REVIEW ARTICLE

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Hepatic Encephalopathy

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When the liver fails, brain function changes. Acute-on-chronic liver failure is manifested initially as abnormal behavior and compromised cognition. In the absence of preexisting disease, acute, severe liver failure may cause the brain to swell, with patients becoming comatose and losing brain function altogether. Hepatic encephalopathy in patients with chronic liver disease is potentially reversible and manageable, but new, acute (fulminant) hepatic encephalopathy with rapidly rising blood ammonia levels is more difficult to control because of diffuse brain edema and structural brain-stem injury.

Although the onset of hepatic encephalopathy can rarely be pinpointed clinically, it is a clinical landmark in patients with advanced liver disease, invariably signaling a worsening medical condition. Severe hepatic encephalopathy in patients with cirrhosis is associated with a mortality of more than 50% in the first year alone.[1,2] Hepatic encephalopathy in patients with cirrhosis does not decisively limit eligibility for liver transplantation, although patients often die while they are on the waiting list for a transplant.[3] Similarly, among patients with fulminant hepatic failure, progression from acute hepatic encephalopathy to brain edema is associated with a high mortality. The rate of death is substantially lower for patients who receive a transplant. The survival rate is more than 70% in the first 5 years after transplantation,[4] although only one of five patients with fulminant hepatic failure receives a transplant.[5]

Hepatic encephalopathy is not diagnosed and graded exclusively by specialists in chronic liver failure. Patients may first see a general practitioner, an emergency physician, or a hospitalist. These practitioners may consult the neurologist (or neurointensivist) for a detailed assessment of presumptive hepatic encephalopathy, to rule out treatable mimicking disorders, and in fulminant forms, to manage brain edema. This review addresses the manifestations, diagnosis, and in-hospital management of acute hepatic encephalopathy from the neurologist's perspective.

Hepatic Encephalopathy and Hyperammonemia

The pathogenesis of hepatic encephalopathy has been incompletely understood since the first neuropathological descriptions of the disorder.[6] Concepts explaining the pathophysiological features have been discussed elsewhere,[7,8] and Figure 1 shows a potential pathway. Rapidly progressive hepatic encephalopathy in patients with fulminant hepatic failure is a clinical syndrome associated with cerebral edema.

Colonic bacteria and mucosal enzymes break down digested protein, releasing ammonia from the gut. Ammonia enters the portal circulation of the liver and is converted to urea through the urea cycle. In cases of hepatic failure, ammonia accumulates and is shunted into the systemic circulation. Hyperammonemia results in neuronal dysfunction, leading to hepatic encephalopathy. Brain edema

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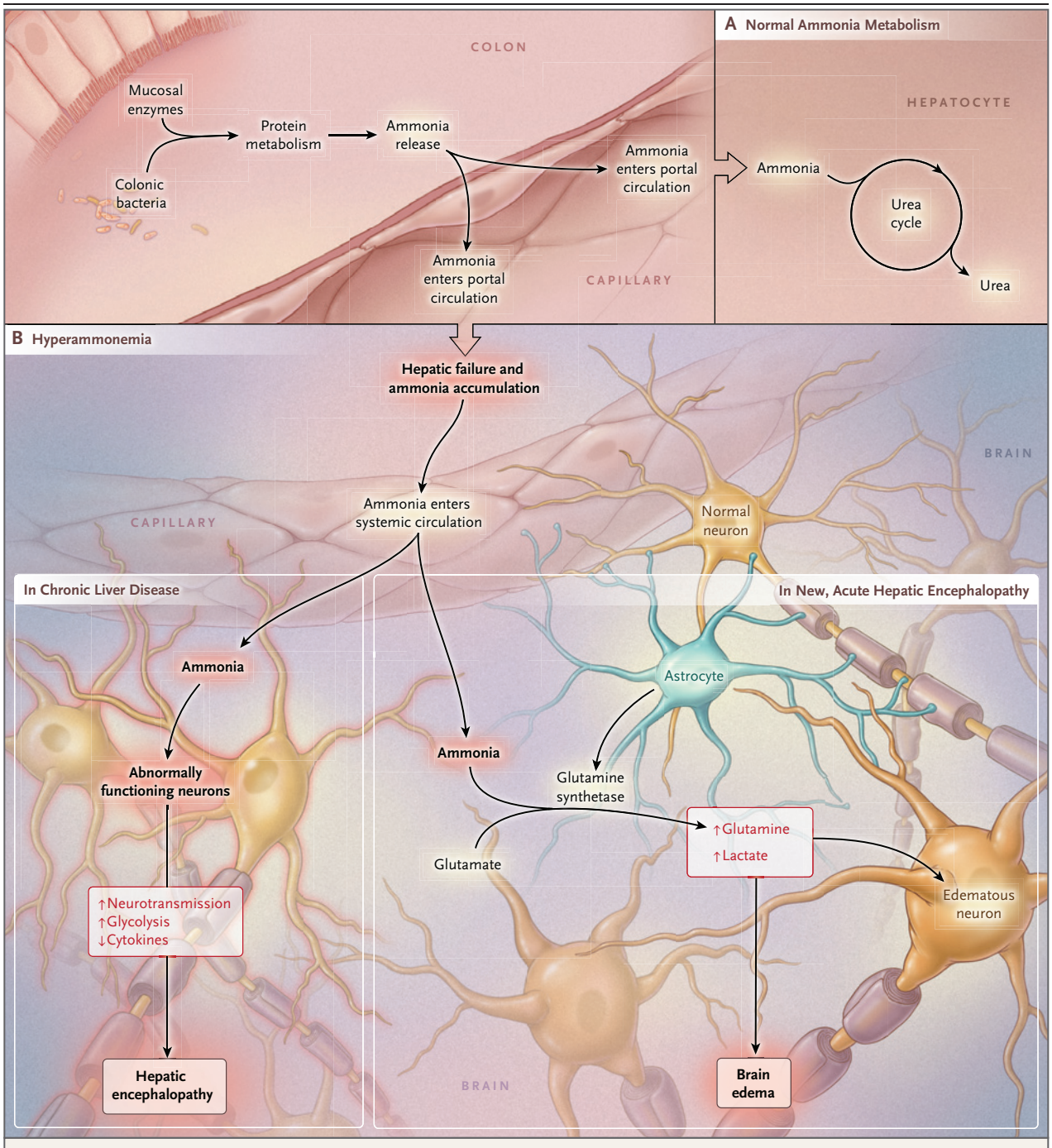

Figure 1. Putative Mechanisms Underlying Hepatic Encephalopathy and Brain Edema.

A potential pathway conceptualizes the pathophysiological features of hepatic encephalopathy and hyperammonemia.

may occur in conjunction with a rapid rise in ammonia levels, particularly in patients with no prior liver failure.[9] At high levels, ammonia can cross the blood–brain barrier, where astrocytic glutamine synthetase converts ammonia and glutamate into glutamine, which in turn acts as an osmolyte and increases cerebral volume.

Ammonia is one of many neurotoxic substances resulting in decreased excitatory neurotransmission.[10] The role of benzodiazepine re-

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ceptors in hepatic encephalopathy has been established. In a study of treatment with flumazenil, a γ-aminobutyric acid (GABA)–benzodiazepine receptor antagonist, patients had both clinical and electroencephalographic evidence of improvement, but the response rate was low and the responses were unsustained.[11] Moreover, the findings in some studies may have been confounded by prior administration of benzodiazepines.[12] The recent discovery that the neurosteroid allopregnanolone activates GABA type A ($GABA_A$) receptors, causing inhibition through a chloride-channel opening, has prompted efforts to develop agents that antagonize $GABA_A$ receptor–potentiating neurosteroids.[13] Another possible contributor to hepatic encephalopathy, particularly in patients with long-standing cirrhosis, is manganese toxicity, which appears on magnetic resonance imaging (MRI), especially on T_2-weighted imaging, as abnormalities in the globus pallidus.[14] Mercaptans, short fatty acids, decreased glutaminergic synaptic function, lactate, and dopamine metabolites have also been implicated.[13]

Neuroinflammatory responses can play a role if an intercurrent infection or sepsis is responsible for hepatic encephalopathy in patients with advanced liver disease. Inflammatory cytokines may enhance ammonia-induced neurotoxicity through the blood–brain barrier.[15] Microscopically, hyperammonemia may cause enlarged, pale (because of decreased chromatin) astrocytes (Alzheimer type II astrocytes) but only after long-term exposure and not in the context of fulminant hepatic failure.[6]

A video showing manifestations of hepatic encephalopathy is available at NEJM.org

The increase in serum ammonia levels remains central to our understanding of hepatic encephalopathy, and therapies remain directed toward lowering ammonia levels in patients with signs of hepatic encephalopathy. The correlation between serum ammonia levels and the severity of hepatic encephalopathy in patients with cirrhosis is monotonic but is not linear or exponential.[16] Long-term increases in serum ammonia levels may not necessarily lead to hepatic encephalopathy, and diuretic use or renal failure may play a role.[17] The correlation appears to be stronger in patients with fulminant hepatic failure, and the risk of cerebral edema increases with arterial ammonia levels that exceed 200 μmol per liter (340 μg per deciliter).

Emerging or worsening hepatic encephalopathy is a complication in 30 to 50% of patients with cirrhosis who undergo transjugular, intrahepatic portosystemic shunting.[18-20] Minimal hepatic encephalopathy before the procedure may progress to marked hepatic encephalopathy afterward, with a documented steep rise in venous ammonia levels.[21]

DEFINITION AND GRADING OF HEPATIC ENCEPHALOPATHY

CLINICAL FEATURES

Initially, the terms "hepatic coma" and "hepatic encephalopathy" were used interchangeably.[22-27] Sherlock and colleagues introduced the term "portal-systemic encephalopathy."[28] Hepatic encephalopathy and disturbance of consciousness had been noted in von Frerichs's classic work on liver disease.[29] Jaundice preceded the development of delirium, convulsions, and coma, as well as observed phases of "gloomy, irritable temper and restlessness," "quiet, harmless wandering," and "maniacal paroxysms." One third of the patients had convulsions; most of these patients had delirium and "progressed to a deep coma from which no shouting or shaking could arouse [them]."

A landmark clinicopathological study by Adams and Foley further delineated clinical symptoms and pathological changes in the brain and also introduced asterixis as a key observation.[6] The term "asterixis" (from the Greek *sterixis*, meaning "fixed position," with the prefix *a*, meaning "without") denoted an inability to keep outstretched arms and hands in place (see video, available with the full text of this article at NEJM.org).

Clinical features of hepatic encephalopathy can progress from mild to severe in patients with acute-on-chronic liver disease or acute liver disease. New-onset hepatic encephalopathy is syndromic but unpredictable in its manifestations. Reduced awareness of surroundings and stimuli, yawning, and dozing off are characteristic of the earlier stages, but new irritability and maniacal excitement have also been reported.[6,28] Hepatologists have graded the severity of hepatic encephalopathy according to the West Haven criteria[30] (Table 1) and, more recently, have identified covert hepatic encephalopathy in patients with no particular symptoms beyond abnormal behavior on psychometric tests.[32,33] Although covert hepatic encephalopathy is mild and occurs mostly in patients with cirrhosis, it is associated with

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frequent falls, incompetent driving, fatigue, disinterest, distraction, and serious socioeconomic consequences. Given its nonspecific nature, this low-grade encephalopathy may be indistinguishable from general malaise, frailty, and continual alcohol consumption, factors that potentially further compromise cognitive decline.[33]

Impairment of consciousness characterizes progression to grade 3 or 4 hepatic encephalopathy. Fluctuating attention and slow responses to requests are typical. Patients are incapable of the three features of memory: registration, retention, and recall. The immediate memory span for digits is markedly reduced. Overactivity and unrest, delusions, repetitive picking movements, and disorientation with respect to place become evident in grade 3 hepatic encephalopathy. There is progression to stupor, with minimal verbal output, and a noxious stimulus (unfortunately, with easy bruising) is often required to obtain a sustained response. At this stage, patients have tachypnea, with loss of the usual chemical control of breathing, often leading to respiratory alkalosis.[34] Grading of hepatic encephalopathy categorizes it in clinical stages of stepwise worsening. The description of each grade varies somewhat in the literature, but differences between adjacent grades are clear enough to be helpful in clinical practice, although neurologic descriptors are sparse. One study showed that for patients who become comatose, the Full Outline of Unresponsiveness (FOUR) score is more discriminating than the West Haven grading system because it includes brain-stem and respiration assessment, which are not further differentiated in the West Haven system[31,35] (Table 1).

In patients who have acute fulminant hepatic failure without chronic liver disease, the clinical development of hepatic encephalopathy is a more condensed process. Rigid extremities (and neck muscles) and resistance to passive movements (paratonia) are seen, as is worsening confusion. Extensor posturing, suggesting structural brain injury, characteristically occurs in grade 4 encephalopathy and may be completely reversible after correction of ammonemia. Grasp reflexes may be observed.[6]

The pupils of patients with early hepatic encephalopathy are normal, and the pupillary responses are preserved. In grade 3 or 4 encephalopathy, the pupillary reaction becomes sluggish and, because of diffuse cerebral edema, eventu-

Table 1. A Comparison of West Haven and FOUR Score Criteria for Grading Hepatic Encephalopathy.*

West Haven		FOUR Score				
Grade	Features	Score	Eye Response	Motor Response	Brain-Stem Reflex	Respiration
0	No abnormalities detected	4	Eyelids open or manually opened; tracking or blinking on command	Thumbs up, fist, or peace sign on command	Pupillary and corneal reflexes present	Not intubated, regular breathing
1	Unawareness (mild), euphoria or anxiety, shortened attention span, impairment of calculation ability, lethargy or apathy	3	Eyelids open but no tracking	Localized response to pain	One pupil wide and fixed	Not intubated, Cheyne–Stokes breathing
2	Disorientation to time, obvious personality change, inappropriate behavior	2	Eyelids closed but open to loud voice	Flexion response to pain	Pupillary or corneal responses absent	Not intubated, irregular breathing
3	Somnolence to stupor, responsiveness to stimuli, confusion, gross disorientation, bizarre behavior	1	Eyelids closed but open to pain	Extension response to pain	Pupillary and corneal responses absent	Breathing above ventilator rate
4	Coma	0	Eyelids remain closed to pain	No response to pain, or generalized myoclonus status	Pupillary, corneal, and cough reflexes absent	Breathing at ventilator rate or apnea

* Patients with minimal hepatic encephalopathy (grade 1 with the use of the West Haven criteria) would be classified as having covert hepatic encephalopathy. Patients with West Haven grade 2 or higher encephalopathy would be classified as having overt hepatic encephalopathy.[30,31] The FOUR (Full Outline of Unresponsiveness) score clinical grading scale takes into account four components of neurologic function. Scores range from 0 to 16, with lower scores indicating a lower level of consciousness.

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ally disappears as a consequence of progressive brain-stem injury. Pupil size is mostly unchanged in grade 1 or 2 encephalopathy, but the pupils enlarge and become midposition (3 to 5 mm) in grade 3 or 4 encephalopathy. Oculocephalic responses, although brisk, usually remain intact. Periodic lateral or dysconjugate gaze or a fixed dysconjugate gaze has been reported, which disappears after serum ammonia levels are reduced.

Jactitations (restless tossing and muscle or limb twitching) are common with progressive encephalopathy and may merge with multifocal myoclonus (see video). Abnormal movements such as dystonia, orofacial dyskinesias, and parkinsonian features may point to Wilson's disease, which in rare cases may be characterized by acute hepatic failure.[36]

ELECTROPHYSIOLOGICAL FEATURES

Generally, worsening hepatic encephalopathy is associated with major changes in the electroencephalographic (EEG) pattern, such as dyssynchronization of fast activity, increased dysrhythmicity, and slower delta activity followed by mixtures of slow-with-fast frequencies, more frequent delta activity, and disorganization.[24,37,38] Triphasic-wave patterns, defined as generalized, bilaterally synchronous, bifrontal periodic waves, are often associated with background slowing and appear in grade 2 or 3 hepatic encephalopathy but disappear in the comatose state.[39] These wave patterns are seen more often in patients with encephalopathy and subcortical brain atrophy than in patients with encephalopathy and no subcortical atrophy.[40] Once triphasic waves appear, the outcome worsens.[41] A recent study emphasized increased fast beta activity in patients with alcoholic liver disease and suppressed variability in patients with hepatic encephalopathy.[42] The role of evoked potentials in detecting covert hepatic encephalopathy for diagnosis or confirmation of hepatic encephalopathy has not been established, but brain-stem–evoked potentials are the most sensitive for detection of subclinical hepatic encephalopathy.[43-45] There is renewed interest in using spectral EEG to diagnose hepatic encephalopathy.[46,47]

It is unclear whether findings on EEG and evoked potentials help clinicians. The main practical use of EEG in assessing patients for hepatic encephalopathy is to rule out nonconvulsive status epilepticus.

MIMICKING DISORDERS

Wernicke–Korsakoff's syndrome, especially the amnestic state of Korsakoff's syndrome, may mimic hepatic encephalopathy. A global confusional state shares all the characteristics of early hepatic encephalopathy, including inattention, poor perceptional abilities, and irrational responses to questions, including a tendency to drift away from the topic. Confabulation (fabrication of answers or stories) is sometimes present early in Korsakoff's syndrome,[48] but an amnestic syndrome (anterograde amnesia) involving an inability to retain words, names, and tasks is invariably present. Wernicke's disease, known for ophthalmoplegia (lateral rectus paralysis and paralysis of horizontal or vertical conjugate gaze), gaze-evoked nystagmus, and ataxia, may be delayed. Patients with a history of alcohol abuse often receive intravenous thiamine soon after admission, which effectively treats the thiamine deficiency and makes Wernicke–Korsakoff's syndrome a less likely alternative explanation.

The features of acute alcohol-withdrawal delirium overlap those of worsening hepatic encephalopathy, but alcohol-withdrawal delirium, unlike hepatic encephalopathy, is characterized by coarse and rhythmic tremor, shouting, elided speech, and dysautonomia with cold sweats.[49] Neurologic findings are usually unremarkable.

New metabolic derangements reduce responsiveness and occur with dilutional hyponatremia, hypoglycemia, and metabolic alkalosis. The effect of these acute metabolic changes on clinical grading of hepatic encephalopathy is small because they are typically transient and rapidly corrected. Although hyponatremia can be severe, particularly in patients with acetaminophen toxicity, it is unlikely to confound the clinical examination in patients with chronically low sodium levels. However, sodium values have ranged from 110 to 147 mmol per liter in patients with hepatic encephalopathy.[50] A large reduction in sodium values is required to cause a change in responsiveness or a seizure. Conversely, aggressive correction (and overcorrection) of serum sodium levels (i.e., an increase of >8 mmol per liter in the first 12 hours) may lead to central pontine myelinolysis, particularly in patients with alcoholic hepatitis or cirrhosis.

Nonconvulsive status epilepticus has been described[51] but is a challenging diagnosis to establish. It requires specialized expertise in the inter-

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pretation of EEG findings because the triphasic-wave pattern that may be observed is somewhat similar to generalized periodic epileptiform discharges. This becomes particularly pertinent when triphasic waves are recorded in patients with hepatic encephalopathy who have altered consciousness and automatisms.

Chronic or acute subdural hematoma may mimic hepatic encephalopathy, except that focal signs are often present on neurologic examination. Alcohol addiction and chronic liver disease also increase the risk of subdural hematoma but not the risk of intracranial hemorrhage.[52,53]

TREATMENT

INITIAL THERAPY

The goal of initial management of hepatic encephalopathy is to reduce ammonia absorption from the intestinal lumen with the use of lactulose or lactilol. These nonabsorbable disaccharides have laxative effects and change the gut microbiome to non–urase-producing bacteria, reducing intestinal ammonia production.[54] Protein restriction is ill advised, since normal protein intake does not appear to exacerbate hepatic encephalopathy.[55,56] Guidelines recommend lactulose at a dose of 25 ml twice daily as a first-line agent, adjusted for the production of three bowel movements daily.[55] Intravenous L-ornithine–L-aspartate lowers ammonia levels by providing an alternative substrate for the urea cycle; its use is considered in patients who do not have a response to lactulose. For recurrent hepatic encephalopathy in patients with cirrhosis, rifaximin (550 mg twice a day), which alters gut microbiota, is added to lactulose; this combined treatment can reduce the frequency of hospitalization and prolong the time to a new bout of encephalopathy.[57] Probiotics (e.g., yogurts with lactobacillus or saccharomyces) have been shown to prevent or ameliorate hepatic encephalopathy in patients with cirrhosis.[58] Infection, which could precipitate gastrointestinal hemorrhage and dehydration, should be treated, and correction of hyponatremia and hypovolemia is warranted. Treatment may lead to impressive amelioration of symptoms; however, the clinical outcome often remains poor, with periods of worsening, partly because of poor adherence to medication regimens in cognitively incapacitated patients. Over time, the relationship between blood ammonia levels and the severity of hepatic encephalopathy becomes less clear, and intercurrent infections or other causes may be implicated.

SECOND-LINE TREATMENTS

For patients with hepatic encephalopathy and cirrhosis who do not have a response to standard treatments, large portosystemic shunts are considered. End-stage liver disease can be an indication for liver transplantation, and in the past 5 years, the system for allocating transplants has been refined. The Model for End-Stage Liver Disease (MELD) is used to determine disease severity. The MELD score is calculated as follows: $3.78 \times \ln(\text{serum bilirubin in milligrams per deciliter}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{serum creatinine in milligrams per deciliter}) + 6.43$, where ln is the natural logarithm and INR is the international normalized ratio for prothrombin time. Scores range from 6 to 40, with higher scores indicating more severe disease.[59] Once a patient has had a major-index complication (e.g., ascites, hepatic encephalopathy, or variceal hemorrhage) or has a MELD score higher than 15, transplantation is considered.[60] The current allocation system uses the MELD score plus the sodium level.

INTENSIVE CARE

Measures to reduce hyperammonemia, the main driver of brain edema, are instituted in patients presenting with acute liver failure and in those presenting with acute-on-chronic liver failure. Acute fulminant hepatic failure requires intensive care to manage hypovolemic or distributive shock and renal failure, as well as severe coagulopathy and thrombocytopenia, which are equally worrisome.[61] As soon as hepatic encephalopathy progresses to brain edema, management of increased intracranial pressure is urgent.[62-65]

A venous ammonia level of 150 to 200 μmol per liter (255 to 340 μg per deciliter) is a well-known risk factor for increased intracranial pressure in patients with fulminant hepatic failure. In one study, intracranial hypertension developed in 25% of patients with fulminant hepatic failure who had plasma ammonia levels of less than 250 μmol per liter (425 μg per deciliter).[66]

Assessment of fulminant hepatic failure involves a neurologic evaluation and careful scrutiny of the computed tomographic (CT) scan. Disappearance of sylvian fissures and sulci characterizes early brain edema; narrowing or full

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obliteration of the basal cisterns follows (Fig. 2). Diffuse brain edema causes coma with extensor posturing or no motor response to stimuli and, frequently, early brain-stem involvement with loss of pupillary responses and corneal reflexes. In patients with fulminant hepatic failure, abnormalities are clearly identifiable on the CT scan, but radiologic assessment can be difficult (Fig. 2). One study showed that half of patients with grade 4 or 5 hepatic encephalopathy had CT-scan abnormalities,[67] and in a study of acetaminophen toxicity with specific attention to differentiation between gray and white matter, 40% of patients had cerebral edema.[68] The true incidence of brain edema, with or without increased intracranial pressure, remains unknown. In some situations, brain edema and tonsillar herniation are present on autopsy (Fig. 3).

Intracranial pressure-monitor placement has been considered in several studies for management of acute liver failure. An intracranial hemorrhage rate of 10% was reported in one prospective cohort of 92 patients with grade 3 or 4 encephalopathy in whom intracranial pressure

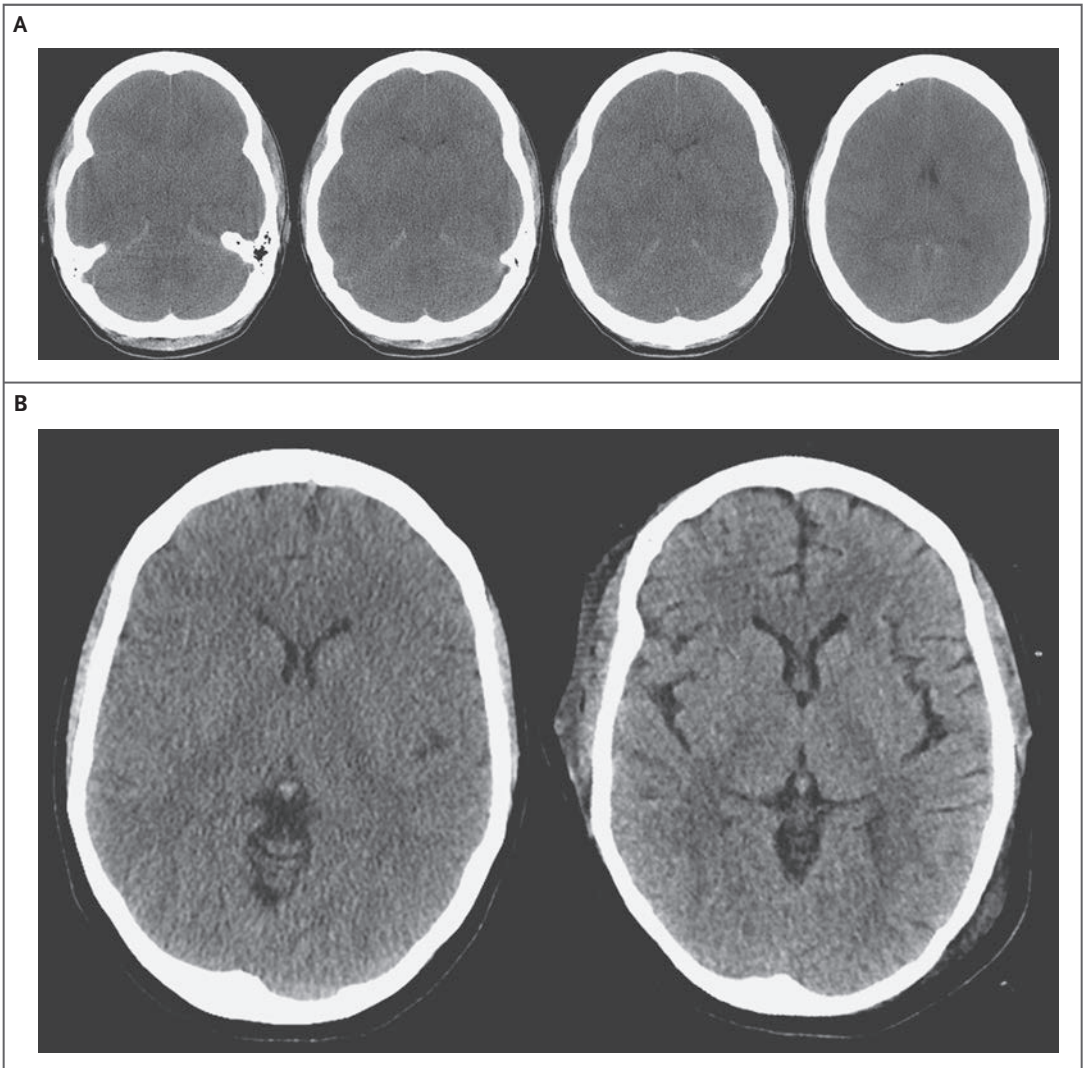

Figure 2. CT Findings in Fulminant Hepatic Failure.

In the CT scans shown in Panel A, in a patient with fulminant hepatic failure, the basal cisterns are absent, and there is loss of sulci and loss of differentiation between gray matter and white matter due to diffuse brain swelling. The CT scans in Panel B, obtained after mannitol administration in a young patient with acute hepatic failure and prior drug and alcohol use, are characterized by pseudonormal findings and show preexisting atrophy.

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monitors were implanted, but half of the patients with hemorrhages were asymptomatic.[69] More recent studies showed a 7% hemorrhage rate among 56 patients with intracranial pressure monitors[70] and showed that the frequency of hemorrhage depends on postimplantation imaging.[71] Correction of the INR with prothrombin-complex concentrate or recombinant activated factor VII can normalize the INR, but it may not fully correct the coagulopathy. Neurosurgeons recommend correction of the INR before monitor insertion, but prolonged control of the INR or thrombocytopenia is neither feasible nor necessary. Intracranial pressure monitoring is associated with a considerable risk of hemorrhage, and management without such monitoring has not been compared with management on the basis of CT-scan features and clinical examination. In fact, an intracranial pressure monitor is inserted in less than 15% of patients, and the proportion has declined in recent large cohorts.[5] Placement of an intracranial pressure monitor in a comatose patient with CT-scan evidence of brain edema should be strongly considered.

The best approach to managing increased intracranial pressure in patients with fulminant hepatic failure is not known, but for most intensivists managing brain edema, the goal is to reduce intracranial pressure to less than 20 mm Hg. Cerebral perfusion pressures may be increased because of poor cerebral autoregulation and may need to be limited to a range of 50 to 70 mm Hg. There is insufficient experience with multimodal monitoring (e.g., a combination of tissue oxygenation, intracranial pressure, and electrophysiological monitoring), and it is unclear whether this approach could provide more precise information on ongoing neuronal injury and improve the outcome. Treatment may include elevating the head of the bed to 30 degrees and avoiding patient–ventilator dyssynchrony with the use of short-acting sedatives. Induced hypocapnia (a decrease of 15 mm Hg or more in the carbon dioxide level), resulting in alkalotic cerebrospinal fluid, constricts pH-dependent precapillary resistance vessels, reducing cerebral blood volume and thus intracranial pressure. Spontaneous hyperventilation is common in comatose patients with fulminant hepatic failure, and it is not known whether an additional lowering of the partial pressure of arterial carbon dioxide, to 20 to 25 mm Hg, may lead to critically reduced cerebral blood flow.

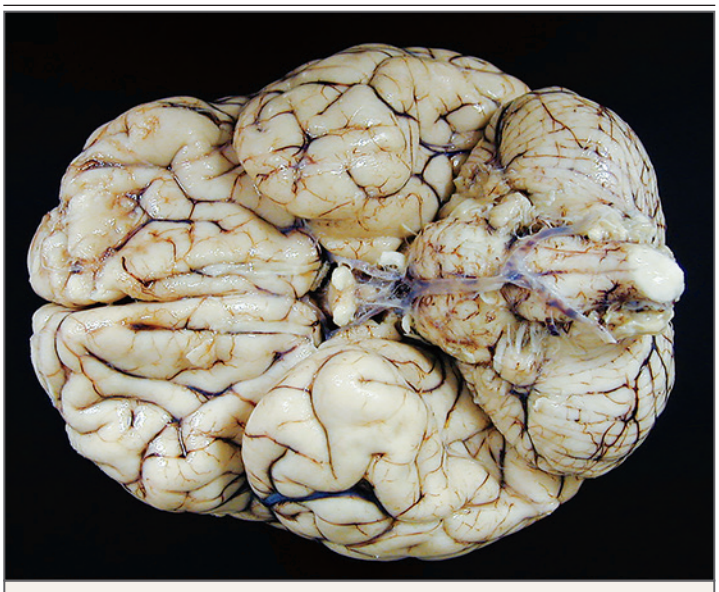

Figure 3. Gross Photograph of Brain Edema and Tonsillar Herniation in a Patient with Fulminant Hepatic Failure.

Therefore, in patients with evidence of cerebral edema on a CT scan, the best option is the administration of mannitol or a hypertonic saline bolus. A continuous hypertonic saline infusion lowers the osmotic gradient after the initial effect has passed, and it may be more difficult thereafter to change the gradient quickly with osmotic agents. One study used a prophylactic infusion of hypertonic saline (30%) in 15 patients, resulting in sodium levels of 145 to 155 mmol per liter and a sustained decrease in intracranial pressure, but this trial included patients receiving renal-replacement therapy, in whom the saline load depended on the hemofiltration rate.[72] Repeated administration of a bolus of 10 or 23% hypertonic saline in response to increased intracranial pressure may be a reasonable option.

Most intensivists favor adjunctive fever control. A randomized, controlled trial of targeted temperature management (34°C) to prevent intracranial pressure and acute liver failure did not prevent increased intracranial pressure, and the mortality rate in the targeted-temperature group was the same as the rate in the control group.[73] The data were confounded because the number of patients who underwent transplantation was lower in the targeted-temperature group. In most patients, intracranial pressure at onset was less

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than 27 mm Hg (up to 73% of patients with peak intracranial pressure in the mid-30s range).

Escalation to pentobarbital treatment before transplantation should probably be avoided because the neurologic examination will be confounded if a patient has no motor response and has possible involvement of brain-stem reflexes. If available, transcranial Doppler may indicate absent or reverberating flow, confirming increased intracranial pressure readings and avoiding transplantation in a brain-dead patient.

The molecular-adsorbent recirculating system (MARS), which dialyzes against a high-flux, albumin-coated polysulphone filter, is effective in preparing patients with fulminant hepatic failure for liver transplantation.[74,75] However, MARS therapy can potentially worsen coagulopathy and was tentatively associated with intracranial hemorrhage in one study.[74]

SUMMARY

Hepatic encephalopathy has Janus-faced characteristics, with clinical manifestations of chronically reduced neural metabolic function and acute cerebral edema. Hyperammonemia can be incriminated in both clinical scenarios, but other compounds contribute to them. Although cerebral edema in fulminant hepatic failure is largely cytotoxic, vasogenic components may play a role. Hyperemia as a result of increased cytokines may result in extracellular edema.[76,77] It raises the question of whether extracellular cerebral edema may occur in worsening hepatic encephalopathy associated with cirrhosis.[78,79] Increased apparent diffusion coefficient values on diffusion-weighted imaging in patients with varying degrees of cirrhosis indicate astrocyte swelling that correlates with venous ammonia levels.[80] Cerebral edema was seen on a CT scan in a patient with the terminal stage of cirrhosis.[81] A recent experimental study could not confirm brain edema in earlier stages of hepatic encephalopathy.[82]

Treatments for the two forms of acute encephalopathy also may differ. Lactulose or rifaximin can be beneficial for the treatment of gradual-onset encephalopathy in patients with prior cirrhosis, but additional, aggressive treatment of brain edema with osmotic diuretics is required in new, fulminant forms to prevent secondary, permanent brain-stem damage and to sustain patients through liver transplantation.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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