. Other tests have been developed, but their use is also limited by a lack of validation and by copyright laws. These factors constitute major obstacles to the diagnosis of subclinical hepatic encephalopathy in the United States. Nonetheless, physicians who suspect minimal hepatic encephalopathy may start lactulose therapy[37] and schedule frequent follow-up visits to address and manage potential precipitating factors for overt hepatic encephalopathy.

TABLE 4

Precipitating factors in hepatic encephalopathy

Acidosis, alkalosis
Constipation
Diuretic use, dehydration
Gastrointestinal bleeding
Hyponatremia
Infection
Protein excess
Renal decompensation
Sedative use
Trauma

Staging the severity of the encephalopathy

When symptoms are overt, staging should be done to define the severity of the disease. The most commonly used staging scales are the West Haven Grading System (TABLE 2)[38] and the Glasgow Coma Scale (TABLE 3).[39]

It is essential to exclude stroke, cerebral bleeding, and brain tumor before making a diagnosis of a first episode of hepatic encephalopathy. Thereafter, such exclusion must be guided by whether the patient has risk factors for these conditions or persistent symptoms of encephalopathy that do not respond to medical therapy.

Symptoms often resolve if precipitating factors are treated (TABLE 4). The most common precipitating factors include infections, dehydration, drug toxicity, and variceal bleeding.

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Laboratory tests can identify metabolic derangements

Although laboratory tests are not diagnostic for hepatic encephalopathy, they can identify metabolic derangements that could contribute to it.

Blood ammonia levels are often measured in cirrhotic patients suspected of having hepatic encephalopathy, but this is not a reliable indicator, since many conditions and even prolonged tourniquet application during blood-drawing can raise blood ammonia levels (TABLE 5).

Imaging can help exclude other diagnoses

Conventional imaging studies of the brain, ie, computed tomography and MRI, are use-

TABLE 5

Conditions that may cause elevated ammonia levels

Bacterial overgrowth (may be seen in proton pump inhibitor intake and atrophic gastritis)
Citrullinemia
Drug toxicity (valproic acid)
Extreme exercise
Fulminant hepatic failure
High-protein meals
Inherited disorders of urea cycle
Poor assay technique—eg, prolonged use of a tourniquet, blood specimen not transported on ice
Portosystemic shunting
Reye syndrome
Zinc deficiency

ful only to exclude a stroke, a brain tumor, or an intracranial or subdural hematoma. They may identify changes in the white matter and deposits of manganese in the basal ganglia in patients with cirrhosis with or without subclinical hepatic encephalopathy, but they are not likely to show low-grade brain edema.[40]

Neurophysiologic imaging studies such as magnetic resonance spectroscopy, magnetic transfer imaging, and water-mapping techniques have helped elucidate pathologic mechanisms of hepatic encephalopathy and are available in research centers, but they are not currently considered for diagnosis.

Every cirrhotic patient is at risk of encephalopathy; address precipitating factors during regular clinic visits

SEVERAL LINES OF TREATMENT

Treatment of hepatic encephalopathy involves a preemptive approach to address potential precipitating factors, medical therapy to reduce the production and absorption of ammonia from the gut, and surgical or interventional therapies. A multidisciplinary approach for testing the severity of neurologic impairment and response to therapy is needed to help determine if and when liver transplantation is required.

Prevent potential precipitating factors

An important concept in managing hepatic encephalopathy is to recognize that every cirrhotic patient is at risk and to make an effort to address potential precipitating factors during regular clinic visits. This includes reviewing medication dosing and adverse effects, emphasizing abstinence from alcohol and other toxic substances, and preventing bleeding from esophageal varices with endoscopic band ligation.

Diet therapy

The prevalence of malnutrition in cirrhosis may be as high as 100%. Vitamin and nutritional deficiencies should be evaluated by a nutrition specialist, and nutritional needs should be reassessed on a regular basis. Protein restriction is no longer recommended and may even be harmful.

Guidelines of the European Society of Parenteral and Enteric Nutrition in 2006 recommended that patients with liver disease should have an energy intake of 35 to 40 kcal/kg of body weight daily, with a total daily protein intake of 1.2 to 1.5 mg/kg of body weight.[41] Frequent meals and bedtime snacks are encouraged to avoid periods of prolonged fasting and catabolism of muscle protein and to improve nitrogen balance. Branched-chain amino acids and vegetable protein supplements are suggested to help meet the daily requirements.[42]

Drug therapy to reduce neurotoxins

Drug treatment is directed at reducing the neurotoxins that accumulate in cirrhosis. A variety of agents have been used.

Lactulose (Kristalose) is approved by the US Food and Drug Administration (FDA) as a first-line treatment. It has been shown to improve quality of life and cognitive function in patients with cirrhosis and minimal hepatic encephalopathy, although it has failed to improve mortality rates.[37]

Lactulose, a cathartic disaccharide, is metabolized by colonic bacteria into short-chain fatty acids. The acidic microenvironment has three major effects:

- It aids the transformation of ammonia to ammonium ($NH4^+$), which is then trapped in the stool, leaving less ammonia to be absorbed
- It has a cathartic effect

- It reduces the breakdown of nitrogenous compounds into ammonia.[43]

Lactulose has an excessively sweet taste. Its side effects include flatulence, abdominal discomfort, and diarrhea. The usual oral dose is 15 to 45 mL/day given in multiple doses to induce two to three soft bowel movements daily. At this dosage, the monthly cost varies between $60 and $120.

Lactilol, a nonabsorbable disaccharide, is as effective as lactulose but with fewer side effects. It is not available in the United States.

Rifaximin (Xifaxan), a derivative of rifamycin, is FDA-approved for the maintenance of remission of hepatic encephalopathy but is not recommended as a first-line agent. It inhibits bacterial RNA synthesis in the gut. Less than 0.4% of an oral dose is absorbed.[44]

In a randomized, double-blind, placebo-controlled trial in patients who had had at least two episodes of hepatic encephalopathy while on lactulose therapy, taking rifaximin 550 mg twice a day for 6 months provided a prolonged remission from recurrences of encephalopathy compared with placebo.[45] Side effects included nausea, vomiting, abdominal pain, weight loss, and *Clostridium difficile* colitis, which was reported in two cases in the study.[45]

Unfortunately, the effects of this drug beyond 6 months of therapy have not been studied. In addition, the drug is expensive: 1 month of treatment with rifaximin can cost between $700 and $1,500. Combining lactulose and rifaximin adds to the costs and the side effects, and contributes to poor adherence to therapy.

Other antibiotics such as metronidazole (Flagyl), vancomycin, and neomycin have been used as alternatives to lactulose, based on the principle that they reduce ammonia-producing bacteria in the gut. However, their efficacy in hepatic encephalopathy remains to be determined.

In controlled trials, neomycin combined with sorbitol, magnesium sulfate, or lactulose was as effective as lactulose, but when used alone, neomycin was no better than placebo.[46,47] Neomycin was approved many years ago as an adjunct in the management of hepatic coma, but it has since fallen out of favor in the management of hepatic encephalopathy because of poor trial results and because of neurotoxicity and ototoxicity.

Branched-chain amino acids (leucine, isoleucine, and valine)[48] are reported to increase ammonia intake in muscle and to improve cognitive functions on the PSE scale in minimal hepatic encephalopathy,[49,50] but they did not decrease the rate of recurrence of hepatic encephalopathy.[51] While debate continues over their efficacy in the management of hepatic encephalopathy, branched-chain amino acids may be used to improve nutritional status and muscle mass of patients with cirrhosis. However, the dosing is not standardized, and long-term compliance may be problematic.

Other medical therapies include zinc,[16] sodium benzoate,[50] and L-ornithine-L-aspartate[52,53] to stimulate residual urea cycle activities; probiotics (which pose a risk of sepsis from fungi and lactobacilli); and laxatives.

Liver dialysis

Adsorbing toxins from the blood via liver dialysis or using a non-cell-based liver support system such as MARS (Molecular Adsorbent Recirculating System, Gambro, Inc.) appears to improve the amino acid profile in hepatic encephalopathy, but its role has not been clarified, and its use is limited to clinical trials.[54,55]

Transjugular intrahepatic shunts and large portosystemic shunts may need to be closed in order to reverse encephalopathy refractory to drug therapy.[26,27,56]

Liver transplantation

The current scoring system for end-stage liver disease does not include hepatic encephalopathy as a criterion for prioritizing patients on the transplantation list because it was originally developed to assess short-term prognosis in patients undergoing transjugular intrahepatic shunting. As a consequence, patients with end-stage liver disease are at increased risk of repeated episodes of encephalopathy, hospital readmission, and death. Therefore, the American Association for the Study of Liver Diseases recommends referral to a transplantation center when the patient experiences a first episode of overt hepatic encephalopathy to initiate a workup for liver transplantation.[34]

Liver transplantation improves survival in patients with severe hepatic dysfunction, but the presence of neurologic deficits may result in significant morbidity and in death.[57,58] Af-

The reversibility of neurologic impairment after transplantation depends on pretransplant neurologic deficits, age, and alcohol intake

ter transplantation, resolution of cognitive dysfunction, brain edema, and white-matter changes have been reported,[59] but neuronal cell death and persistent cognitive impairment after resolution of overt hepatic encephalopathy are also described.[60–63]

Whether neurologic impairment will resolve after liver transplantation depends on a number of factors: the severity of encephalopathy before transplantation; the nature of the neurologic deficits; advanced age; history of alcohol abuse and the presence of alcoholic brain damage; persistence of portosystemic shunts after transplant; emergency transplantation; complications during surgery; and side effects of immunosuppressive drugs.[57,58,64]

The optimal timing of liver transplantation is not clearly defined for patients who have had bouts of hepatic encephalopathy, and more study is needed to determine the reversibility of clinical symptoms and brain damage. It is in these situations that neuropsychiatric testing and advanced neuroimaging can help determine the efficacy of therapeutic interventions, and it should be considered part of the pretransplantation evaluation.

Managing sleep disturbances

Insomnia and other changes in sleep-wake patterns are common in patients with cirrhosis, especially advanced cirrhosis.[65] It is not known whether these changes represent early stages of hepatic encephalopathy.[66] Patients often complain of fatigue, the need for frequent naps, and lethargy during the day and restlessness and inability to sleep at night. This affects the patient's behavior and daytime functioning, and it also burdens household members and caregivers.

Long-acting benzodiazepines should be avoided when treating sleep disorders in cirrhosis because they may precipitate the encephalopathy. In a randomized controlled trial, hydroxyzine (Vistaril) at a dose of 25 mg at bedtime improved sleep behavior in 40% of patients with cirrhosis and subclinical hepatic encephalopathy, but 1 of 17 patients developed acute encephalopathy, which reversed with cessation of the hydroxyzine.[66] Clearly, caution and close monitoring are required when giving hydroxyzine for sleep disorders in cirrhotic patients.

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