Neurological Recovery After Recovery From Acute Liver Failure: Is it Complete?

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Neurologic dysfunction characterised by Hepatic Encephalopathy (HE) and cerebral oedema are the most dramatic presentations of Acute Liver Failure (ALF) and signify poor outcome. Improved critical care and wider availability of emergency Liver Transplantation (LT) has improved survivability in ALF. In most cases absence of clinically overt encephalopathy after spontaneous recovery from ALF or after LT is thought to indicate complete neurologic recovery. Recent data suggests that neurologic recovery may not always be complete. Instances of persistent neurologic dysfunction as well as neuropsychiatric abnormalities are now being recognised and warrant active follow up of these patients. Although evidences irreversible neurologic damage is uncommon after ALF, neuropsychiatric disturbances are not uncommon. Complex pathogenesis is involved in neurocognitive disorders seen after many other conditions including LT that require critical care. Structural damage and persistent neurological abnormalities seen after ALF are more likely to be related to cerebral edema, raised intracranial tension and cerebral hypoxemia, while neurocognitive dysfunctions may be a part of a wider spectrum of disorders commonly seen among those who recover from any critical illness (J CLIN EXP HEPATOL 2019;9:99–108)

Acute Liver Failure (ALF) is a rare life threatening consequence of rapidly deteriorating liver function primarily characterised by evolving hepatocellular disorder associated with neurologic dysfunction and coagulopathy. It frequently affects young individuals resulting in high short term morbidity and mortality.¹ Reports from US estimate that there are approximately 2000 cases of ALF annually accounting for 6% of all liver related death.² Over last couple of decades the overall ALF outcome have improved substantially with advances in intensive care and optimized management with the wider availability of emergency liver transplantation (LT).³

Irrespective of the definition used, neurologic dysfunction has been the key element defining the course of Acute liver failure.^{4,5} The etiology of liver failure may vary with different geographical location of the hospital (Table1).⁶

Drug induced liver injury is the commonest cause of ALF in the west accounting for ~50% cases in western Europe and North America whereas most cases in South-east Asian and other developing countries are due to viral hepatitis (A, B and E)⁷ Hepatitis A & E are the commoner cause in India, China, Pakistan and other South-east Asian countries.⁸ The consistent central core of diagnosis of ALF involves jaundice, encephalopathy and coagulopathy as a manifestation of loss of liver function. Intense pro-inflammatory response resulting from ongoing hepatocyte necrosis leads to systemic inflammatory response syndrome with propensity to evolve as a complicated multi-systemic disease⁶ (Figure 1).

NEUROLOGIC MANIFESTATIONS OF ACUTE LIVER FAILURE

Neurologic manifestations of ALF can vary from subtle personality changes to life threatening complications from worsening encephalopathy, vascular complications from coagulopathy, seizures, cerebral oedema, intracranial hypertension, brain herniation eventually leading to coma and death.⁹ The initial symptoms in most cases may include apathy, excess sleep, poor cognitive functions, impairment in thoughts, judgment and memory with progression to disorientation.^{10,11} As encephalopathy worsens, spasticity, hyperreflexia and even clonus follows. These findings are more consistent with encephalopathy of acute liver failure than in encephalopathy of cirrhosis. Seizures have been reported in up to a third of patients and the possible reasons for this could be ammonia neurotoxicity, metabolic disturbances and mitochondrial dysfunction.¹² Subclinical seizures are difficult to diagnose at

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Abbreviations: ALF: Acute Liver Failure; APAP: Acetaminophen; BBB: Blood Brain Barrier; CARS: Compensatory Anti-Inflammatory Response Syndrome; CVVH: Continuous Veno-Venous Hemodialysis; DAMPS: Damage Associated Molecular Pattern; DWI: Diffusion-Weighted Imaging; EEG: Electroencephalography; FLAIR: Fluid-Attenuated Inversion Recovery; HE: Hepatic Encephalopathy; LT: Liver Transplantation; MPT: Mitochondrial Permeability Transition; PET: Positron Emission Tomography; SIRS: Systemic Inflammatory Response Syndrome
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Table 1 Etiology of Acute Liver Failure According to Different Geographic Locations in the World.

	Hepatitis A virus	Hepatitis E virus	Hepatitis B virus	Drug induced		Unknown	Others
				Acetaminophen	Others		
India	2%	44%	15%	0	1%	31%	7%
Bangladesh	3%	75	13	0	3%	6%	0
Japan	7%	1%	42%	0	9%	34%	7%
Sudan	0	5%	22%	0	8%	38%	27%
Germany	4%		18%	15%	14%	21%	28%
United Kingdom	2%	1%	5%	57%	11%	17%	7%
USA	4%		7%	39%	13%	18%	19%

Data compiled from Ref. 6

Figure 1 Brain dysfunction is an important part of multisystem involvement in Acute Liver Failure.

bedside and often need Electroencephalography (EEG) to confirm. Persistent and unrecognized subclinical seizures may lead to cerebral hypoxia and enhanced oedema. Pupillary reactions are initially normal but later, sluggish reaction and fixed mid-dilated pupils is suggestive of the brain herniation. Oculocephalic responses are usually normal but occasionally may become brisk or transiently disappear.¹³ The West Haven Criteria (Table 2) for grading encephalopathy in four stages I to IV is perhaps the best known scoring system.^{14,15} Clinical signs classically seen in raised intra cranial pressure, such as Cushing's response of systemic hypertension and bradycardia are not always present. Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) scans should be done to document

cerebral oedema in grade 3/4 coma and rule out any obvious structural or infectious cause for the same.

PATHOPHYSIOLOGY OF ENCEPHALOPATHY AND CEREBRAL OEDEMA IN ACUTE LIVER FAILURE

The pathophysiology of encephalopathy and cerebral oedema in ALF remains poorly understood and is likely to be a complex interplay of multifactorial events (Figure 2). The release of damage associated molecular patterns (DAMPs) from necrotic hepatic cells causes activation of the innate immune system (Kupffer cells and

Table 2 West Haven Criteria for Grading Hepatic Encephalopathy.

Grade	Level of consciousness	Personality and intellect	Neurologic signs	Electroencephalogram (EEG)
0	Normal	Normal	None	None
Sub-clinical	Normal	Normal	Abnormal only on psychometric testing	None
1	Day/night sleep reversal, restlessness	Forgetfulness mild confusion, agitation, irritability	Tremor, apraxia, incoordination, impaired handwriting	Triphasic waves (5 Hz)
2	Lethargy, slowed response	Disorientation to time, loss of inhibition, inappropriate behavior	Asterixis, dysarthria, ataxia, hypoactive reflexes	Triphasic waves (5 Hz)
3	Somnolence, confusion	Disorientation to place, aggressive behavior	Asterixis, muscular rigidity, Babinski signs, hyperactive reflexes	Triphasic waves (5 Hz)
4	Coma	None	Decerebration	Delta/slow wave activity

Modified from Refs. 14,15

Figure 2 Pathogenesis of cerebral edema and raised intracranial pressure in Acute Liver Failure (see text for details).

circulating monocytes) which in turn induce an intense systemic pro-inflammatory response (SIRS).¹⁶ The cerebral autoregulation which maintains a fine balance between carotid arterial pressure and intracerebral pressure (cerebral perfusion pressure = mean arterial pressure – intracranial pressure) is also lost in ALF. Circulatory disturbances as a result of pro-inflammatory cytokines, apart from affecting cerebral autoregulation results in marked splanchnic vasodilatation, increased cardiac

output, low systemic vascular resistance, hypotension, reduced cerebral perfusion pressure resulting in cytotoxic cerebral oedema.¹⁷ Systemic inflammatory mediators exacerbate vasodilatation causing endothelial dysfunction and disruption of the blood brain barrier (BBB).¹⁸ Damage blood-brain barrier accentuates uncontrolled movement of plasma and water into extracellular areas in the brain resulting in vasogenic oedema through microglial activation. Accumulation of several neurotoxins in brain

have been implicated in the pathogenesis of hepatic encephalopathy in acute liver failure. Ammonia released from the failing liver due to a lack of urea synthesis, by far is the key toxin involved and the most important pathogenic factor for development of encephalopathy and cerebral oedema. Arterial ammonia concentrations of $>100 \mu\text{mol/L}$ predicts the onset of severe encephalopathy with 70% accuracy¹⁹ and $>150 \mu\text{mol/L}$ predicted a greater likelihood of dying from brain herniation.²⁰ In an Indian cohort ammonia of $>124 \mu\text{mol/L}$ was predictive of poor outcome.²¹ Ammonia easily crosses the BBB and regulates both excitatory and inhibitory neurotransmission. Removal of brain ammonia depends almost exclusively on the synthesis of glutamine due to lack of urea cycle in the brain. In addition astrocytes are rich in the enzyme glutamine synthetase which catalyses the conversion of ammonia and glutamate into glutamine.²² This results in accumulation of glutamine within astrocytes that exerts an osmotic effect, causing astrocytes to swell resulting in cytotoxic brain oedema. Disturbances in other neurotransmitter systems and neuromodulators including increased GABA-ergic tone, serotonergic, noradrenergic, adenosine, acetylcholine and other false neurotransmitters also likely to contribute. Ammonia, hypo-osmotic swelling, inflammatory cytokines induce free radical formation (reactive oxygen and nitric oxide species) within the astrocyte mitochondria. Increasing evidence suggests that oxidative and nitrosative stress plays significant role in the development of cerebral oedema by inducing mitochondrial permeability transition (MPT), a state of 'power failure' due to mitochondrial dysfunction. Energy dependent compensatory mechanisms that normally regulates astrocyte volume fails to function in a state of mitochondrial dysfunction resulting in astrocyte swelling and cerebral oedema.²³ Astrocytes per se play a critical role in maintaining CNS functions by their ability to modulate both excitatory and inhibitory neurones. Recent evidences suggests ALF is associated with alterations in genes coding for three key astrocytic proteins regulating important CNS function.^{24–27} Microglia are the modified resident macrophages of the brain which get activated in response to a number of wide homeostatic challenges including tissue damage, vascular disturbances as well as changes in pH and impending energy failure. Activated microglial cells and astrocytes have the ability to produce a full repertoire of pro-inflammatory cytokines in the brain.²⁸ This results in a state of neuro-inflammation in ALF. Whether it is a part of, or is different from systemic inflammation is yet to be established.²⁹ Apart from the usual pro-inflammatory response, a compensatory anti-inflammatory response (CARS) also develops to counteract the excess proinflammatory state and limit the extent of tissue injury.³⁰ This CARS functionally impairs circulating monocytes by reduction in monocyte HLA-DR expression with a predisposition to infection.³¹ Systemic

inflammatory response and sepsis together is now increasingly thought to plays a crucial role in modulating the expression of severe encephalopathy and its progression to multi-organ failure and death.

REVERSIBILITY OF NEUROLOGIC DYSFUNCTION IN ACUTE LIVER FAILURE

Historically hepatic encephalopathy in ALF is thought to be potentially reversible after recovery. This hypothesis is recently challenged with the advent of liver transplantation when more and more ALF survivors tends to present with residual neurologic deficits.^{48–52} However, the rarity, severity and heterogeneity of ALF make it a uniquely difficult condition to study in randomized clinical trials. For all practical purpose absence of clinically overt HE is thought to be neurologic recovery in cirrhotic after transplant.³² Whether the same definition can be applied to ALF survivors is not clear. Several studies published on outcomes of liver transplantation after ALF do not mention any neurological sequelae.^{33,34} With liver transplantation the functional capabilities of liver restore to normal, hence it is expected that the clinically overt neurologic symptoms as well as those on psychometric tests should resolve completely.³⁵ Others have debated that these patients after an initial overt bout of HE are never the same.³⁶ With the availability of standardized neuropsychiatric tests, proving normality of brain function post-transplant is not an easy task. Moreover, it is practically difficult to discern if the neurological deficits are the result of direct effect of the pre-existing encephalopathy, worsening of underlying degenerative brain injury or a new onset neurologic deficit. Further evaluation using MR imaging with or without spectroscopy, PET (Positron Emission Tomography) scan and EEG (Electroencephalography) reveals structural abnormalities as well as cognitive impairment. Studies using functional brain imaging like PET scan, MR spectroscopy and other newer techniques like Magnetization Transfer Ratio (MTR), Fluid-Attenuated Inversion Recovery (FLAIR) and Diffusion-Weighted Imaging (DWI) of brain in post liver transplant period showed normalization of MR findings may take several months.^{37–39}

PROPOSED MECHANISMS FOR NEUROLOGIC IRREVERSIBILITY IN ALF AFTER RECOVERY

In consideration of persistent neuro-dysfunction following LT, possible causes other than previous HE should also be considered (Table 3). Persistent hyperammonemia and alterations in other neurotransmitters may account for short term residual encephalopathy. Pre-existing neuro-degeneration owing to previous stroke, alcohol

Table 3 Possible Causes of Neurologic Dysfunction in Survivors of Acute Liver Failure With or Without Liver Transplantation.

Factors related to ALF pre-transplant	Persistent hyperammonemia or neurotoxins
	Drug induced: Cyclosporins, Tacrolimus, Steroids, Anti-convulsants, Opiates, Sedatives
	Ischemic brain injury: Hypotension induced hypoperfusion during transplant, Cerebral edema during surgery
	Central pontine myelinosis
	Acquired hepatocellular degeneration (Wilson's disease)
	Seizure disorder
	Pre-existing CNS events: Stroke, Alcohol intake, Trauma, dementia
	Pre-existing cerebellar degeneration, alcoholism
	Vitamin B12, Folate and Niacin deficiency
	Septic encephalopathy
	Infections: Cytomegalo virus, Progressive Multifocal Leukoencephalopathy, Human Immunodeficiency virus, Cryptococcal infection, Neurosyphilis
	Vasculitis, Porphyria, Thyroid disorder
Factors related to transplantation	Hypoxic-ischaemic encephalopathy
	Hypotension
	Cerebral haemorrhage
	Central pontine myelinosis
	Gas embolism
	Paradoxical embolism
Factors in early post-transplant	Calcineurin inhibitors
	Corticosteroids
	OKT3
	Cerebrovascular complications
	Persistent porto-systemic shunts
Factors in late post-transplant period	CNS infections
	Primary CNS Lymphoma
	Recurrent disease
	Cerebrovascular complications

Modified from Refs. 46, 67

intake, trauma or dementia will remain unaffected in post-transplant period. In early post-transplant period around 10% to 25% of patients may have neurologic complications like seizures, metabolic/septic encephalopathy, drug induced complications or CNS infections like CMV, Cryptococcus and PML (progressive multifocal leuco-encephalopathy).⁴⁰ Intra-operative events like blood loss, fluctuating hemodynamics, rapid change in acid-base and electrolyte status can lead to decreased cerebral metabolism especially among those with encephalopathy and predispose them to high risk of neurologic injury when they are rapidly corrected after graft reperfusion. Resulting ischemic brain injury due to cerebral hypoperfusion is another cause.⁴¹ These potential causes for *de novo* neurological dysfunction may be confused with relatively rare residual brain damage due to encephalopathy. Although majority of ALF survivors with or without

transplant may have complete neurologic recovery, there is fair evidence of persistent neuro-deficit post ALF recovery in literature. Neurologic complication in post-transplant period has been reported between 10 and 47%.^{42,43} A large number of MRI abnormalities have been described during ALF and after liver transplantation, but most of them are reversible.⁴⁴ Autopsy studies show neuropathological abnormalities in about 60–70% patients.⁴⁵ Neurologic complications after LT may be grouped into those caused during LT (ie. Surgery related) and after LT (Early and Late post-transplant) complication 46([Table 3](#))

NEUROLOGIC SEQUELAE AFTER RECOVERY FROM ALF

Most publications on long term outcome in survivors with ALF do not mention about residual neurologic deficits.^{47,48}

In management of serious disease like ALF, one does not often think of sensitive tests and formal neuro-psychologic evaluation after recovery. This may account for instances of subtle neurologic dysfunction which may go undetected. Growing evidence supports neurologic irreversibility in selected group of patients post recovery from ALF.⁴⁸⁻⁵² Initial evidences are in the form of case reports of incomplete recovery. Fiasse et al. in 1974 reported a case with dysphasia for months after recovery from fulminant viral hepatitis.⁴⁹ In 1977 Tubbs et al. described permanent cortical and optic atrophy in a young female following acetaminophen induced fulminant hepatic failure.⁵⁰ In 1987 Brien et al.,⁵¹ reported two cases with localised persistent residual neurologic deficits after recovery from fulminant hepatic failure. A French study by Ichai et al in 1995 reported 152 patients who underwent liver transplant for ALF.⁵² Fifteen patients (9.8%) were found to be brain dead soon after liver transplantation. Seven (4.6%) survivors studied over more than 1 month had severe neurological sequelae like frontal syndrome, cerebellar ataxia, dementia, intellectual and memory deficits. All of these were on mechanical ventilation and had grade 4 encephalopathy. Six of these 7 had features of raised ICP and were treated with mannitol and/or CVVH (Continuous Veno-Venous Hemodialysis). CT Scan had shown Cisternal dilatation in 4, frontal hypodensity in 2, and cortico-subcortical atrophy in 6. None with spontaneous recover had any such changes. In another study reported by Hattori et al in 1998,⁵³ 11 children with fulminant hepatic failure who had encephalopathy (grade II to IV) were assessed after liver transplant. Two of the 5 children who had grade IV encephalopathy and cerebral oedema showed short term neuro-dysfunction but none of the other 8 children who survived, revealed any long term neurologic deficit. Two year outcome after initial survival in ALF was assessed in a study by Fontana et al in 2015.⁵⁴ Neurologic complications were the cause for death in 6.3% acetaminophen (APAP) group, 4.1% non-APAP group and in 10% in LT recipient group. Persistent neurologic complications at last follow up was found in 26.7% in non-APAP, 39.3% in APAP and 32.6% in LT recipient groups. Higher neurologic sequelae in APAP group may be due to pre-existing psychological abnormalities. Tan et al. in 2012⁵⁵ examined pre transplant neurologic status in 90 ALF patient who underwent liver transplant to studied the risk factors predicting severe post-transplant brain injury. After transplant, 7 patients as per the study definition had severe post-transplant neurologic complication. Of these 4 died in early post-operative period, 3 patient survived with chronic irreversible neurologic sequelae requiring assistance living affecting their quality of life. A study by Chan et al.⁵⁶ assessed long term outcome of emergency liver transplant in 60 patients with acute liver failure from 1994 to 2007, and reported post-transplant neurologic complications in 8(13%) patients. Six patients had major neurologic issues: central pontine myelinolysis (2 patients), anoxic injury (3 patients),

seizures (2 patients) and cerebrovascular ischemia (1 patient). Four of them died of sepsis and multi-organ failure. Two patient survived with chronic neurological deficits in the form of permanent cognitive, gait and speech disturbances. Six of the 8 patients with neurological complications or death had radiological evidence of pre-transplant cerebral oedema. Pre transplant cerebral oedema was found to be an important predictor of post-transplant neurologic complication in this study. In patients with acute liver failure, the effects of post-transplant neurologic sequelae on neuro-psychologic functions is largely unknown. Unpublished Indian data from PGIMER Chandigarh (personal communication Kumar, Dhiman & Chawla 2016) shows prevalence of cognitive impairment in 9 ALF survivors to be 33% to 66% at discharge and 22% at 8 weeks follow up. Cognitive changes found were significant memory impairment, mild mood disturbances, anxiety and impaired physical and mental quality of life. Acute Liver failure Study Group analysed 773 ALF patients from 1998 to 2010.⁵⁷ Of these 282 survivors (125 after transplantation) were followed up for up to two years with battery of tests to judge quality of life scores. In a case control study by Jackson et al.⁵⁸ with an intent to assess neuro-psychologic functions in post-transplant period, compared patients with ALF and those with chronic liver disease. Both groups underwent 2-hour battery of tests, which included measures of attention, memory, motor performance, abstract conceptualization, and visuospatial perception. Significant differences were found on general IQ and vocabulary, abstract conceptualization and verbal memory. Nearly all patients in both group complained of memory loss after transplant. However, concentration difficulties were more in patients with ALF than chronic liver disease. This was a very useful study which suggested that patients after recovery from ALF after transplant may have more neuro-psychologic dysfunction than expected.

NEUROLOGICAL RECOVERY AFTER RECOVERY FROM OTHER CRITICAL ILLNESSES

Persistent neurocognitive impairment has also been seen after recovery from other critical illness. Critical illness survivors frequently have poorly defined cognitive impairment. Cognitive dysfunction is a growing health problem especially in critically ill patients being treated in Intensive Care Units (ICUs). In one study, 821 patients with respiratory failure or shock in the medical or surgical intensive care unit (ICU) were evaluated for in-hospital delirium and its relationship to global cognition and executive function at 3 and 12 months after discharge. Six percent had cognitive impairment at baseline. At 3 and 12 months significant number had cognitive deficit and those with longer duration of delirium are more prone to

have worse cognitive scores.⁵⁹ Analysis of 10 cohorts with 455 patients that were assessed for chronic neurocognitive impairments following critical illness, reported neurocognitive impairments in 25 to 78 % of ICU survivors.^{60,61} A study by Hopkin et al in 2005⁶² reported neurocognitive impairments in 70% of patients with ARDS at discharge. Examined at 1 year and at 2 years, authors found the impairment in 45% and 47% respectively. Another study by Jackson et al in 2003⁶³ studied 34 ICU survivors at 6 month and found chronic neurocognitive impairment in 33%. Other supporting evidences of neurocognitive impairment in critically ill patients came from prospective study by Hopkins et al⁶⁴ in 2005 who reported neurocognitive impairment in 91% of 32 critically ill patients who received long term mechanical ventilation (i.e. 5 days) at discharge and in 41% at 6 month of follow up. Acute liver failure also requires critical care management in ICU and sometimes mechanical ventilation. Hence majority of neurocognitive changes seen in other critical illness may also be expected post recovery in ALF. Several studies have reviewed neurological complications after orthotopic liver transplantation for indications other than.⁶⁵⁻⁶⁷ In addition, a feature unique to ALF is existence of cerebral oedema, its neurologic sequelae and Liver transplant related neurologic and neurocognitive dysfunction. Needless to say immunosuppressant drugs and post-transplant CNS infections also contribute to neurologic manifestations in this group of patients. However, assessment for neurologic dysfunction after recovery from ALF is mostly neglected. Neurocognitive outcome in ALF survivors is a subject of immense interest, and more research work is required to gain insight into the natural history, prognosis, and potential mechanisms of these long term neurologic sequelae.

PREVENTION OF NEUROLOGIC SEQUELAE AFTER ALF

Prevention of neurologic complications after recovery from ALF depends on the intensive management of cerebral oedema and hepatic encephalopathy in ALF. A comprehensive approach with knowledge of the key pathogenic mechanisms is essential in managing these patients. ALF does have potential for recovery through regeneration of native liver. The aim of supportive care should be to optimize conditions for spontaneous hepatic regeneration and prevent complications. These patients should ideally be managed in intensive care setting especially in a centre capable of emergent liver transplant if required. Management should include necessary steps to prevent infection, adequate restoration of circulating volume, proper sedation, ventilatory and vasopressor support if required, adequate nutrition and correction of hypo-osmolality and metabolic disturbances. The role of

invasive intracranial pressure monitoring remains controversial with studies suggesting little clinical benefit and associated complications.⁶⁸ Short acting anaesthetic agents like propofol are commonly used to facilitate mechanical ventilation and reduce the risk of seizure activity. Vasopressor agents like noradrenaline may be required to achieve diastolic blood pressure > 40 mmHg higher than ICP to ensure sufficient capillary blood flow. Generally, the cerebral perfusion pressure is maintained above 55 mmHg. Adequate volume expansion with a colloid and crystalloids with early initiation of continuous renal replacement therapy is recently found to significantly increases in renal ammonia excretion resulting in a reduction in plasma ammonia concentration.⁶⁹ The use of hypertonic saline to keep serum sodium between 145 and 150 mmol/L may help to restore the normal osmotic gradient across the BBB thus reducing brain water content hence lowering the ICP.⁷⁰ Mannitol may also be used but with a target to keep serum osmolality < 320 mosm/L. Overt bleeding is uncommon in ALF despite significant coagulopathy hence routine administration of coagulation factors is not indicated. Broad spectrum antibiotics and antifungals are given empirically in addition to strict infection control standards is essential to reduce the risk of sepsis and progression to severe encephalopathy. In cases with resistant raised ICP, induction of mild hypothermia can be lifesaving as lowering the body temperature slows down the rate of metabolic processes involved in development of cerebral oedema. Non-steroidal anti-inflammatory drug (NSAID) indomethacin has been shown to effectively improve intracranial hypertension and cerebral oedema. However, the use of these NSAIDs may be complicated by impaired cardiovascular and renal hemodynamics by blocking the cyclooxygenases pathway predisposing these patients to increased risk of renal dysfunction.⁷¹ Special emphasis should be paid to maintain the nutritional status, enteral nutrition should be initiated as early as possible. If enteral nutrition is not tolerated intravenous feeding may be considered.⁷² Arterial ammonia should be monitored as hyperammonemia may be triggered by protein loads in enteral feeds. 20% and 50% dextrose should be used as required to maintain normoglycaemic status. Extracorporeal Liver Assist Devices (ECLAD) [both biological and non-biological] have long been sought as a means to temporarily augment liver function and stabilize clinical condition while awaiting definitive transplantation or native liver regeneration. In doing so it might increase the proportion of patients surviving with medical management alone. However, despite decades of research no device has yet been shown to be of definitive benefit to patients with ALF.⁷³

The introduction of emergency liver transplantation for critically ill patients with ALF in mid-1980s has been a landmark shift in the prognosis, survival as well as for prevention of neurological complications of these patients

since then. King's College Hospital (KCH) series of over 3300 patients with ALF, the overall survival rate was 16.7% in 1973 which improved to 62.2% in 2008 with the advent of liver transplantation.

VERDICT

Are residual abnormalities seen patients with ALF similar to those found in other critical illnesses? Neurocognitive disturbances seem to have complex pathogenesis which may be somewhat similar to that seen in other critical illnesses including liver transplantation. However specific neurological syndromes may be related to structural brain damage, which may be a complication of brain oedema and hypoxia.⁷⁴ The most devastating manifestation of ALF is worsening hepatic encephalopathy especially when associated with severe cerebral oedema which is seen in 33.3% on imaging.⁵⁵ Cerebral oedema is a potentially reversible condition following liver transplantation although a number of neurological disorders may occur in 14–47% of patients (Figure 3).⁷⁵ Intracranial hypertension normally resolves by 48 h following liver transplant assuming graft function is good. Data continues to emerge demonstrating the potential persistence of cognitive deficits associated with HE, even after liver transplant. Therefore, proper management of HE and prevention of cerebral edema in the pre-transplant state may improve outcomes among those patients admitted to the ICU. Cerebral oedema not only risks ALF patients for immediate death but also post-transplant neurologic sequelae including severe or irreversible brain injury despite liver transplant. Severity of preoperative cerebral oedema has been shown to be a strong predictor of postoperative neurological morbidity. Possible explanations for these

irreversible neurologic sequelae after ALF are, (a) Cerebral oedema in ALF can cause vascular interruption to vital brain structures leading to permanent irreversible brain damage. (b) Cerebral hypoxia from earlier attack of cardiac arrest, especially those in ICU and critical care settings (c) The compressive effects on the brain stem by of severe and prolonged cerebral oedema. (d) Cerebral oedema, by critically reducing cerebral perfusion pressure and therefore cerebral blood flow may lead to infarction in the territory supplied. However neurocognitive dysfunctions may also be a part of a wider spectrum of disorders commonly seen among survivors of many critical illnesses like ALF. Thus, patients with ALF may experience subtle neuro-psychologic deficits that are not discernible by interview alone, hence often go undetected. Detailed Neuro-psychologic testing is required to conclusively document these findings. The mechanisms by which delayed neuro-psychologic dysfunction may develop are not known. Memory functions are centered in the temporal lobe and hippocampus, although other subcortical structures, such as the thalamus, are involved as well. A recent study has evaluated changes in regional cerebral blood flow in patients with ALF who required mechanical ventilation. Cerebral blood flow appeared to normalize after resolution of HE. Thus, it is possible that changes in cerebral blood flow during ALF could render certain regions of the brain more susceptible to transient hypoxia, resulting in measurable changes in neuro-psychologic function after transplantation.⁷⁶

CONCLUSION

Neurologic manifestations of ALF in most patients is expected to completely normalize after recovery. Evidence supporting this concept is based on magnetic resonance spectroscopy studies showing gradual normalization of glutamine/glutamate and choline signals in a majority of patients. However in a proportion of patients neurologic or neurocognitive are irreversible even after recovery from ALF either spontaneous or after LT. Severity of HE and cerebral edema is a risk factor for neuropsychiatric symptoms after recovery. Subtle findings may be missed unless detail neuropsychiatric tests are done. Most patients undergoing LT do not develop irreversible neurocognitive ailment however incidences of permanent cognitive dysfunction despite lifesaving LT cannot be denied. Existing knowledge in this aspect is inadequate and more research is necessary to gain a clearer understanding of the key demographics and disease characteristics that are required to better identify patient subpopulations at greatest risk for neurologic complications after recovery from ALF. Future research should focus on methods of identifying the minority of patients who will develop permanent neurocognitive dysfunction and assessing means of neuro-prevention.

Figure 3 Prevalence of various neurological abnormalities in acute liver failure.

Modified from Ref. 46

CONFLICTS OF INTEREST

The authors have none to declare.

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