

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Neurologic Considerations and Complications Related to Liver Transplantation

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THE pathophysiology of liver failure is associated with multisystem derangement including metabolic disequilibrium, low systemic vascular resistance, hyperdynamic circulation, anemia, a rebalanced state of coagulation, and impaired cerebral autoregulation. Liver transplantation is the only definitive treatment for end-stage liver disease and, although outcomes after liver transplant continue to improve, the postoperative phase remains challenging for both patients and clinicians.¹ Perioperative organ injury, including injury to the brain, is a leading cause of death in the United States.² Compared to the transplantation of other solid organs, liver transplant is associated with a higher incidence of neurologic complications, which are reported to be between 9 to 42%³ and frequently accompanied by devastating morbidity and mortality.⁴ It is critical for the field of perioperative medicine to make advances toward the prevention and treatment of perioperative organ injury, in general, and for brain injury, in particular. Identifying patients at risk for neurologic complications is of vital importance for successful transplantation, may help stratify organ recipients, and has the potential to reduce perioperative risk. Here we present a review of the relevant literature to describe hepatic encephalopathy as a noteworthy consideration for transplant anesthesiologists as well as the incidence, pathophysiology, and prognosis of the major neurologic complications related to liver transplant surgery. We will describe both monitoring and preventive strategies for selected conditions across various phases of care.

Hepatic Encephalopathy

Overt hepatic encephalopathy has an incidence of between 30 to 45% in patients with cirrhosis and has a profoundly negative impact on patient survival, both with and without liver transplantation.⁵ Hepatic encephalopathy is the second most common reason for hospitalization for patients with cirrhosis and has an admission cost that is 30% greater than those associated with heart failure or chronic respiratory illness.⁶ Hepatic encephalopathy is potentially preventable and

is typically associated with a reversible spectrum of neuropsychiatric sequelae. The World Gastroenterology Organization classification of encephalopathy helps to guide specific therapy and is based on the etiology: type A, secondary to acute liver failure; type B, secondary to portosystemic shunting; and type C, secondary to cirrhosis with or without shunting.⁷ The West Haven Criteria are used to stage hepatic encephalopathy by the severity of symptoms: minimal, grade 0 through coma, grade 4. Even though this system is pragmatic in classifying the spectrum of encephalopathy and has prognostic significance, it is inaccurate in differentiating between minimal and no hepatic encephalopathy; psychometric testing may be required.

Ammonia, which is normally produced by intestinal bacteria (50%) and the kidney (40%), undergoes extensive first pass metabolism by the liver. A small amount is also cleared by skeletal muscle. The pathogenesis of hepatic encephalopathy and precipitating factors are described in figure 1. Portosystemic shunting, an important component of end-stage liver disease, contributes to the development of hepatic encephalopathy primarily because of the impaired first pass clearance of ammonia. Additionally, hyperammonemia is readily precipitated by systemic infection or inflammation in patients with cirrhosis.⁸ Ammonia easily crosses the blood brain barrier⁹ and is thought to induce hepatic encephalopathy *via* an increase in glutamine in astrocytes. An osmotic imbalance between the extracellular fluid and astrocytes ensues, with resultant astrocytic swelling. Ammonia also binds to γ -aminobutyric acid (GABA) receptors located on astrocytes, which in turn produce neurosteroids. Neurosteroids are potent agonists of GABA (A) receptors; dysregulation of inhibitory neurotransmission is thought to contribute to the manifestations of hepatic encephalopathy. Other causal factors include elevated plasma concentration of manganese, the generation of benzodiazepine-like and GABA-like substances, and impaired dopaminergic neurotransmission^{10–12} in the

This article is featured in "This Month in Anesthesiology," page 1A. Figure 1 was enhanced by Sara Jarret, C.M.I.

Submitted for publication October 12, 2017. Accepted for publication January 29, 2018. From the Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan.

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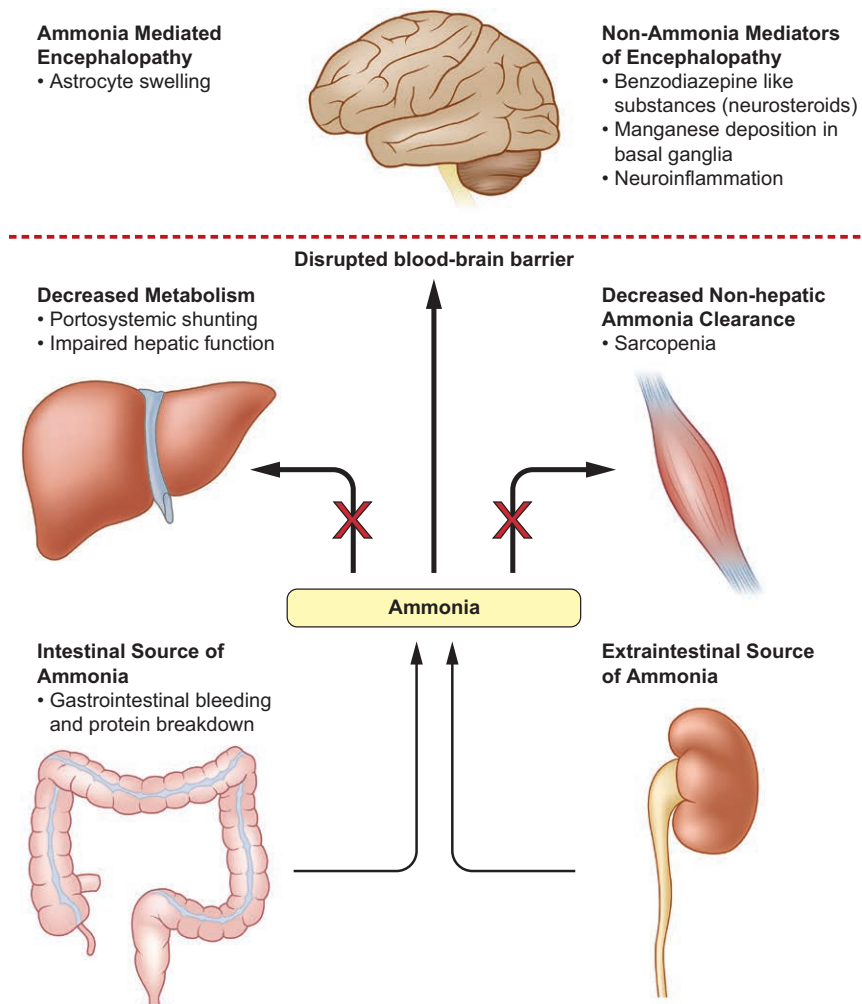


Fig. 1. Major determinants of hepatic encephalopathy.

brain. Diminished hepatic clearance of manganese results in changes to astrocyte morphology and function, which can lead to hepatic encephalopathy.¹³ If uncorrected, hepatic encephalopathy may persist within the postoperative phase. Any neuroinflammatory process could also be generated or exacerbated by transplant related hypoxia-reperfusion; hypoxia increases the expression of nuclear factor kappa-light-chain-enhancer of activated B cells and causes disruption of vascular integrity, potentially exacerbating cerebral edema and brain injury.¹⁴ Acute phase proteins and inflammatory markers like C-reactive protein and β -amyloid have also been implicated as a cause for altered mental status and may contribute.⁸

Acute fulminant hepatic failure occurs as a result of severe hepatocellular dysfunction and also results in encephalopathy. Although this presentation is uncommon, it is associated with a mortality of between 50 to 90% despite appropriate critical care.¹⁵ The neurologic manifestations include cerebral edema, with cerebral herniation being a frequent cause of death. The pathogenesis of elevated intracranial pressure is thought to be related

to the cytotoxic effects of ammonia, glutamine, and cytokines, as well as disruption of the blood brain barrier. Aquaporin-4, a water channel, has also been implicated.¹⁶ Computed tomography may be unreliable for the detection of cerebral edema in this patient population; invasive monitoring may be required to diagnose elevated intracranial pressure and guide treatment.¹⁷

Neurologic Complications after Liver Transplantation

Seizures

Seizures after liver transplant are common and debilitating. The reported incidence of first-onset presentation ranges between 3 to 42%, and exhibits a bimodal distribution with increased events occurring during the first week and between 5 to 16 weeks after transplantation. There is a higher incidence of seizures (33%) in patients who receive two or more transplants.¹⁸ The etiology of seizures is multifactorial and includes metabolic causes, drugs, hypoxia, infection, and structural lesions in the

brain. Generalized seizures are more common; focal seizures should prompt the search for a structural lesion. The metabolic derangements frequently associated with seizure pathogenesis after liver transplant include hypomagnesemia, hypocalcemia, and hyponatremia.¹⁹ Calcineurin inhibitors (cyclosporine, tacrolimus) used for immunosuppression are neurotoxic and commonly implicated; seizures related to immunosuppression have a better prognosis than other etiologies.²⁰ For drug-induced etiologies, diagnosis is usually by exclusion, with cessation of seizures after altering the dose or discontinuing the drug. In general, status epilepticus is more common in pediatric patients than adult recipients. Tranexamic acid, used for the treatment of fibrinolysis, can cause seizures in higher concentration by competitive inhibition of glycine receptors. This leads to inhibition of N-methyl-D-aspartate glutamatergic receptors, as well as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate subtypes of ionotropic glutamate receptors.²¹ Glycine is a co-agonist of N-methyl-D-aspartate receptors, and inhibition of glycine binding sites by tranexamic acid results in the adverse side effects noted in higher concentrations of the drug.

Osmotic Demyelination Syndromes

Central pontine myelinolysis is a disorder of osmotic demyelination, has a reported incidence of 17% after liver transplant²² and can be devastating. Improvements in radiologic techniques now also allow for the diagnosis of subclinical forms of the condition. Metabolic acidosis due to the impaired conversion of lactate to bicarbonate, impaired

serum sodium homeostasis, impaired glucose homeostasis, and insulin resistance are key factors that may contribute to the development of demyelination-related neurologic complications after liver transplantation.²³ Lesions are classically described within the pons (fig. 2A), but extrapontine lesions occur in 10% of cases. The widespread application of Model of End-stage Liver Disease sodium (MELD-sodium) scoring systems has resulted in an increased number of patients presenting for liver transplantation with significant hyponatremia. A clear survival benefit has been shown in patients with MELD scores greater than 11 and hyponatremia, supporting this approach.²⁴ Central pontine myelinolysis is a serious neurologic condition associated with poor prognosis and protracted clinical course.²⁵ It most typically occurs when serum sodium is elevated at a rate greater than 1 to 2 mEq/h or more than 12 mEq per 24 h. Patients with high MELD scores, those who require massive resuscitation, and those with large fluctuations in serum sodium are at higher risk for the development of central pontine myelinolysis.²⁵ In addition, other causes of hyperosmolality, such as hyperglycemia,²⁶ can cause pseudohyponatremia and osmotic demyelination in the absence of true perturbations of serum sodium. Central pontine myelinolysis can present independently of sodium concentrations; tacrolimus has been associated with the radiologic and clinical features of central pontine myelinolysis without changes in serum sodium.

Posterior Reversible Encephalopathy Syndrome

The reported incidence of posterior reversible encephalopathy syndrome ranges from 0.5 to 7%.^{4,27} Presenting features

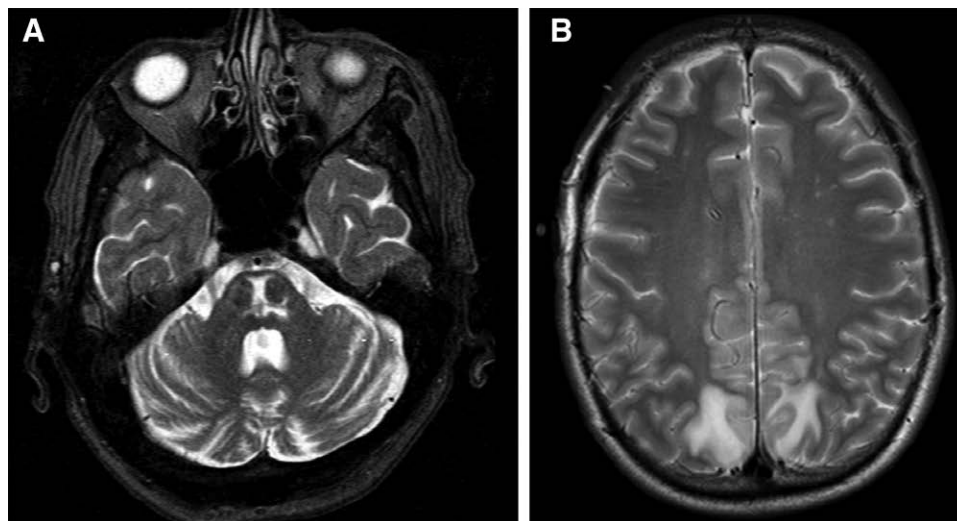


Fig. 2. (A) Magnetic resonance imaging of a patient who presented with progressive mental status decline, tremor, and hyponatremia between postoperative day 3 and 8 after orthotopic liver transplantation. The findings reveal patchy foci of T2 hyperintensity with associated restricted diffusion in the central and peripheral pons and are consistent with central pontine myelinolysis. (B) Magnetic resonance imaging of a patient who underwent orthotopic liver transplantation for acute liver failure and developed seizures after commencement of immunosuppression. The seizures were refractory to conventional treatment and alteration of immunosuppressive medications. T2 weighted images acquired during this period reveal symmetrical hyperintensity in the parietal-occipital cortices bilaterally, which is consistent with posterior reversible encephalopathy syndrome.

include reversible confusion, headache, visual disturbances, seizures, loss of consciousness, paresthesia, insomnia, and tremor. In the acute phase, vasogenic edema in the subcortical parietal-occipital white matter is the classic feature (fig. 2B) and best demonstrated with magnetic resonance imaging. Calcineurin inhibitors²⁸ are directly causal in liver transplant recipients. The differential diagnosis includes progressive multifocal leukoencephalopathy and central pontine myelinolysis. Rarely, cyclosporine is associated with cortical blindness due to leukoencephalopathy.²⁹

Other Neurologic Complications

Tremor or involuntary movements have an incidence of 30% in liver transplant recipients³⁰ and, in general, are primarily related to the neurotoxic effects of immunosuppressive agents. In patients with preexisting tremor, the amplitude may be increased after liver transplant with subsequent negative impact on quality of life.³¹ A characteristic form of speech apraxia consistent with pathology of left frontotemporoparietal regions of the brain has been described in a case series with a reported incidence of 1% in liver transplant recipients.³² Protein-calorie malnutrition, as well as vitamin and micronutrient deficiencies (B12, folate, and niacin) are well recognized in liver transplant recipients, and are associated with neuropsychiatric and a wide array of neurodegenerative conditions including Wernicke encephalopathy, Korsakoff syndrome, and cirrhosis-related Parkinsonism.³³

Predictors of Neurologic Complications

Identifying and understanding the risk factors and predictors of neurologic complications is important for risk stratification and, with appropriate intervention, may help to improve morbidity and mortality related to liver transplant. The most notable pretransplant associations with postoperative neurologic complications are infection, hepatic encephalopathy, malnutrition, renal insufficiency, and hyponatremia. Additionally, coagulopathy, high MELD score, the presence of alcoholic or metabolic liver disease, and the requirement of pretransplant mechanical ventilation have been incorporated into predictive models used to stratify risk for the occurrence of postoperative neurocognitive complications.³⁴ A retrospective study of 227 consecutive liver transplant surgeries found infection in the week prior to transplant to be an independent predictor of posttransplant neurologic complications, which included encephalopathy and ischemic stroke, although the exact pathophysiology of this process is unclear.³⁰ Bacterial infection, in particular, is associated with poor neurologic outcome and the risk of central nervous system infection in patients with preexisting bacterial infection is high. The requirement for immediate posttransplant immunosuppression may account for further dissemination of subclinical infections. In a recent single-center case control study, 295 adult liver transplant

recipients were evaluated to identify risk factors for early neurologic complications. Almost half of these patients exhibited neurologic complications within the first 30 days after surgery. The risk factors included recipient age younger than 29 or 60 yr or older, along with body mass index less than or equal to 21.6 or greater than or equal to 27.6 kg/m², hepatic encephalopathy, psychiatric disorder, seven-day tacrolimus level greater than or equal to 8.9 ng/ml, and intra-abdominal infection.³⁵

Monitoring Options

Once risk factors are identified, the application of appropriate monitoring to help guide clinical care is important. Cerebral autoregulation is an important protective mechanism in the brain that can be impaired in patients undergoing liver transplantation, particularly those presenting with fulminant liver failure.¹⁷ When cerebral autoregulation is impaired during other surgeries (*e.g.*, during cardiac bypass), it is associated with increased risk of stroke.³⁶ In the setting of disrupted autoregulation, blood flow to the brain is dependent on systemic pressure; during the intraoperative phase of liver transplant, hypotension is common and thus, cerebral hypoperfusion is likely frequently encountered. Since cerebral perfusion pressure equals mean arterial pressure minus intracranial pressure, clinicians can attempt to measure cerebral perfusion through a combination of an arterial catheter and an intracranial pressure monitor. Other techniques, such as transcranial Doppler or near-infrared spectroscopy, can provide surrogates of cerebral blood flow and oxygenation, respectively. Finally, electroencephalography provides functional information on the perfusion to the brain. Numerous challenges in measuring, monitoring, and optimizing cerebral perfusion remain.

Despite its numerous limitations, near infrared spectroscopy is a noninvasive tool for the measurement of regional cerebral oxygenation that may one day help to predict postoperative neurologic complications, with implications for preventive strategies. During liver transplantation, cerebral oximetry has been used to demonstrate impaired cerebral autoregulation, cerebral deoxygenation during the anhepatic phase, and hyperoxygenation after reperfusion of the donor graft.³⁷ It is unknown, however, whether or not strategies designed to mitigate changes in cerebral oximetry have any impact on any outcome after liver transplant. Invasive intraparenchymal intracranial pressure monitoring is useful in the setting of acute liver failure to help guide treatment and optimize cerebral perfusion, and has been recommended for patients with grade 3 or 4 hepatic encephalopathy.³⁸ There is, however, considerable variation between centers for the placement of invasive intracranial pressure monitors; benefits must be balanced against considerable risks especially for coagulopathic patients. The risk of intracranial hemorrhage ranges between 5 to 22%,³⁹ but protocol-driven insertion can be safely achieved and may positively impact outcomes

particularly for the subset of patients with cerebral edema.⁴⁰ In addition to cerebral monitoring modalities, acid-base status, electrolytes, blood glucose levels, and viscoelastic testing should be employed.

Prevention and Treatment Options

Optimizing pretransplant nutritional status is a simple intervention to improve posttransplant neurologic outcome. Screening for infectious and inflammatory processes along with the evaluation of neurologic status is also important. The main focus of treatment for hepatic encephalopathy is to reduce the ammonia load with oral nonabsorbable disaccharides (lactulose, lactitol) and antibiotics (rifaximin).^{10,11} Central α_2 agonists may also be helpful; in a recent randomized controlled study in patients undergoing liver transplantation, patients who received dexmedetomidine compared to controls demonstrated a decrease in β -amyloid and τ proteins, which have been linked to hepatic encephalopathy, as well as a reduced incidence of postoperative agitation and altered mental status.⁴¹

For patients with elevated intracranial pressure, elevation of the head of the bed, the maintenance of low central venous pressure and adequate cerebral perfusion pressure, as well the selection of anesthetic agents which minimize cerebrovascular dilation (*e.g.*, total intravenous anesthesia with propofol), are logical choices.⁴²

In cardiac surgery, the use of tranexamic acid is associated with a fourfold increase in the rate of seizures,⁴³ particularly when higher doses are used (30 mg/kg bolus followed by 15 mg \cdot kg⁻¹ \cdot h⁻¹ infusion). Although administration of tranexamic acid for liver transplant recipients appears safe,⁴⁴ use should be supported by clinical

and laboratory evidence of hyperfibrinolysis. Newer anticonvulsants (*e.g.*, levetiracetam or lacosamide) can be safely used to treat seizures due to calcineurin inhibitors. Long-term anticonvulsant therapy is not typically required.

Maintaining normal electrolyte balance and preventing the rapid correction of sodium are logical goals in the prevention of osmotic demyelination. Goal-directed coagulation management using viscoelastic testing may help to avoid unnecessary sodium containing blood products.⁴⁵ Intraoperatively, the use of coagulation factor concentrates to facilitate the avoidance of sodium containing plasma products, is reported to be safe.⁴⁶ During liver transplantation, shifts in plasma sodium concentration are significantly greater when sodium bicarbonate is used as an exogenous buffer; tromethamine may be used as an alternative and is not associated with changes in serum sodium concentration.⁴⁷ Recent changes in organ allocation based on MELD-sodium and the national shortage of tromethamine have increased the risk of fluctuations in serum sodium in patients presenting for transplantation, and simultaneously reduced the therapeutic options available. Tolvaptan, a vasopressin receptor (V2) antidiuretic hormone receptor antagonist, is effective for the treatment of hyponatremia in patients with cirrhosis,⁴⁸ but treatment must be started in the evaluation phase when the normalization of serum sodium will decrease the MELD-sodium score and may become an inadvertent barrier to transplantation. The use of continuous renal replacement therapy in patients with severe hyponatremia may help maintain sodium stability in the perioperative period.⁴⁹

The first line treatment of posterior reversible encephalopathy syndrome includes: (1) dose reduction or alteration of immunosuppression; and (2) systemic blood pressure

Table 1. Neurologic Complications after Liver Transplant

Condition	Etiology	Monitoring and Diagnosis	Treatment/Prevention
Hepatic encephalopathy	Ammonia Benzodiazepine-like substance Manganese Fulminant hepatic failure	Clinical evaluation Neuroimaging Consider intracranial pressure monitoring if elevated intracranial pressure	Reduction in ammonia load (lactulose, rifaximin) Reduce intracranial hypertension Optimize cerebral perfusion pressure and oxygenation
Seizures	Immunosuppression Infection Metabolic causes Structural lesions	Monitoring levels of immunosuppression Screening for infections Metabolic screening including electrolytes Neuroimaging	Conservative management Anticonvulsants Modification of immunosuppressive regimen Correct metabolic derangement Antimicrobials Judicious use of antifibrinolytics
Posterior reversible encephalopathy syndrome	Calcineurin inhibitors	Repeated clinical evaluation Monitoring levels of immunosuppression Neuroimaging	Modification of immunosuppressive regimen
Osmotic demyelination	Hyperosmotic states Rapid fluctuations in plasma sodium levels	Clinical evaluation Plasma sodium Plasma glucose Neuroimaging	Controlled plasma sodium correction: No greater than 1–2 mEq/h or 12 mEq/24 h Minimize sodium load Goal directed coagulation management Factor concentrates Avoid sodium bicarbonate as buffer

control. The prompt withdrawal of cyclosporine has resulted in improved speech for patients presenting with cortical apraxia and speech disorders after liver transplantation.³²

In terms of diagnostic testing, diffusion tensor imaging tractography may be more sensitive than magnetic resonance imaging in delineating white matter tracts, as well as differentiating between osmotic demyelination and other pathologies.⁵⁰ Future research may suggest a specific role for tractography in both diagnosis and prognosis for patients presenting with neurologic complications after liver transplantation.

Conclusions

Outcomes after liver transplantation have significantly improved, but central nervous system complications remain common and are frequently not considered by anesthesiologists. Although mostly transient, neurologic complications after liver transplant can be devastating. To improve outcomes and prevent, identify, and treat neurologic complications, risk stratification and regular standard neurologic examination are recommended in the perioperative period (table 1).

Hepatic encephalopathy is an important risk factor and is associated with neurologic complications after liver transplantation; elevated plasma ammonia concentration from portosystemic shunting, infection, or inflammation is a critical causal factor. New-onset seizures are very common after liver transplantation and are often caused by neurotoxicity related to immunosuppressive medications; this etiology has a better long-term prognosis compared to seizures from other causes. The survival benefit for patients with low sodium has led to significant changes to the organ allocation system for potential liver transplant recipients; the perioperative management of the plasma sodium concentration is now vital. Impaired cerebral autoregulation can be associated with cerebral hypoperfusion and ischemia; future research to evaluate cerebral blood flow, cerebral autoregulation, cerebral oxygenation, and cerebral metabolism in patients with end-stage liver disease and, more specifically, during liver transplantation is of great importance. Hypoxia and inflammation are interlinked and targeting the signaling mechanisms for hypoxia is a potential future treatment strategy. The current evidence is based on basic science, retrospective studies, and poorly standardized prospective investigations. Future work targeting the use of new drugs to reduce the known mediators of hepatic encephalopathy is of importance, and the quest continues for immunosuppressive agents that are not associated with neurotoxicity. It is critically important that anesthesiologists collaboratively engage to evaluate effective monitoring of the brain for liver transplant recipients, as well as interventions to mitigate and treat neurologic complications within this population.

Acknowledgments

The authors would like to thank Jennifer Lucaj, B.A., University of Michigan Department of Anesthesiology, Ann Arbor, Michigan, for help developing Figure 1.

Competing Interests

The authors declare no competing interests.

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