Neurological Complications Occurring After Liver Transplantation: Role of Risk Factors, Hepatic Encephalopathy, and Acute (on Chronic) Brain Injury

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Orthotopic liver transplantation (LT) remains the only way to definitively cure patients with the most severe liver diseases. Because the survival rate is now fairly high, important questions about neurological sequelae or quality of life after LT have emerged. Indeed, LT represents a peculiar situation because up to 30% of patients present with neurological symptoms after LT compared with only 4% after cardiac transplant and 0.5% after renal transplant. These postoperative neurological symptoms have long been interpreted as sequelae of hepatic encephalopathy (HE). However, postoperative decompensation of an unknown cerebral condition due to the pathophysiology of cirrhosis or undiagnosed neurodegenerative disorders or aging constitute other possibilities that are underrecognized. Some patients who undergo LT for acute liver failure and patients with cirrhosis without episodes of HE and without any previous cerebral alteration also display post-LT neurological symptoms. This latter situation speaks in favor of a direct adverse effect of either general anesthesia, the surgical procedure, or factors related to the postoperative intensive care unit (ICU) environment. The role of inflammation, which has been described in the ICU setting, could also be a crucial determinant. In this review, we will discuss the neurological complications associated with LT, the neurocognitive complications after LT, and how to assess the LT-related neurological or neurocognitive complications. Furthermore, we will review the various hypotheses surrounding post-LT neurocognitive impairment and will conclude with recommendations for future directions.

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Orthotopic liver transplantation (LT) is the only definitive cure for patients with the most severe acute liver failure (ALF) and cirrhosis.[1,2] The most frequent causes of ALF are over-the-counter acetaminophen ingestion, nonacetaminophen drug-induced liver injury, acute viral hepatitis (hepatitis A, B, and E viruses), and, less frequently, an acute flare of autoimmune hepatitis, acute Budd-Chiari syndrome, or an infection due to *Herpesviridae*. Because of both improvements in diagnostic strategies and to the aging of the population, the incidence of cirrhosis is increasing every year. In addition to excessive alcohol intake, viral infections (hepatitis B, C, D, and E viruses), autoimmune diseases, and metabolic syndrome, which is responsible for nonalcoholic steatohepatitis (NASH), represent the other etiologies.[2] Recent modifications in the management of classical complications of cirrhosis,[3] namely, upper-gastrointestinal bleeding or ascites, have improved the prognosis. These include the broad use of transjugular intrahepatic portosystemic

Abbreviations: ^{1}H-MRS, proton magnetic resonance spectroscopy; ALF, acute liver failure; ALFF, amplitude of low frequency fluctuation; Chol, choline; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CNS, central nervous system; Cr, creatine; CT, computed tomography; DMN, default mode network; DTI, diffusion tensor imaging; EBV, Epstein-Barr virus; EEG, electroencephalogram; FA, fractional anisotropy; FLAIR, fluid low attenuation inversion recovery; Glx, glutamate; Glu, glutamine; HCV, hepatitis C virus; HE, hepatic encephalopathy; HEV, hepatitis E virus; HHV, human herpesvirus; HSV, herpes simplex virus; ICAN, Institut de Cardiométabolisme et Nutrition; ICU, intensive care unit; IHU-A-ICM, Institut Hospitalo-Universitaire-A-Institut du Cerveau et de la Moelle; LT, liver transplantation; mI, myoinositol; MD, mean diffusivity; MELD, Model for End-Stage Liver Disease; MHE,

shunt (TIPS) along with the development of direct antiviral agents.

Survival after LT is now high, with 85% at 1 year and 75% at 5 years.[4] Important questions about neurological sequelae or quality of life have emerged since survival after LT increased. Indeed, LT represents a peculiar situation because up to 30% of patients present with neurological complications after LT compared with only 4% after cardiac transplant and 0.5% after renal transplant.[5-8]

Because most patients with cirrhosis display neurological symptoms primarily due to hepatic encephalopathy (HE) before LT, it has been suggested that the sequelae of neurological complications are only a consequence of HE. However, patients who undergo LT for ALF and patients with cirrhosis without episodes of HE prior to LT also exhibit post-LT neurological symptoms. This latter situation speaks in favor of a direct adverse effect of either the causal disease, an undiagnosed condition, general anesthesia, surgical procedure, or factors related to the postoperative intensive care unit (ICU) environment.[9-11] The role of inflammation, which has been described in the ICU setting, could also be a crucial determinant.[12-15]

We will successively discuss in this review the neurological complications of LT, the neurocognitive complications after LT, and how to assess neurological or neurocognitive complications of LT. In addition, we will review the hypotheses surrounding post-LT neurocognitive impairment and will conclude with recommendations for future directions.

minimal hepatic encephalopathy; MMS, minimental state; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTR, magnetization transfer ratio; NAA, N-acetylaspartate; NASH, nonalcoholic steatohepatitis; ODS, osmotic demyelination syndrome; PET, positron emission tomography; PRES, posterior reversible encephalopathy syndrome; PT, prothrombin time; ROI, region of interest; TIPS, transjugular intrahepatic portosystemic shunt; VZV, varicella zoster virus.

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Neurological Complications of LT

The most frequent neurological complications of LT are listed in Table 1. Those are described outside the scope of early graft function impairment that could indirectly lead to neurological complications through modification of drug metabolism, renal function impairment, sepsis, and impaired ammonia clearance.

STROKE

Candidates for LT frequently display severe coagulopathy and thrombocytopenia. The LT procedure is furthermore associated with hypotension, blood loss, electrolyte disturbances, and possible postoperative multiorgan failure. All of these factors constitute risk factors for stroke, intracranial or subdural hemorrhage, and, to a lesser extent, subarachnoid hemorrhage.[7,17-19] The same patients are also at risk for ischemic stroke for several reasons. Because of the age of the patients, the sex ratio, and the increase in the incidence of NASH, several patients have cardiovascular risk factors and can develop a stroke secondary to arterial emboli originating from the carotid or the intracranial arteries. However, 1 study could not find evidence of a higher incidence of major arterial stenosis in patients with cirrhosis before LT.[19] In this study, a high Model for End-Stage Liver Disease (MELD) score and female sex were associated with more frequent ischemic strokes, whereas a high MELD score and a history of stroke were associated with more frequent hemorrhagic strokes. Furthermore, during the LT procedure, declamping creates a situation in which the blood flow, especially cerebral blood flow, is decreased. In the presence of intracranial arterial stenosis, even if asymptomatic, the consequences could be even worse. Finally, cirrhosis complicated by HE is associated with compromised cerebral blood flow regulation.[49,52] The consequences of a sudden correction of liver function could thus be deleterious. Some recent data also suggest that the consequence of cerebral hypotension could be worse in the presence of hyperammonemia.[52,53] Interestingly, both ischemic

TABLE 1. Neurological Complications of LT and Their Relative Frequencies

Type of Complications	Notes	Frequency	References
Symptomatic neurological complications		15%	
Seizures	Generalized mainly, partial possible	1%-10%	Bronster et al.[5] (2000); Agildere et al.[6] (2006); Amodio et al.[7] (2007); Wijdicks et al.[16] (1996)
Ischemic stroke	Hypotension, associated vascular risk factors	1%-4%	Feltracco et al.[17] (2017); Zivković[18] (2013); Chung et al.[19] (2017)
Hemorrhagic stroke	Decreased PT, thrombocytopenia	1%-3%	
ODS	Rapid correction of hyponatremia	2%-4%	Crismale et al.[20] (2017)
PRES	Elevated blood pressure, impaired renal function, and anticalcineurins	1%	Hinchey et al.[21] (1996); Fugate and Rabinstein[22] (2015); Cruz et al.[23] (2012)
CNS infections	*Herpesviridae*, *Mycobacterium tuberculosis*, *Aspergillus* spp.	5%-10%	Bronster et al.[5] (2000); Amodio et al.[7] (2007); Lewis and Howdle[24] (2003); Pedersen and Seetharam[25] (2014); Fishman[26] (2007); Phan et al.[27] (2018); Charlier et al.[28] (2017); European Association for the Study of the Liver[29] (2016); Imbert et al.[30] (2017); Imbert et al.[31] (2016); Kamar et al.[32] (2016); Kamar et al.[33] (2008); Dalton et al.[34] (2017); Péron et al.[35] (2007)
ICU-acquired weakness	Importance of ICU, previous neuropathy or sarcopenia		Kress and Hall[36] (2014); Jolley et al.[37] (2016); Höckerstedt et al.[38] (1992); van den Berg et al.[39] (2014); Abravanel et al.[40] (2018)
Neurocognitive complications		30%	
Decompensation of previous altered cerebral condition related to cirrhosis	Alcohol, HCV, diabetes mellitus, cardiovascular risk factors for NASH		Ahluwalia et al.[41] (2015); Weinstein et al.[42] (2018); Wu et al.[43] (2015); Dirks et al.[44] (2017); Pflugrad et al.[45] (2016)
Decompensation of previous altered cerebral condition unrelated to cirrhosis	Hypertension, previous stroke, undiagnosed neurodegenerative disease		Ahluwalia et al.[41] (2015); Weinstein et al.[42] (2018); Wu et al.[43] (2015); Dirks et al.[44] (2017); Pflugrad et al.[45] (2016)
Peroperative and postoperative adverse effect			Aceto et al.[9] (2015); Bernhardt et al.[10] (2015); Fu et al.[11] (2014); Hanning[46] (2005); Moller et al.[47] (1998); Newman et al.[48] (2007)
General anesthesia	Direct neurotoxicity, hypotension		
Surgical procedure	Even more important if surgery is complicated (see Table 3)		
Anticalcineurin toxicity	Difficult to study since their use is mandatory		
HE sequelae	Rare, discussed		Romero-Gómez et al.[49] (2015); Weiss et al.[50] (2018); You et al.[51] (2017)

and hemorrhagic strokes are now easily recognized by brain imaging, especially brain magnetic resonance imaging (MRI). Brain MRI should be preferred because it enables a positive diagnosis in the acute phase of both ischemic and hemorrhagic strokes without any contrast enhancement agent. In rare cases, MRI also enables the diagnosis of cerebral thrombophlebitis.

OSMOTIC DEMYELINATION SYNDROME

Osmotic demyelination syndrome (ODS) corresponds to what was previously referred to as central pontine and extrapontine myelinolysis.[20,54,55] The common pathophysiological background of ODS is a sudden osmotic shift due to the rapid correction of hyponatremia, which damages oligodendrocytes. This leads to central nervous system (CNS) demyelination that is preferentially located in the pons with relative preservation of the neurons. An osmotic shift that occurs secondary to sudden modifications in urea or ammonia has also been reported.[55] In patients with cirrhosis, the production of idiogenic osmoles needed to compensate for the rapid osmotic shifts is impaired and probably explains the higher frequency of ODS in this population. ODS complicating LT occurred in as many as 10%-30% of patients in the early days of LT. Currently, the incidence is approximately 2%-4%.

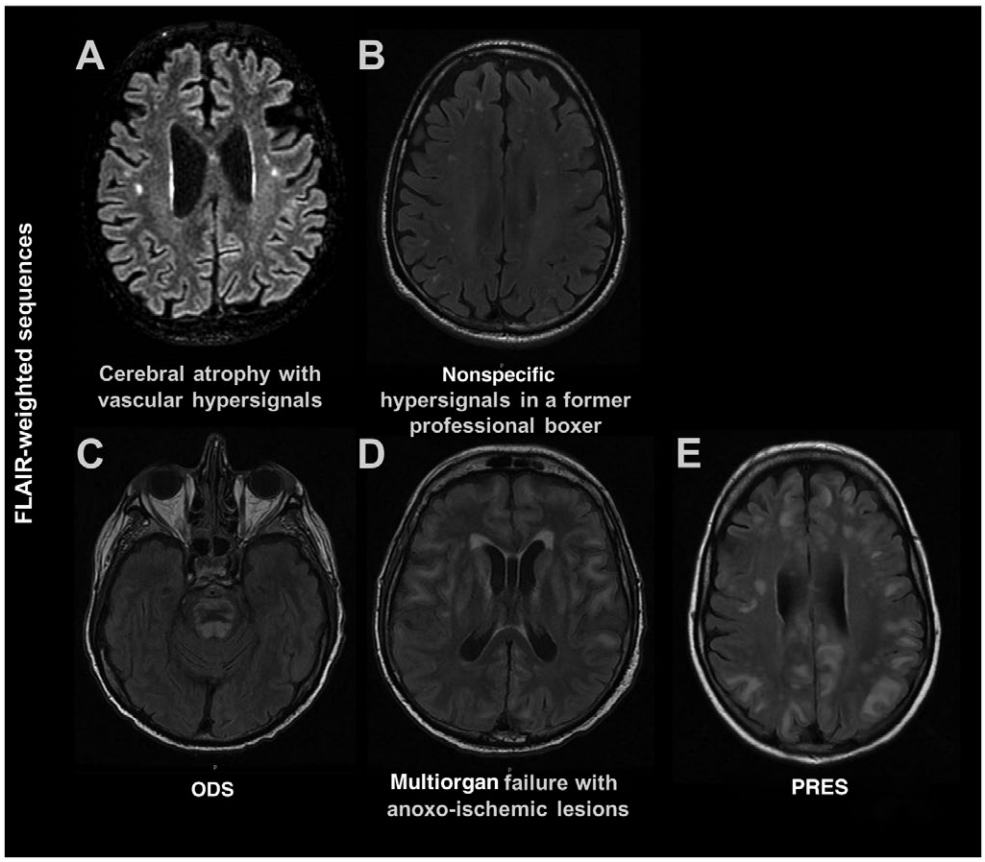

FIG. 1. MRI findings not associated with cirrhosis but responsible for neurological symptoms. Cerebral FLAIR-weighted sequences. (A) Diffuse cerebral atrophy associated with vascular hypersignals. Empty spaces between the cerebral cortex are clearly visible in black. In both hemispheres, punctiform vascular hypersignals are visible in white. (B) Nonspecific hypersignals in a former boxer. In both hemispheres, mild punctiform hypersignals are visible in white. (C) Pontic hypersignals in a patient with typical ODS. A hypersignal located in the center of the pons is visible in light gray. (D) Diffuse cortical hypersignals in a patient with multiorgan failure. Hypersignals of the cortices are present in white in the 2 hemispheres. (E) PRES. Symmetrical hypersignals are present in the parieto-occipital regions in the white matter. Milder hypersignals are present in the frontal regions.

The clinical spectrum is wide, ranging from encephalopathy or delirium to the classical pseudobulbar palsy with tetraplegia.[20] Inability to speak or swallowing problems after LT should prompt a search for ODS, and MRI will confirm the diagnosis (Fig. 1). Risk factors for ODS after LT have recently been reviewed (see Crismale et al.[20] for review). A serum sodium below 125 mEq/L before LT, the magnitude of change in sodium levels before and after LT, a higher positive intraoperative fluid balance, and the presence of postoperative hemorrhagic complications all constitute risk factors for ODS after LT. Preventive strategies could potentially be developed in this setting. Despite scarce data, the correction of serum sodium levels below 125 mEq/L in patients on the waiting list could be proposed to prevent ODS. Outside the scope of ODS, serum sodium levels below 135 mEq/L and, even more, below 130 mEq/L constitute a risk factor for HE in the 28 days later in patients with cirrhosis according to a large population survey.[56] The optimal treatment strategy has still to be determined in this specific population, but a correction rate no higher than 10 mEq/day could be proposed according to current guidelines.[57] Some authors suggest that the inclusion of the serum sodium level in the MELD score may contribute to the increase in the incidence of ODS because the accessibility to grafts is higher in patients with low sodium. It should be emphasized that even with the various possible sequelae, the prognosis of ODS has improved over the years such that, even

in the more severe forms with tetraplegia, a favorable outcome is possible.[58] Thus, ODS should not be an argument for withholding care in these patients.

SEIZURES

Seizures represent one of the most frequent neurological complications after LT, with a prevalence that can reach 10%.[5-7,11,16] The seizures can be either partial or generalized and can present as typical tonic-clonic seizures. In most cases, seizures are secondary to a neurological complication (such as hemorrhagic stroke, punctiform brain hemorrhage, sudden electrolyte or osmotic modifications, or infection).[16] This explains why the natural history is typically one of slow improvement. Furthermore, the electroencephalogram (EEG) can be normal, without any epileptic discharge in the intercritical period. Brain imaging, especially MRI, can also remain completely normal. In this situation, neurotoxicity associated with immunosuppressors like calcineurin inhibitors (CNIs) is the main cause of seizures.[59] Nevertheless, it seems that the avoidance of intravenous cyclosporine and close monitoring of tacrolimus plasma levels have resulted in a slow decrease in the frequency of seizures secondary to neurotoxicity.[7] Neurotoxicity or electrolyte disturbances trigger generalized seizures in the absence of any brain lesion on brain imaging. However, some rare cases of partial seizures without any identified brain lesion have also been observed after LT. The pathophysiological significance of these situations is still under discussion. It should be noted that some drugs, such as fluoroquinolones, some β-lactams (carbapenems), neuroleptics, and tramadol, which are frequently prescribed after LT, can decrease the epileptic threshold and are considered triggering agents.

CNS INFECTIONS AND BRAIN ABSCESSES

Between 5% and 10% of patients present with CNS infections after LT, mainly due to opportunistic agents,[5,7,24-26] with the leading risk factor being the use of immunosuppressive drugs. The most frequently identified pathogens in cases of encephalitis or meningoencephalitis are *Herpesviridae*, ie, cytomegalovirus (CMV) and herpes simplex virus (HSV). Among *Herpesviridae*, human herpesvirus (HHV) 6 is an opportunistic agent that has been recently reported to be a possible causative agent of encephalitis in LT patients.[27] The clinical presentation includes fever and an erythematous rash. Progressive multifocal leukoencephalopathy associated with the JC virus is also possible. Bacteria, *Listeria* spp.,[25,26,28,29] and fungi are more frequently responsible for meningitis. The presence of a brain abscess or infectious vasculitis after LT should prompt a search for infection by *Aspergillus* spp., which is more frequent in LT patients,[30,31] as well as *Nocardia* spp. Several months after LT, meningitis can be secondary to *Mycobacterium tuberculosis*. It should be noted that another emerging agent is the hepatitis E virus (HEV) that has been recently reported as the causative agent responsible for several neurological manifestations, including encephalitis.[32-35] Figure 2 summarizes the timeline of these different complications.[25,26]

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

The incidence of posterior reversible encephalopathy syndrome (PRES) is increasing, most likely because of improved recognition of the syndrome. It could be particularly frequent after LT.[21-23] Thus, in a retrospective study in the United States, 19 patients out of 1923 LTs (1%) presented PRES.[23] This corresponded to 5% of the neurological complications presented by the patients.

Clinical features include visual disturbance, headache, variable altered consciousness, and seizures, including status epilepticus (for a review see Fugate and Rabinstein[22] and Roth and Ferbert[60]). A brain MRI is the key diagnostic study. Classical findings are symmetrical hyperintensities on T_2 and fluid low attenuation inversion recovery (FLAIR)–weighted sequences in the white matter of the hemispheres, predominantly in the parieto-occipital regions (Fig. 1). Frontal regions are frequently involved in association with posterior regions. Atypical features, such as cortical involvement or asymmetrical lesions, have been described, but these features are rarely isolated. Because the computed tomography (CT) scan shows mild hypodensities in less than 50% of cases, the diagnosis should not be ruled out even if the CT is normal. The latter should prompt an MRI study. The pathophysiology of the disease resides in vasogenic brain edema resulting from either the loss of cerebral vascular autoregulation, endothelial dysfunction, or may be due to a mean arterial pressure

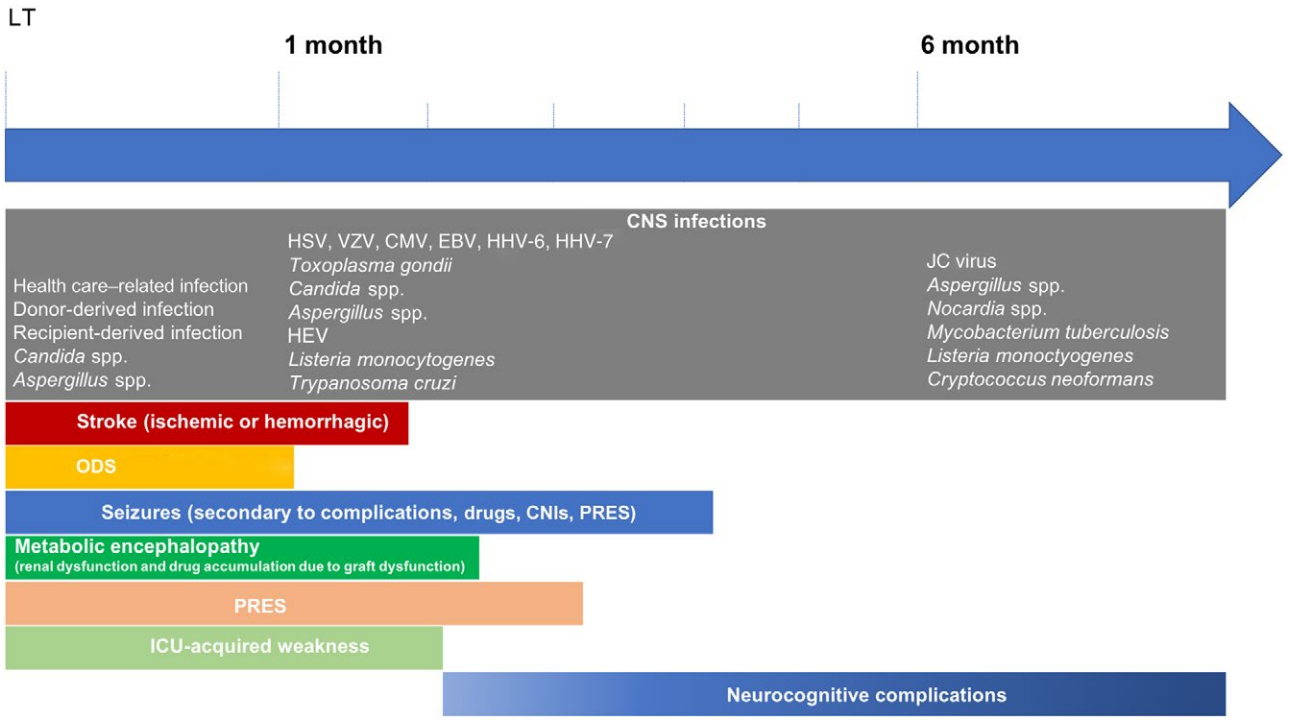

FIG. 2. A timeline of neurological complications after LT.

higher than 150 mm Hg, ie, the limit of the cerebral autoregulation.[61,62] After LT, PRES is mostly due to endothelial dysfunction secondary to CNIs. Because of the loss of autoregulation, the cerebral perfusion pressure correlates linearly with the systolic arterial pressure. This explains why lowering blood pressure, in association with withdrawing triggering agents and antiepileptic drugs, can rapidly improve the neurological status. In the absence of cortical involvement or hemorrhagic complications, the prognosis is favorable with improvement occurring within a few weeks. Antiepileptic drugs can also frequently be stopped several months after the disease.[23,63] It should be noted that, in the case of CNI intake in LT, PRES can occur in the absence of elevated blood pressure. Altered renal function may also be an independent risk factor,[22] as could be a history of alcoholic liver disease or hypomagnesemia.[23]

ICU–ACQUIRED WEAKNESS

ICU-acquired weakness occurs in as many as 80% of patients after an ICU stay (for a review see Kress and Hall[36] and Jolley et al.[37]). In addition to the presence of classical critical illness neuropathy, secondary to multiorgan failure and major systemic inflammation, this condition also involves decompensation of previous neuropathy or sarcopenia and only seldom is associated with an acquired neurological disease such as Guillain-Barré syndrome.[7,17,38] In addition to ICU-related complications from the surgery and a prolonged ICU stay, patients undergoing LT are also at risk of decompensation from previously known or unknown diseases such as alcoholic or diabetic neuropathy, carential neuropathy, or severe sarcopenia.[38] All of these factors contribute to ICU-acquired weakness after LT. Recently, HEV has been shown to infect patients after LT and has been associated with several neurological complications, including Guillain-Barré syndrome and severe myositis.[39] Although no neurological symptoms related to HEV infection have been reported after LT, 1 case has been reported after kidney transplantation.[40] In the absence of conclusive data, HEV should be sought in atypical acquired weakness after LT. Mechanical plexopathies secondary to abnormal posturing during the surgical procedure are currently less frequent because of improvement in anesthetic procedures.

Neurocognitive Complications After LT

Most patients with neurocognitive symptoms before LT improve during the months following surgery.[7,10,64] Nevertheless, some patients show persistent neurocognitive symptoms after LT that are still present even years after the transplant.[9,65-72] Although two-thirds of patients with cirrhosis exhibit neurocognitive abnormalities prior to LT, 20% still show impairment long after the procedure, despite normal liver function tests and the absence of HE before LT. Although CNIs have been implicated as possible contributors, they cannot account for all the reported abnormalities.[73] Because the gross neurological examination is frequently normal, neurocognitive-associated complications are usually considered if quality of life is affected or after concerns are raised by the caregivers. These neurocognitive deficits are assessed by extensive psychometric neurocognitive testing and have been confirmed by EEG, different MRI techniques and positron emission tomography (PET) scanning.[65,71,74] On the one hand, post-LT improvement has been shown in the setting of HE on the basis of EEG and PET scan results.[65,72] On the other hand, MRI studies that use standard sequences, magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and functional MRI (Table 2) can show both improvement in cerebral abnormalities that were present prior to LT because of HE (see Table 2 for review) and persistent abnormalities after LT.[74-90] Spontaneous T_1-weighted sequence basal ganglia hypersignals, white matter changes in the corticospinal tract, magnetization transfer ratio (MTR), and the HE profile on MRS normalize months after LT.[74] MRS peaks can normalize as early as 3 months after LT (Table 2). Despite limited data from DTI, it appears that mean diffusivity (MD) decreases after LT, suggesting a correction of vasogenic edema with the normalization of liver function.[80,82-84] Only scarce data are available from functional MRI, though what is available also suggests an improvement in the functioning of the previously altered networks after LT.[80,84-89] However, several data also suggest persistent cerebral abnormalities after LT. Standard MRI sequences can provide evidence of reduced brain volume and a decrease in the MRS *N*-acetylaspartate (NAA)/creatine (Cr) ratio, both of which suggest the presence of fixed brain lesions and brain atrophy.[79] In some patients following LT, preliminary DTI data have identified possible persistent decreased fractional anisotropy (FA) that confirms axonal degeneration,[83,84] and functional MRI has shown persistent altered functioning.[80,90] However, the latter data should be confirmed with other studies. For neuropsychological testing, treatment with CNIs presents a bias that may not be easily overcome in these studies. Nevertheless, a recent report found that although the dosage of CNIs affected neuropsychological testing, there was no impact on brain atrophy as assessed by brain MRI.[73]

How to Assess Neurological or Neurocognitive Complications of LT

Once neurological or neurocognitive impairment is suspected after LT, a common etiological workup should be performed. A timeline of neurological or neurocognitive complications of LT can be found in Fig. 2. First, the classical complications of LT must be ruled out. CT scan or brain MRI should be able to rule out intracerebral hemorrhage or ischemic stroke. Following LT, clues suggesting PRES should be sought on brain MRI. Cerebral MRI is particularly relevant to exclude certain neurological complications of LT, such as stroke, PRES, or some CNS infections, but cannot be relied upon to confirm other causes of neurological or neurocognitive impairment (Fig. 1). When fever and inflammatory symptoms are present, CNS infection should be ruled out, and lumbar puncture is frequently necessary to identify classical causes of meningitis/encephalitis as well as *Mycobacterium tuberculosis*, *Aspergillus fumigatus*, *Candida* spp., *Nocardia* spp. *Listeria* spp., or *Herpesviridae*. An EEG will rule out seizures as well as metabolic and drug-induced encephalopathies. A detailed analysis of the patient's medical history and preoperative, perioperative, and postoperative history should be performed. Elevated ammonia levels and/or persistent portosystemic shunts despite LT suggest the possibility of persistent HE. Apart from early graft rejection, post-LT HE with elevated ammonia levels has been only rarely reported, as in the case of the grafting of a liver taken from a patient who died from a urea cycle defect.[91,92] Hence, verifying normal

TABLE 2. Brain MRI Findings Reported After LT

References	Methods	Population	MRI Findings After LT
Conventional MRI sequences (T_1-, T_2-, FLAIR-weighted sequences)			**Summary:** **Improvement in globus pallidus T_1 hypersignals** **Correction of edema: white matter T_2 lesions decrease, MTR increase** **Brain atrophy** **CNI seems not associated with brain atrophy but with T_2 hypersignals**
Weissenborn et al.[75] (1995)	1T MRI scanner, T_1, T_2 Before and after LT Only 7 MRIs after LT	50 cirrhotic patients No alcoholic cirrhosis 7 Child-Pugh A, 22 Child-Pugh B, and 21 Child-Pugh C patients 20 no HE, 17 MHE, and 13 overt HE (grade I) patients	Bilateral T_1 hypersignals of the globus pallidus before LT (92% of the patients); absent 3 months after LT T_2 hypersignals in the corticospinal tract (18% of the patients) No correlation between the T_1 signal intensity and liver function, neurological status, or grade of encephalopathy
Córdoba et al.[74] (2001)	1.5T MRI scanner, magnetization transfer imaging, ^{1}H-MRS Before and after LT (1 month and 1 year) Only 11 MRIs after LT	24 cirrhotic patients No alcoholic cirrhosis 4 Child-Pugh A, 18 Child-Pugh B, and 2 Child-Pugh C patients 0 overt HE patients 70% MHE patients 10 healthy controls	Bilateral T_1 hypersignals of the globus pallidus still present at 1 month after LT but normalized at 1 year MTR increase in frontal and parietal lobes
Rovira et al.[76] (2002)	1.5T MRI scanner, T_2, Fast-FLAIR, magnetization transfer imaging Before and after LT (1 month and 1 year) Only 11 MRIs after LT	24 cirrhotic patients No alcoholic cirrhosis 4 Child-Pugh A, 18 Child-Pugh B, and 2 Child-Pugh C patients 0 overt HE patients 17 MHE patients 12 healthy controls	White matter T_2 hypersignals in the corticospinal tract Decrease after LT
Rovira et al.[77] (2007)	1.5T MRI scanner, T_2, Fast-FLAIR Before and after LT (6 to 14 months)	27 cirrhotic patients Alcohol cirrhosis included, 7 patients Child-Pugh 10.0 $\pm$ 1.6 versus 8.3 $\pm$ 1.4 for patients without and with white matter lesions 0 overt HE patients	White matter T_2 hypersignals; decrease after LT White matter lesions were more common in cirrhosis of viral etiology
García Martínez et al.[78] (2010)	1.5T MRI scanner, T_2, Fast-FLAIR Before and after LT (6-12 months and 6-9 years)	22 cirrhotic patients Alcohol cirrhosis included, 6 patients 4 Child-Pugh A, 10 Child-Pugh B, and 8 Child-Pugh C patients 0 overt HE patients 13 healthy controls matched for age and sex	White matter T_2 lesions decrease, particularly in patients with previous bouts of HE before LT Brain atrophy estimated at 8% decrease compared with before LT in short-term assessment and at 22% decrease in longterm assessment
Garcia-Martinez et al.[79] (2011)	1.5T MRI scanner, ^{1}H-MRS After LT (6-12 months)	24 cirrhotic patients Alcohol cirrhosis included, 8 (33%) MELD 17 $\pm$ 6 0 overt HE patients	Reduced brain volume in older patients, alcohol etiology of cirrhosis, prior HE and increased time from first episode of HE Age-related decrease in brain volume was higher in patients with prior HE

TABLE 2. *Continued*

References	Methods	Population	MRI Findings After LT
Ahluwalia et al.[80] (2016)	1.5T MRI scanner, T_1, T_2 Before and after LT (6 months) Only 35 MRIs after LT	43 cirrhotic patients Alcohol cirrhosis included, alcohol only 10%, and alcohol and HCV 16% 21 HE 14 No HE	No abnormalities on standard weighted sequences NB: ROIs were parietal white matter, posterior grey matter, anterior cingulate cortex
Pflugrad et al.[73] (2017)	3T MRI scanner, T_1, T_2 After LT	85 patients who underwent LT Patients under low-dose CNI versus patients under standard dose CNI versus patients under immunusuppression without CNI Healthy controls matched for age, sex, and education	Higher white matter hypersignals in patients under CNI but no brain atrophy Patients had more brain atrophy than controls Patients under CNI had lower neuropsychological performance (possible link with microangiopathy)
^{1}H-MRS			**Summary:** **Normalization of HE profile: Glx/Cr ratio decrease in 1-2 months; mI/Cr ratio increase in several months** **Brain atrophy: NAA/Cr ratio decrease**
Naegele et al.[81] (2000)	1.5T MRI scanner, ^{1}H-MRS Before and after LT (3 to 7 months) Only 8 MRIs after LT	22 patients scheduled for LT	Glx/Cr ratio had normalized in all the patients after LT mI/Cr ratio normalized in 5 out of 8 patients (63%)
Córdoba et al.[74] (2001)	1.5T MRI scanner, MTR, ^{1}H-MRS Before and after LT (1 month and 1 year) Only 11 MRIs after orthotopic LT	24 cirrhotic patients No alcoholic cirrhosis 4 Child-Pugh A, 18 Child-Pugh B, and 2 Child-Pugh C patients 0 overt HE patients 70% MHE patients 10 healthy controls	Glx/Cr and Chol/Cr ratio normalized after LT in 1 month mI/Cr ratio increased but was still lower than in controls NAA/Cr mild decrease 1 month after LT Negative correlation between MTR and Glx/Cr ratio
Garcia-Martinez et al.[79] (2011)	1.5T MRI scanner, ^{1}H-MRS After LT (6-12 months)	24 cirrhotic patients Alcohol cirrhosis included 8 (33%) patients MELD 17 ± 6 0 overt HE patients	MRS in the normal range, not altered NAA/Cr correlated to brain volume
Ahluwalia et al.[80] (2016)	1.5T MRI scanner, T_1, T_2 Before and after LT (6 months) Only 35 MRIs after LT	43 cirrhotic patients Alcohol cirrhosis included, alcohol only 10%, and alcohol and HCV 16% 21 HE patients 14 No HE patients	Glx/Cr ratio decrease after LT Chol/Cr and mI ratio increase No modifications in NAA/Cr Patients having previous HE displayed higher improvement in MRS NB: ROIs were parietal white matter, posterior grey matter, anterior cingulate cortex

TABLE 2. *Continued*

References	Methods	Population	MRI Findings After LT
DTI			**Summary:** **Correction of edema: MD decrease** **Possible FA modification (but still discussed)**
Chavarria et al.[82] (2011)	1.5T MRI scanner Before and after LT (12 months) Only 24 MRIs after LT	41 cirrhotic patients Alcoholic cirrhosis included if abstinent for more than 6 months 11 Child-Pugh A, 19 Child-Pugh B, and 11 Child-Pugh C patients 0 overt HE patients 12 MHE patients 16 healthy controls	MD values decrease in both parietal white matter and corticospinal tract back to normal values FA values increase in parietal white matter back to normal values FA values increase in corticospinal tract but without return to normal values No correlation with clinical or neuropsychological markers NB: ROIs were parietal white matter and corticospinal tract
Ishihara et al.[83] (2013)	3T MRI scanner, Before and after LT (6 months) Only 12 MRIs after LT	14 cirrhotic patients No alcoholic cirrhosis 14 Child-Pugh C patients Possibly 14 MHE patients 15 healthy controls matched for age, sex, and education	MD values decrease in frontal, temporal lobes, and cerebellum FA values increase in frontal lobe Permanent FA decrease in some patients and in some areas
Lin et al.[84] (2014)	3T MRI scanner, Before and after LT (6-12 months)	28 cirrhotic patients 17 Child-Pugh B and 9 Child-Pugh C patients 28 MHE patients 30 healthy controls matched for age and sex	No difference in white matter integrity between patients before LT and controls and between MHE patients after LT and controls MD values decrease in the right anterior cingulate, left claustrum, and left postcentral gyrus Improvement in visuospatial function was correlated with MD correction in right anterior cingulate FA values decrease in the right parahippocampal gyrus Decreased axonal diffusivity after LT in several clusters, including left anterior cingulate, right anterior cingulate, left claustrum, and left postcentral gyrus Decreased gray matter volume after LT in putamen compared with controls and altered FA with higher radial diffusivity in right temporal lobe Persistent memory and language function
Ahluwalia et al.[80] (2016)	1.5T MRI scanner, T_1, T_2 Before and after LT (6 months) Only 35 MRIs after LT	43 cirrhotic patients Alcohol cirrhosis included, alcohol only 10%, and alcohol and HCV 16% 21 HE patients 14 patients without HE	MD values increase in the posterior internal capsule No modification in FA LD values increase in the posterior internal capsule and the splenium of the corpus callosum NB: ROIs were parietal white matter, posterior grey matter, and anterior cingulate cortex

TABLE 2. *Continued*

References	Methods	Population	MRI Findings After LT
Functional MRI			**Summary:** **Improvement in the DMN compared with before LT** **Persistent alteration in the DMN however present after LT suggesting nonreversible lesions**
Lin et al.[85] (2014)	3T MRI scanner, Resting state Before and after LT (6-12 months)	26 cirrhotic patients Etiology of cirrhosis and severity not available No overt HE 35 healthy controls	Compared with before LT where functional connectivity was decreased in the DMN, dorsal attention network, executive control network, and salient network, after LT functional connectivity normalized Neuropsychological performances increased with improvement in functional connectivity
Cheng et al.[86] (2015)	3T MRI scanner, resting state, regional homogeneity Before and after LT (1 month) Only 12 MRIs after LT	26 cirrhotic patients No alcoholic cirrhosis 7 Child-Pugh B and 19 Child-Pugh C patients 13 overt HE (9 grade I, 4 grade II) patients 8 MHE patients 5 patients without HE 26 healthy controls	Connectivity in the bilateral inferior frontal gyrus, right inferior parietal lobule, right supplementary motor area, right supra temporal gyrus, and left middle frontal gyrus increased after LT compared with before LT At 1 month after LT, most of the brain connectivity nearly normalized Changes in connectivity in the right supplementary motor area, supra temporal gyrus, and inferior frontal gyrus were correlated with neuropsychological performances (digit symbol test)
Zhang et al.[87] (2015)	3T MRI scanner, resting state, functional connectivity density Before and after LT (1 month) Only 15 MRIs after LT	27 cirrhotic patients No alcoholic cirrhosis 7 Child-Pugh B and 20 Child-Pugh C patients 14 overt HE patients 8 MHE patients 5 patients without HE 27 healthy controls matched for age, sex, and education	Long- and short-range functional connectivity in the most of the brain areas that were altered before LT reversed after LT Increased connectivity after LT in the right supplementary motor area, precentral gyrus, right inferior frontal gyrus, right postcentral gyrus, inferior frontal gyrus, middle frontal gyrus, middle occipital gyrus and decreased connectivity in the right rectus gyrus, left medial prefrontal gyrus, left middle temporal gyrus The reduced long-range functional connectivity in the right posterior cingulate cortex and left middle frontal gyrus, and the reduced short-range functional connectivity in the right precuneus persisted in the early period after LT At 1 month reduced long-range functional connectivity in the right rectus gyrus and the left medial prefrontal cortex and reduced short-range functional connectivity in the left middle temporal gyrus were still present Neuropsychological performances (digit symbol test) was correlated with long-range connectivity in the right precentral gyrus and the right supplementary motor area

TABLE 2. *Continued*

References	Methods	Population	MRI Findings After LT
Zhang et al.[88] (2017)	3T MRI scanner, resting state Before and after LT (1 month) Only 30 MRIs after LT	57 cirrhotic patients No alcoholic cirrhosis 2 Child-Pugh A, 18 Child-Pugh B, and 37 Child-Pugh C patients 27 HE patients 30 patients without HE 34 healthy controls matched for age, sex, and education	Brain activity in regions regulating motor function, vision, attention, and working memory were normalized in both groups (with and without HE) after LT Persistent impairments and new-onset impairments in regions related to cognitive functions were observed in each group (with and without HE) after LT Cognitive performance improved in both groups
Cheng et al.[87] (2017)	3T MRI scanner, resting state, ALFF method Before and after LT (1 month) 13 previously reported in Zhang et al.	20 cirrhotic patients No alcoholic cirrhosis 3 Child-Pugh B and 17 Child-Pugh C patients 13 overt HE patients 5 MHE patients 2 patients without HE 25 healthy controls matched for age, sex, and education	Decreased connectivity in the regions related to vision, sensorimotor control, and the default mode network was restored after LT An early increase of connectivity in the temporal and frontal lobe was present after LT Persistent connectivity decrease was present in the right supplementary motor area, the inferior parietal lobule, and calcarine sulcus Patients with HE (evaluated by number connection test-A) had decreased connectivity in the right precuneus
Cheng et al.[90] (2017)	3T MRI scanner, resting state, functional connectivity density Before and after LT (1 month)	33 cirrhotic patients No alcoholic cirrhosis 2 Child-Pugh A, 8 Child-Pugh B, and 23 Child-Pugh C patients 15 overt HE patients 18 no overt HE patients 30 healthy controls matched for age and sex	Before LT, long- and short-range functional connectivity strength decrease in each group (with and without HE) compared with controls with a normalization in the patients without HE after LT except for the cerebellum, precuneus, and orbital middle frontal gyrus Abnormal connectivity was preserved in the patients with HE in cognition-related (frontal and parietal lobes) and vision-related areas (occipital lobe, cuneus, and precuneus) before LT that normalized after LT In patients with HE, functional connectivity abnormalities remained after LT in the DMN Functional connectivity in the left postcentral and right middle frontal gyrus correlated with alterations in neuropsychological performance and ammonia levels
Ahluwalia et al.[80] (2016)	1.5T MRI scanner Functional MRI, correct lure inhibition and inhibitory control test Before and after LT (6 months) Only 35 MRIs after orthotopic LT	43 cirrhotic patients Alcoholic cirrhosis included, alcohol only 10%, and alcohol and HCV 16% Among patients who underwent MRI: 21 HE patients and 14 patients without HE	Improvement in patients cognitively impaired and in HE patients after LT The correct lure inhibition test needs activation in the dorsolateral prefrontal and posterior parietal cortex, orbitofrontal cortex, insular cortex, and anterior cingulate cortex; this activation is lower after LT

NOTE: Case reports have been excluded. Some studies appear several times in the table according to different MRI techniques.

TABLE 3. Risk Factors for Neurocognitive Complications After Surgery

Circumstances	Risk Factors
General surgery*	Age >60 years
	Cerebrovascular disease
	MMS <20
	Alcohol consumption
	Hypertension
	Postoperative infection
LT†	
Risk factors in the pre-LT period	Elevated MELD scores
	HE, number of bouts, severity of HE bouts (discussed)
	Mechanical ventilation before LT
	Second transplantation
	Emergent surgery
	Infection before LT
Risk factors in the per-LT period	Number of packed red blood cells
	Number of fresh frozen plasma packs
	Administered volumes
	Surgical procedure duration
Risk factors in the post-LT period	Surgical reintervention
	Postoperative extrarenal replacement therapy
	Mechanical ventilation duration
	Severe postoperative infection

*Hanning[46] (2005); Moller et al.[47] (1998); Newman et al.[48] (2007); Monk et al.[103] (2008).
†Aceto et al.[9] (2015); Bernhardt et al.[10] (2015); Fu et al.[11] (2014).

ammonia levels is one of the first steps that should be taken when neurological symptoms are diagnosed following LT. MRI is less informative in this setting since both central gray nucleus T_1-weighted hypersignals and the specific HE profile on spectroscopy take time to disappear after LT (Fig. 3). Neuropsychological testing is important to perform once the patient is discharged from the ICU since it might be able to distinguish between the different neurocognitive profiles (HE, vascular dementia, depression, and Alzheimer's dementia). If suspected, specific procedures should be performed as part of the etiological workup, such as lumbar puncture to identify neurodegenerative biomarkers and cerebral scintigraphy or PET scan if neurodegenerative disorders are considered.[93]

Until now, MRI sequences other than the standard ones or MRS have not been readily available. DTI, which has been used in some research studies, could be performed in this setting in the near future because these sequences are now commonly available and provide important information about pathophysiology (Fig. 4).[94] In addition, DTI is used to more precisely determine the longterm prognosis after acute brain injuries, such as in cases of cardiac arrest or traumatic brain injury.[95-98]

Hypotheses to Explain Post-LT Neurocognitive Impairment

UNMASKING NEUROCOGNITIVE IMPAIRMENT PRESENT BEFORE LT

Most patients display neurological symptoms before LT due to HE. HE is a classical complication of acute or chronic liver disease and/or portosystemic shunt.[49,50] Type A HE corresponds to ALF, and type C HE is associated with cirrhosis. The clinical spectrum of HE is wide, ranging from mild neuropsychological symptoms that can only be diagnosed with appropriate tools to altered consciousness or coma. The incidence of HE varies from 30% to 80% according to diagnostic criteria. Although overt HE, which manifests as disorientation in time and space with asterixis, is easily recognized, minimal hepatic encephalopathy (MHE) often presents as subtle neurological impairment, dysexecutive symptoms, apraxia, or even more subtle abnormalities. As a result, MHE can only be detected with neuropsychological testing, is much more difficult to diagnose, and can easily be missed before LT. Even if HE symptoms mostly disappear after LT, the existence of HE sequelae is still debated.[7,49,50] Several data suggest that the metabolic component of HE almost reverses after LT, whereas the structural component may persist.[82] Two main arguments are in favor of possible sequelae of HE: The correlation between neurological impairment and a history of previous bouts of HE.[51,99]; the longterm neurological impairment associated with hyperammonemia in cases of decompensation due to urea cycle defects.[100,101]

Indeed, even if confounding factors exist, especially the association with systemic inflammation, persistent postoperative cognitive impairment may still be correlated with bouts of HE and their severity.[51] Long-lasting decompensation due to urea cycle defects, the most frequent inborn error of metabolism responsible for hyperammonemia, is clearly linked to neurological impairment,[100,101] validating the need for

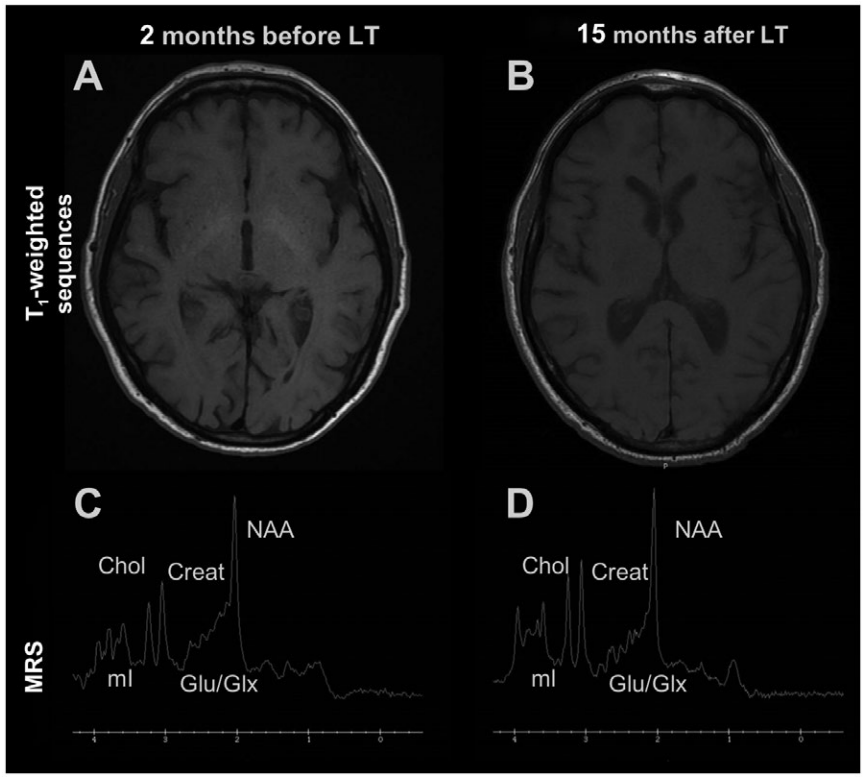

FIG. 3. MRI findings associated with HE and their evolution after LT in the same patient. (A) T_1-weighted sequence performed before LT showing hypersignals in the deep gray nuclei. (B) T_1-weighted sequence performed after LT showing the disappearance of the hypersignals in the deep gray nuclei. (C) Typical HE spectra on MRS before LT showing an increase in the Glu/Glx peak and decreases in the Chol and the mI peaks. (D) MRS findings after LT showing a normalization of the Glu/Glx, Chol, and mI peaks.

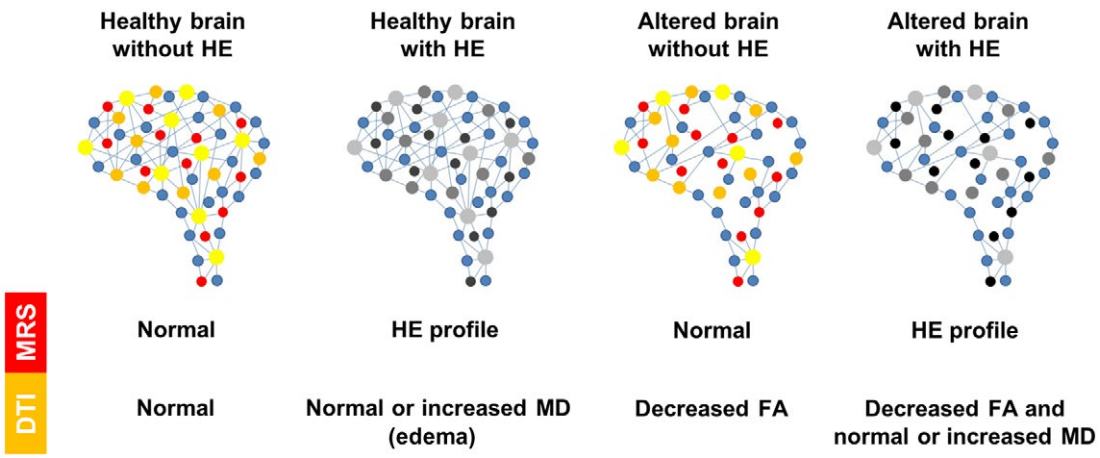

FIG. 4. MRI findings (MRS and DTI) according to neurological symptoms that are or are not related to HE. HE is depicted as faded colors. An altered brain with reduced connectivity is depicted as a sparse brain with fewer lines. HE in an altered brain is depicted as a faded sparse brain. MRS is able to detect typical HE spectra, whereas DTI is able to quantify the connectivity between brain regions and constitutes a surrogate marker of altered cerebral tissue. Combining these 2 sequences distinguishes the different situations: a normal brain without HE that will have neither abnormalities on MRS nor on DTI; a healthy brain (no previous cerebral alteration) with HE having abnormal MRS but normal DTI; an altered brain without HE having normal MRS but abnormal DTI; and an altered brain with HE having both abnormal MRS and DTI. Before LT, MRS could thus quantify the possible reversible component of HE, whereas DTI could quantify the previously altered cerebral component with milder or no reversibility.

ammonia-lowering strategies. In ALF, the rapid onset of hyperammonemia could explain the neurological sequelae that follows HE. In cases of cirrhosis, ammonia levels are frequently less elevated and increase progressively allowing time for compensatory mechanisms to be activated. Other investigators claim that HE is totally reversible and that the so-called sequelae represent competitive brain injuries. As previously stated, hyperammonemia could indirectly lead to ischemic or anoxo-ischemic brain injuries.[52,53]

Many patients who undergo LT, especially patients with cirrhosis, also have classical risk factors for neurocognitive alterations. These include factors like age or those more directly related to the etiology of cirrhosis like alcoholism. In addition, risk factors associated with NASH, namely, diabetes mellitus, hypertension, obesity, and dyslipidemia, also play a role. These risk factors are totally independent of previous bouts of HE.[41,42] For example, patients with alcohol-related cirrhosis display more severe neurocognitive alterations and more cortical lesions as assessed by cerebral MRI after TIPS placement than patients with cirrhosis from other etiologies.[41] Recent data also suggest the presence of early cerebral atrophy in patients with NASH, which could correspond to premature brain aging.[42] In large epidemiological studies, hepatitis C virus (HCV) infection has been associated with an increased risk of neurodegenerative disorders, both in Alzheimer's and Parkinson's diseases.[43] The importance of reversing these cerebral abnormalities with direct antiviral agent therapy is still being debated.[44,45]

ADVERSE EFFECTS OF THE LT PROCEDURE (ANESTHESIA, SURGICAL PROCEDURE, POST-LT ICU STAY)

Some patients who have no evidence of HE or history of cerebral impairment still exhibit neurological impairment after LT. Direct adverse effects of general anesthesia, the surgical procedure itself, or factors linked to a stay in a postoperative ICU have been suggested as possible causative factors (Table 3).[12-15,46-48,102,103] Postoperative cognitive dysfunction, defined as impairment of the mental processes of perception, memory, and information processing after a surgical intervention, has been recognized as a common problem that is independently associated with increased mortality outside the scope of LT.[48] Even if a distinction is usually made between postoperative cognitive dysfunction and the residual effects of sedation or postoperative delirium, a common pathophysiological mechanism could still underlie these conditions, such as an association with systemic inflammation.[102] LT may represent a peculiar situation since both patients with ALF and cirrhosis have very high levels of systemic inflammation before LT that could worsen with the additional inflammation associated with the surgical procedure (Table 3). This could explain why both the duration of the surgery and its potential complications, infections, and mechanical ventilation before LT have all been reported as risk factors.[9] Furthermore, patients with cirrhosis have been shown to demonstrate long-lasting cognitive impairment after infection.[104] Changes in systemic hemodynamics and possible reduced cerebral blood flow are also implicated as causes for cerebral impairment. Finally, some patients will display postoperative complications leading to a prolonged ICU stay. Several causes of ICU admission associated with systemic inflammation, such as severe infection or acute respiratory distress syndrome, have been associated with longterm neurocognitive impairment that currently is well described.[12-15] Similar findings may be associated with post-LT ICU stays for the most severe patients.

Future Directions

PREVENTIVE MEASURES

Presently, there are no recommendations of professional or learned medical societies for preventing neurological or neurocognitive complications after LT. Measures that could be proposed to prevent these complications include the following: control of sodium levels to prevent ODS, evaluation for possible carotid artery stenosis in patients with cardiovascular risk factors, or emphasis on the importance of assessing sarcopenia. However, to date, there are no data investigating the usefulness of such strategies. Although modulation of the systemic inflammatory response in the pre-, peri-, and post-LT periods is clearly a promising approach, none of the different strategies proposed in the ICU literature have demonstrated any discernible benefit.[105] Thus, more work has to be done in this field.

INCLUDE A NEUROLOGICAL EVALUATION IN THE SELECTION OF CANDIDATES FOR LT

Because some patients may have undiagnosed neurocognitive impairment before LT, the usefulness of a systematic neurological evaluation should be discussed. Indeed, LT could cause further decompensation of an already unstable equilibrium. Brain imaging, especially MRI with standard sequences, could demonstrate wide leukopathy of vascular origin or brain atrophy. Neuropsychological testing could demonstrate a profile that is not typical of HE, but one that is more suggestive of a vascular origin or points to a neurodegenerative disorder. Biomarkers of neurodegenerative disorders that are used with increasing frequency in neurology could also help diagnose a neurodegenerative disorder.[93] Although abnormal findings increase the risk of an unfavorable neurocognitive outcome after LT, whether they should preclude access to LT will require extensive study. On the other side, although a minimal workup could be probably feasible, an overly extensive etiological workup could delay access to LT with potentially deleterious consequences for the patient's outcome. Some patients with HE have a specific indication for LT. This particular indication for LT, which is based on persistent HE that is being adequately treated, has been, until now, based solely on an expert's evaluation and not on any additional and specific complementary exploration. Some of these patients may have been wrongly diagnosed with HE, which could explain an incomplete recovery after LT. How useful would a multimodal MRI be in this setting?[94] Answering this question would open a door that could provide access to LT only to patients with a major chance of improvement and would restrict access to patients with previously undiagnosed cerebral alterations who have a high probability of decompensation after LT.

Conclusion

Neurological and neurocognitive complications are particularly frequent after LT compared with cardiac or renal transplantation. Apart from certain classical neurological conditions that have to either be rapidly ruled out or adequately treated, some patients display neurocognitive impairment that is likely the result of decompensation of an unknown cerebral condition that was present but ignored prior to LT. Previous altered cerebral reserve due to the pathologic mechanism underlying cirrhosis, undiagnosed neurodegenerative disorders/aging, or the conjunction of hyperammonemia, systemic inflammation, and altered blood–brain barrier permeability could all provide a milieu that favors the onset of symptoms.

What is needed is a better understanding of the origin of these impairments and the development of preventive strategies that could improve the patient's neurological prognosis after LT. Research on the precise pathophysiological mechanisms implicated in these neurological/neurocognitive impairments after LT is mandatory. Recent improvements in cerebral MRI techniques, especially DTI, render MRI a promising tool in this setting.

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