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Hepatic Encephalopathy: From Metabolic to Neurodegenerative

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Abstract:	Hepatic encephalopathy (HE) is a neuropsychiatric syndrome of both acute and chronic liver disease. As a metabolic disorder, HE is considered to be reversible and therefore is expected to resolve following the replacement of the diseased liver with a healthy liver. However, persisting neurological complications are observed in up to 47% of transplanted patients. Several retrospective studies have shown that patients with a history of HE, particularly overt-HE, had persistent neurological complications even after liver transplantation (LT). These enduring neurological conditions significantly affect patient's quality of life and continue to add to the economic burden of chronic liver disease on health care systems. This review discusses the journey of the brain through the progression of liver disease, entering the invasive surgical procedure of LT and the conditions associated with the post-transplant period. In particular, it will discuss the vulnerability of the HE brain to peri-operative factors and post-LT conditions which may explain non-resolved neurological impairment following LT. In addition, the review will provide evidence; (i) supporting overt-HE impacts on neurological complications post-LT; (ii) that overt-HE leads to permanent neuronal injury and (iii) the pathophysiological role of ammonia toxicity on astrocyte and neuronal injury/damage. Together, these findings will provide new insights on the underlying mechanisms leading to neurological complications post-LT.

Hepatic Encephalopathy: From Metabolic to Neurodegenerative

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Abbreviations:

AT2A, Alzheimer type II astrocytes
BBB, blood-brain barrier
BDL, bile duct ligation
BDNF, brain-derived neurotrophic factor
CCl4, carbon tetrachloride
cGMP, cyclic guanosine monophosphate
CLD, chronic liver disease
CNS, central nervous system
EEG, electroencephalogram
GS, glutamine synthetase
HE, hepatic encephalopathy
LT, liver transplantation
LTP, long-term potentiation
mHE, minimal HE
MRI, magnetic resonance imaging
NMDA, N-Methyl-D-aspartate
PCA, portocaval anastomosis
TAA, thioacetamide

Abstract

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome of both acute and chronic liver disease. As a metabolic disorder, HE is considered to be reversible and therefore is expected to resolve following the replacement of the diseased liver with a healthy liver. However, persisting neurological complications are observed in up to 47% of transplanted patients. Several retrospective studies have shown that patients with a history of HE, particularly overt-HE, had persistent neurological complications even after liver transplantation (LT). These enduring neurological conditions significantly affect patient's quality of life and continue to add to the economic burden of chronic liver disease on health care systems. This review discusses the journey of the brain through the progression of liver disease, entering the invasive surgical procedure of LT and the conditions associated with the post-transplant period. In particular, it will discuss the vulnerability of the HE brain to peri-operative factors and post-LT conditions which may explain non-resolved neurological impairment following LT. In addition, the review will provide evidence; (i) supporting overt-HE impacts on neurological complications post-LT; (ii) that overt-HE leads to permanent neuronal injury and (iii) the pathophysiological role of ammonia toxicity on astrocyte and neuronal injury/damage. Together, these findings will provide new insights on the underlying mechanisms leading to neurological complications post-LT.

Keywords: Hepatic encephalopathy, liver transplantation, neurological complications, ammonia toxicity, astrocytes, neuronal cell loss

Hepatic encephalopathy (HE)

Hepatic encephalopathy (HE) is a common and debilitating neuropsychiatric complication of chronic liver disease (CLD). HE is classified into two primary forms: covert/minimal HE (mHE) and overt-HE, encompassing sub-clinical and clinical signs, respectively. Characterized by impaired concentration, poor memory and cognition, lower speed of information processing, increased reaction time, mood disorders and disturbance in sleep-wake rhythms, mHE impacts the patients' health-related quality of life [1]. Moreover, mHE is associated with poor performance in daily activities, including the patient's ability to work and the proper capability to drive a car which in turn result in reduced work productivity and lost wages [2]. The prognostic value of mHE has been demonstrated to predict an episode of overt-HE which manifests with clinically evident symptoms such as lethargy, gross disorientation, asterixis, stupor and coma [3]. Overt-HE is associated with a poorer prognosis and higher mortality compared to other complications of cirrhosis [4] and is an independent factor of mortality regardless the degree of liver disease [5]. Between 53% and 83% of patients with CLD develop mHE and the incidence of overt-HE among patients with end-stage liver disease is 25-43%, with a 20% annual risk of developing further episodes of overt-HE [6–8]. HE is further divided into episodic HE defined by one episode of overt-HE occurring during a 6-month period, recurrent HE defined when 2 episodes occur within a 6-month period and persistent HE, defined by a pattern of behavioral alterations that are difficult to treat and never resolve [3].

An incidence of overt-HE is the most common cause for first-time hospitalization as well as for hospital readmissions in patients with CLD, with the mean annual hospital costs outweighing the outpatient costs [9, 10]. The burden of HE is multidimensional, imposing a significant economic burden to the patient, patients' caregivers, healthcare systems, and society. As one of the most frequent complications observed in CLD, the economic burden for HE is heavy, generating costs exceeding $11.9 billion per year (US statistics) [11].

Pathogenesis of HE

The pathogenesis of HE is multifactorial, and to date is not completely understood. Nevertheless, it is well accepted that ammonia plays a major role in disease progression [8]. The gut is the major source of systemic ammonia due to both dietary protein catabolism via amino acid deamination, and through urease containing bacteria which metabolize urea to ammonia [12]. In

healthy conditions, the liver metabolizes and regulates circulating levels of ammonia via the urea cycle; a family of enzymes found exclusively in the liver that metabolize ammonia to less toxic urea. Therefore, during CLD, a reduced capacity to clear ammonia leads to the development of hyperammonemia. Consequently, since ammonia easily cross the blood-brain barrier (BBB), high levels of blood ammonia cause deleterious effects to the brain [13]. It has been well documented that high brain ammonia is associated with dysregulation in metabolic pathways in astrocytes and neurons, microglia activation, and onset of cerebral edema, all believed to be implicated in the pathogenesis of HE [14]. In addition to hyperammonemia, other pathogenic factors such as systemic inflammation, oxidative stress, elevated bile acids, elevated manganese, and zinc deficiency may also synergistically contribute to the development and severity of HE [8].

Neurological complications following liver transplantation

Liver transplantation (LT) is the only curative treatment for end-stage liver disease. By definition, HE is a metabolic disorder and therefore is expected to completely resolve following the correction of the disease with LT. With advances and improvements in the LT surgical procedure and survival being less of a concern (85% at 1 year, 75% at 5 years) [15] quality of outcome, including neurological status and quality of life, has been increasingly supervised [16, 17]. In this context, even though most patients do improve following LT, numerous clinical studies have revealed that up to 47% of liver transplant recipients report neurological complications and enduring symptoms [17, 18]. These neurological outcomes appear to be specific to LT recipients since fewer neurological complications are observed in kidney or cardiac transplant recipients [19, 20]. Clinical neurological complications following LT include seizures, cerebrovascular complications, ischemic stroke, CNS infection, brain hemorrhage (hemorrhagic stroke), osmotic demyelination syndrome, cerebral embolism, central pontine myelinolysis and posterior reversible encephalopathy syndrome [17, 21, 22]. Moreover, some neurological complications after LT such as post-transplant encephalopathy, alteration consciousness, disorientation, confusion, memory impairment, headaches, difficulty concentrating, focal motor deficits, fatigue, sleep impairment, and mood disorders could last for years [16, 23–26] with neuropathological abnormalities found in up to 72% of patients at autopsy

[27]. In some cases, global cognitive impairments were reported to be present 9-12 months following LT [28].

Brain cell connectivity assessments by functional magnetic resonance imaging (MRI) showed that cell connectivity density improved in some but not in all brain regions in patients following LT [29]. In accord, cerebral positron emission tomography (PET) showed persistent reduced cerebral function and metabolism in frontal regions of the brain in 20% of patients with cirrhosis after LT, with no improvement up to 10 years later [30]. In addition, neuropsychological and electroencephalogram (EEG) analysis after LT showed that EEG activity normalized but global cognition remained impaired [28]. It is reported that neurological complications post-LT continue to weigh severely on the patient's quality of life and lead to longer stays in the hospital, thus causing further financial burden on the healthcare system [31]. Even though post-LT neurological complications can occur at any given time, improved survival of transplant recipients has led to increased detection of chronic neurological complications, which themselves impinge on morbidity and mortality [32]. Therefore, it is important to accurately identify the underlying cause(s) responsible for either persistent (HE sequelae) or de novo neurological complications observed following LT. Whether caused by (i) pre-existing HE (prior to LT), (ii) perioperative-induced neurological insults during LT or (iii) post-LT factors that remain to be determined.

Post-LT factors and neurological complications

Following insertion of a new liver, patients are placed on immunosuppressant agents (commonly calcineurin inhibitors) to reduce the risk of graft rejection, increase survival, and improve the longevity of the transplanted liver [33]. However, immunosuppression therapy is frequently associated with side effects, including malignancies, opportunistic infections, metabolic disorders, and organ toxicities infections [34]. Neurologic complications such as seizure, stroke, brain hemorrhage, and encephalopathy are observed in 15-30% of liver allograft which are regularly associated with opportunistic infections and immunosuppressant neurotoxicity [16]. Calcineurin dose, intravenous administration, as well as BBB permeability are believed to be responsible for the various neurological complications post-LT. The risk of infection is higher in immunosuppressed patients and it is well documented that systemic infection/inflammation impacts brain function [35, 36]. Moreover, CNS infections in post-LT are not rare and chronic

immunosuppression leads to a higher risk of developing primary CNS lymphoma [37]. The impact of post-LT complications is significant as they may negatively affect compliance with immunosuppression regimens and complicate post-LT management [38]. The precise underlying factors behind post-LT complications, including infections and chronic immunosuppression, may cause the development of neurological deficits but the association remains unclear (Fig. 1).

Intra-operative factors and neurological complications

During the surgical procedure of removing an ailing liver and inserting a healthy one, there is a risk for hypotension, blood loss (hypovolemia), cerebral hypoperfusion, blood transfusion, ischemia, gas embolism and electrolyte correction (hyponatremia) [28, 32, 39]. These intra-operative factors could impact the brain, causing alterations of cerebrovascular system, seizures, ischemic or hemorrhagic stroke, osmotic demyelination syndrome, and encephalopathy [16, 17, 39, 40]. In addition, general anesthesia during surgery can precipitate post-operative long-term cognitive dysfunction via oxidative stress and neuronal apoptosis, [41] which may contribute to neurological complications after LT. Neurological complications are frequently (75% of cases) observed within the first month after LT. In particular, transplanted patients develop a delirium state, characterized by acute confusion, inattention, disorganized thinking and altered level of consciousness that can last days to weeks [22]. The underlying causes of delirium remain unidentified. However, intrinsic surgical aspects (including duration of surgery/anesthesia) per se may be responsible [26]. This reasoning is reinforced since the prevalence of neurological complications is particularly high in patients having received a LT (47%) compared to patients having undergone cardiac or kidney transplantation (1.7% and 1.6% respectively) [18–20]. The frequent number of neurological complications observed specifically in LT patients suggests that an acquired factor associated with liver disease (e.g., metabolic disorders or HE) or its combination with transplantation-associated insults may be responsible for complications rather than intra-operative transplantation insults. For instance, brain MRI analysis identified alterations in cerebral metabolites in patients with post-transplant encephalopathy vs patients without post-transplant encephalopathy. Moreover, both groups had similar alterations in cerebral metabolites pre-LT, suggesting that intra-operative factors associated with LT (surgery duration, complications, time under anesthesia, and others) may influence cerebral osmolytes and neurological performance after LT [24]. Nevertheless, further studies are needed to precisely

understand to what extent intra-operative factors/insults impact brain function and contribute to neurological complications post-LT.

History of HE before LT and neurological complications post-LT

There is an extensive amount of studies demonstrating the strong association between HE pre-LT and neurological complications post-LT. Campagna et al., demonstrated that patients with a history of overt-HE fared worse on both paper and pencil and computerized psychometric assessments as well as electroencephalographic evaluations post-LT when compared to patients without a history of overt-HE [28]. Sotil et al., demonstrated that patients with a history of overt-HE had a worse performance on neuropsychological testing using the Psychometric Hepatic Encephalopathy Score (PHES) and critical flicker frequency compared to transplanted patients without a history of HE [42]. Garcia-Martinez et al., elegantly demonstrated that the existence of mHE or episodic HE highly impacts cognitive function following LT [43]. In addition, patients with a history of mHE have demonstrated to continue experiencing neurological complications following LT [44–46]. Mechtcheriakov et al., showed that the prior history of mHE leads to incomplete improvement close to 3 years following LT [47]. Together, these discoveries indicate that history of HE is associated with neurological complications and brain structural impairments after LT.

HE: the vulnerable brain

The journey of the brain from the onset of liver disease to post-LT involves multiple encounters with a variety of insults such as etiological factors of liver disease, comorbidities, metabolic alterations, perioperative challenges, post-LT immunosuppression and other complications. Poor brain reserve, characterized by brain structural changes and inability to adapt or tolerate changes, has been shown to modulate the impact of brain disease or neurocognitive insults such as HE [48, 49]. A destabilized HE brain may be more sensitive to intra-operative factors as well as post-LT immunosuppression and complications, including infection. However, which components of HE lead to increased susceptibility is not clear. BBB alterations (increased permeability) in patients suffering from HE may lead to vulnerability [50], particularly in regards to immunosuppression neurotoxicity during the early days following LT [51]. In acute liver failure (ALF), intracranial hypertension impairs cerebral blood flow [52] increasing the risk of

brain injury during LT [53]. Independent of HE, alterations in cerebral osmolytes have been shown to be associated with post-transplant encephalopathy [24]. Different detrimental factors in end-stage liver disease including inflammation, malnutrition/sarcopenia, altered glucose metabolism, and systemic hemodynamics alterations (hyperdynamic state, hypovolemia) are associated in some degree with increased risk of post-transplant neurological complications [40, 54–56].

Dhar et al., wisely demonstrated that HE *at the time* of LT leads to a higher prevalence of neurological complications post-LT [46]. More precisely, patients with severe HE had a higher risk of poorer neurological outcome than patients with mild HE. This study is of great value as it describes the neurological status of patients *at the time* of LT compared to other studies which document the events of HE that occurred in the months leading up to LT. This strongly suggests HE while the surgery renders the brain more susceptible to the perioperative insults of LT. In agreement, we recently demonstrated that in a rat model of CLD with mHE (BDL, bile-duct ligated model), exposition to hypotension leads to neurodegeneration; a finding which was not replicated in naïve rats [57]. This permanent brain injury is primarily due to the hypotension stress which compromises energy supply to the brain; an organ with high energy demand to properly function [58]. This reinforces the proposition that, in the setting of mHE, the compromised brain becomes predisposed to what would normally be an innocuous hypotensive insult, resulting in cell injury and death. This could explain the anticipated susceptibility of patients with mHE to cerebral damage following intraoperative stress (i.e a hypotensive insult) and subsequently the enduring neurocognitive dysfunction following LT. Although the impact of overt-HE on the susceptibility of the brain to intra-operative or post-LT factors is less known, patients with severe HE receiving a new liver had a poorer neurological outcome than patients with mild HE [46]. However, it remains to be determined whether an overt-HE brain is more susceptible to perioperative insults and post-LT factors when compared to a mHE brain.

Etiological factors involved in the progression of liver disease may render the brain vulnerable to insults. Liver cirrhosis associated to alcoholism has been related to neurological complications after LT with a higher rate of encephalopathy and seizures post-LT in alcoholic cirrhosis [59, 60]. Patients with alcohol-induced cirrhosis show poor brain reserve and are more susceptive to insults leading to neurological harm [48]. Patients with viral hepatitis (hepatitis C infection), have been associated with an increased risk of neurodegenerative disorders [61] such as

Alzheimer's and Parkinson's disease. Particularly, hepatitis C infection impairs metabolic pathways of infected cells, autoimmune disorders, systemic or cerebral inflammation and alterations in neurotransmitter circuits [62] which may contribute to brain sensibility to perioperative LT factors. Furthermore, non-alcoholic liver disease has been documented to lead to premature brain aging [63]. During the progression of liver disease, the brain is exposed to many different factors and conditions which may or may not manifest as HE but could render the brain fragile and vulnerable to insults which are normally innocuous to a healthy brain (Fig. 1).

HE and brain damage

For over half a century, accumulating evidence strongly defined HE as "gliopathy" since significant alterations in glial cells are consistently identified. Reactive astrogliosis, described as astrocyte responses or remodeling to abnormal events in the CNS, including neurodegenerative events and diseases, as well as exposure to toxic substances that specifically damage astrocytes (e.g., ammonium in HE). Thus, in response to pathological stimuli astrocytes experience transcriptional, biochemical, morphological, metabolic, and physiological alterations. In turn, diseases astrocytes can initiate or contribute to the disease progression [64]. For instance, astrocyte swelling, including Alzheimer type II astrogliosis (AT2A) are cardinal features of HE in CLD [65]. Morphological changes to neurons have not been well studied or documented, primarily due to the fact that HE is characterized as a metabolic disorder and therefore considered reversible following correction of the disease. However, it is becoming quite evident with studies carefully demonstrating that HE (or certain parameters of HE) do not fully reverse since residual HE (sequelae of HE) exist. This irreversible component of HE suggests permanent cell injury that may be an underlying cause for the observed neurological complications following LT. Moreover, there are multiple studies suggesting that irreversible cell injury occurs following episode(s) of overt-HE. Bajaj et al., demonstrated in cirrhotic patients experiencing their first episode of overt-HE that despite treatment and resolution of altered mental status, cognitive function (learning capacity, working memory) is persistently impaired (defined as persistent HE). In addition, the number of overt-HE episodes correlated with the severity of the persistent cognitive impairment, including a wider spectrum of impairments [66]. Moreover, brain functional MRI analysis in patients with mHE and history of overt-HE demonstrated that brain connectivity in different regions was further impaired compared to patients with current

mHE without history of overt-HE [67]. Brain MRI studies in cirrhotic patients with a history of mHE, without past episodes of overt-HE, demonstrate increased mean diffusivity (MD) of water molecules in frontal and temporal lobes which improves following LT along with improved neurological performance [68]. Furthermore, brain functional MRI in cirrhotic patients without overt-HE showed that functional brain network (connectivity) was normalized along with cognition improvement after LT [69]. Patients with cirrhosis and mHE, without a history of overt-HE, have demonstrated improved cognition with treatment [70]. This suggests mHE with a history of overt-HE may have underlying permanent damage leading to persistent HE compared to mHE without episodes of overt-HE.

There is evidence insinuating overt-HE leads to irreversible brain damage. Brain atrophy (thinning of the cortex) has been documented in patients who have recovered from overt-HE [71] and is associated with persistent HE [72]. Moreover, brain MRI analysis after LT demonstrated that despite cognitive improvement following LT in patients with history of HE, white matter brain atrophy was still detectable short- (6-12 months) and long-term (6-9 years) following transplantation [73]. Furthermore, these findings were associated with a reduction in the neuronal marker NAA (N-acetyl-aspartate), indicating neuronal loss [43].

Independent of HE, etiological factors with chronic exposure have shown to provoke neuronal cell loss/damage. There is evidence to suggest that liver failure contributes to the severity of neuronal loss in Wernicke's encephalopathy (acute neurological condition) [74]. Specifically, Wernicke's encephalopathy is associated with neuronal death in the mammillary bodies, thalamus, hypothalamus, and cerebellum brain regions [75]. Post-mortem brain analysis showed that patients (alcoholic and non-alcoholic) dying from severe HE (hepatic coma) had cerebellar degeneration and thalamic lesions, the latter being a characteristic of Wernicke’s encephalopathy [76]. Further neuropathological evidence for loss of neurons in cirrhosis have been described in acquired (non-Wilsonian) hepatocerebral degeneration and post-shunt myelopathy [74].

Overall, numerous factors during the progression of liver disease, including the underlying causes of end-stage liver disease, as well as episode(s) of overt-HE and persistent HE can lead to permanent cell injury, justifying lasting neurological complications following LT (Fig. 1). However, prospective studies investigating the impact of HE, particularly in identifying which pathogenic conditions or risk factors provoke neuronal cell damage, are warranted.

Ammonia neurotoxicity

Hyperammonemia plays a major role in the pathogenesis of HE. Particularly, hyperammonemia leads to cerebral dysfunction associated with neuropsychiatric and neurological complications including impaired memory, shortened attention span, sleep-wake inversions, brain edema, intracranial hypertension, seizures, ataxia, and coma. Increased brain ammonia leads to abnormalities in intracellular pH, membrane potential and cell metabolism that contribute to a cascade of secondary neurotoxic effects and encephalopathy [13]. Furthermore, even if treatment of the acute episode of overt-HE improves mental status, there is evidence that the metabolic insult associated with overt-HE may cause irreversible neuronal injury. Montoliu et al., found that blood ammonia was higher in patients with mHE who experienced cortical thinning (superior cortex) compared to patients without mHE [77]. While historically it has been thoroughly demonstrated that astrocytes represent the principal target of ammonia toxicity, neurons have also been shown to be directly affected by ammonia [78].

Neurons

Neurons are responsible for communicating information in both chemical and electrical forms. These highly specialized cells transmit and receive signals to allow the regulation of all body functions. Therefore, alteration in their structure, function, connectivity, as well as their death, has been associated with different neurological disorders. There is vast evidence supporting that ammonia toxicity leads to brain cell alterations which are associated with cell structure, morphology, proliferation/density, excitotoxicity, and ultimately cell death [14, 79]. Clinical studies using brain MRI demonstrated that neonatal hyperammonemic encephalopathy resulting from urea cycle disorders (UCD) leads to severe shrinkage and collapse of the brain [79, 80]. The neurotoxicity of ammonia is associated with the activation of different apoptotic substrates/pathways leading to neuronal death [81]. 28-day hyperammonemic cirrhotic-BDL rats showed that neurological impairments were associated with synaptic loss, apoptosis, and neuronal cell death in the hippocampus and substantia nigra compacta [82, 83] via intracellular Ca^{2+} overloading and continuous mPTP opening (mitochondrial permeability transition pore) [83]. Experiments in thioacetamide (TAA) rats, a model of liver injury and hyperammonemia, revealed that Bcl2/Bax apoptotic markers ratio was impaired in brain cortex and cerebellum suggesting a neurodegenerative proapoptotic process in those regions [84]. In addition, the

modulation of neurodegeneration-related genes was found to be impaired in hyperammonemic 5-month portacaval anastomosis (PCA) rats, an effect associated with apoptosis in Bergmann glia of the cerebellum. Moreover, the same study showed a reduction of Purkinje neuron population, increased astrocyte size, and activated microglia in the cerebellum [85]. Hyperammonemic rats (4-week carbon tetrachloride (CCl4) model) demonstrated neurological impairment together with hippocampal neuronal cell loss which was prevented through attenuation of hyperammonemia [86]. Furthermore, acute ammonia neurotoxicity in rats has been associated with major disturbances in mitochondrial function and eventual cellular apoptosis by increasing cytoplasmic protein p53, an essential apoptotic pathway/marker [87]. *In vitro* experiments with cultured primary cortical neurons from newborn rats exposed to different concentrations of ammonia (1-10 mM ammonium chloride for 24 or 48 h) decreased neuronal survival in a dose dependent manner, in which apoptosis was the dominant type of cell death with the highest dose of ammonia (10 mM) [78]. Aside from cell apoptosis, cultured neurons exposed to ammonia (5 mM NH_4Cl for 48 h) showed neurodegenerative changes such as free radical production (oxidative stress), and impaired mitochondrial inner membrane potential [88]. These ammonia-associated apoptotic effects are related to p53 activation, mitochondrial apoptotic pathway activation, and neurite degeneration, along with an increased expression of apoptotic markers such as Bax, caspase 8, caspase 9, and caspase 3 [89, 90].

Together, these findings indicate that the neurotoxicity of ammonia leads to the activation of apoptotic pathways particularly in neurons, a mechanism that contributes to cell death.

Neuroplasticity

Neuroplasticity plays a significant role in brain function including memory, cognition, locomotion, motor-skill learning, and mood regulation [91]. The functional and structural changes of dendrites and dendritic spines are relevant for brain connectivity and long-term synaptic plasticity associated with cognitive processes. Thus, neurodegenerative diseases stem from alterations in neuroplasticity that affect the axons, dendrites, and synapses which proceed to neuronal death and permanent neurological complications [92, 93]. There is evidence showing that neuroplasticity and neurogenesis are impaired in liver disease and HE, particularly in association with hyperammonemia [86, 94]. Experiments in BDL and CCl4 rats with mHE showed that hyperammonemia modified the structure of neurons, which was associated with

motor coordination and cognitive impairments. Particularly, hyperammonemia reduced dendritic spine density in cortical and hippocampal neurons [86, 94]. The role of ammonia is fundamental since attenuation of ammonia improves cognitive function by preserving neuroplasticity and attenuating cell death [86]. Furthermore, hyperammonemia as a result of altered ammonia metabolism (transgenic mice with hyperammonemia from conditional knockout of hepatic glutamine synthetase) is associated with cognitive impairments and disturbed synaptic plasticity in cortico-striatal and hippocampal brain regions [95].

In the adult brain, the hippocampus is highly involved in neurogenesis and neuronal plasticity through a neurophysiological phenomenon named long-term potentiation (LTP), which is considered the hallmark of memory and learning [96]. Experiments in hippocampal brain slices (CA1 region) from hyperammonemic rats revealed that the degree of LTP was reduced [97]. In accord, hippocampal pyramidal neurons directly exposed to ammonia (100 μM acutely) inhibited LTP [98].These results indicate that neurocognitive decline associated with ammonia toxicity in the brain results from a reduction of LTP in the hippocampus which reduces neuronal synaptic strength.

Brain-derived neurotrophic factor (BDNF) plays a major role in brain plasticity, homeostasis and possesses neuroprotective effects including anti-apoptosis, anti-oxidation, and suppression of autophagy [99]. BDNF protects against mitochondrial dysfunction by reducing toxic NMDA receptor signaling, a major cause of excitotoxicity [99, 100]. Therefore, BDNF disruption has been involved in different neurodegenerative disorders such as Alzheimer's disease, in which total BDNF reduction is associated with impaired function on structural (spine density) and functionality (synaptic potentiation) [101]. In liver disease, BDNF's neuroprotective actions against NMDA toxicity [100] may be compromised in hyperammonemia and HE conditions, which are associated with reduced BDNF and overactivation of NMDA receptors. In HE, serum BDNF is reduced in cirrhotic patients [102], while in cirrhotic-BDL rats with mHE, BDNF was found reduced in the hippocampus [103]. In hyperammonemic rats, hippocampal BDNF depletion is associated with a reduction of astrocyte BDNF production [104]. Moreover, cultured astrocytes exposed to ammonia showed that impaired glutamate uptake and glutamate neurotransmission were associated with a reduction of extracellular BDNF [104]. Together, these findings demonstrated that ammonia neurotoxicity impacts neuroplasticity via a reduction in BDNF expression leading to decrease in number of neurons.

Astrocytes

Astrocytes are subtype of glial cells in the CNS a subtype of glial cells involved in regulation of ions, neurotransmitters, metabolism or neuronal synaptic networks that maintain the homeostasis of the brain, whereas loss of homeostasis represents the underlying cause of all brain disorders [105]. Astrocytes, also known collectively as astroglia, are part of the physical structure of the brain that maintains the BBB. Astrocytes provide physical and metabolic support to neurons, including energy metabolism regulation, electrical insulation, neurotransmitter regulation, network homeostasis, extracellular ion balance, and protection from neurotoxins (e.g., ammonia) [105, 106].

Swelling

Astrocytes express the enzyme glutamine synthetase (GS) that metabolizes ammonia. Nevertheless, it has been shown that high ammonia in the brain leads to excessive intracellular formation of glutamine, an osmolyte that results in ion disturbance (osmotic pressure), and astrocyte swelling in high concentrations [14, 107–110]. In addition, cultured astrocytes exposed to ammonia (5 mM for 24 h) showed increased S-100β protein release, a biomarker of astrocytic brain damage [104]. Brain edema is associated with HE, believed to be the consequence of astrocyte swelling. Therefore, ammonia-induced astrocyte swelling may leave the neuronal network unprotected and without astrocyte support, will lead to altered neuronal integrity and function [88].

Post-mortem brain tissue from patients who died in hepatic coma as well as *in vivo* and *in vitro* models of hyperammonemia, have shown that ammonia toxicity is associated with a reduction of brain glial fibrillary acidic protein (GFAP), a cytoskeletal protein in astrocytes that maintain cell communication and the functioning of the BBB [86, 111, 112]. Thus, ammonia can impair the structure and function of astrocytes, and consequently synaptic integrity, astrocytic-neuronal trafficking substrates, provoke neuronal loss and worsen neurological performance [113].

Alzheimer type II astrogliosis (AT2A)

AT2A are morphological features in astrocytes characterized by enlarged pale nuclei and lack of cytoplasm (unrelated to Alzheimer disease), first described in Wilson's disease by Alois

Alzheimer. AT2A are a pathological reactive astrocyte seen in systemic metabolic disorders, particularly those associated with hyperammonemia, which contributes to the development of HE. For instance, AT2A is a distinctive morphologic alteration in brain of humans and experimental animals suffering HE characterized by enlarged pale nuclei and lack of cytoplasm [114]. Indeed, AT2A is deemed the histopathologic hallmark of HE. However, the role of AT2A on astrocyte function and associated brain consequences remain to be elucidated. Nevertheless, considering that astrocytes carry out key function relevant for neuronal functioning (e.g., neurotransmitter uptake, and ion regulation), AT2A may be associated to neuronal dysfunction [114]. Nevertheless, AT2A has also been reported in a small percentage of cirrhotic patients without HE [65], suggesting that hyperammonemia, regardless HE, promotes AT2A. *In vitro* and *in vivo* experimental models of hyperammonemia confirmed that AT2A is associated with high ammonia levels [109, 114, 115]. For instance, cirrhotic-BDL rats on hyperammonemic diet displayed further increased brain ammonia levels and developed AT2A along with exacerbated motor incoordination as compared to BDL rats on regular diet [115]. Nonetheless, the exact neurological consequences of ammonia induced AT2A remains unknown, but it is possible that AT2A not only contributes to irreversible changes in astrocytes but also impacts neuronal function.

Senescence

Cellular senescence (arrest in synthesis phase of the cell cycle) in astrocytes has been associated in the progression of neurodegenerative and cognitive decline. For instance, post-mortem brain tissue analysis showed an up-regulation of oxidative stress and senescence markers (senescence-associated-β-D-galactosidase) in tissue from cirrhotic patients with history of HE but not in those without HE. In accord, elevated oxidative stress and astrocyte senescence markers along with reduced astrocyte proliferation were found in cultured rat astrocytes (but not in cultured neurons) when exposed to ammonia (5 mM NH_4Cl for 24, 48 and 72 h), a mechanism associated with the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) inflammatory pathway and up-regulation of heme oxygenase (HO-1; protective response to oxidative stress) [116, 117]. Thus, the inhibition of oxidative stress (reactive oxygen species, ROS formation) associated to ammonia toxicity in cultured astrocytes prevented senescence marker elevation, which may restore astrocyte proliferation [117, 118]. Moreover, ammonia-induced senescence in astrocytes

is associated with mitochondrial metabolism dysfunction including ROS formation, and membrane potential impairment, two factors that lead to astrocyte degeneration, and swelling, but it does not affect astrocyte viability. Therefore, impaired astrocyte network (quantity and quality) may affect synaptic connectivity (strength and number), astrocyte-neuronal communication, neurotransmission, and neuronal survival [116].

Healthy astrocyte = healthy neuron

As mentioned above, astrocytes are strategic specialized cells that support and control neuronal activity via expression of ion channels, neurotransmitter receptors, and subcellular calcium dynamics, which critically contribute to neuronal transmission. Indeed, the communication between neurons and astrocytes is vital in achieving coordinated activity among neuronal ensembles. For instance, one astrocyte in the hippocampus is involved in approximately 120,000 synapses from either excitatory and inhibitory neurons, indicating that astrocyte activity regulates glutamatergic and GABAergic neurotransmission [119], while human astrocytes can cover from 270,000 to 2 million synapses [120]. Therefore, altered balance of astrocyte–neuronal signaling could cause different neuropathological states including HE [119]. Thus, astrocyte impairment (cell swelling, AT2A) due to ammonia toxicity will significantly tamper synaptic transmission and cause dysfunction (Fig. 2).

Glutamate is the major excitatory neurotransmitter involved in most of the brain functions including memory, learning, cognitive, emotional, and endocrine regulation. However, glutamate levels elevated above normal lead to uncontrolled continuous depolarization of neurons, a toxic process called excitotoxicity that results in neuronal death [121, 122]. Astrocytes play a vital role in clearing the synaptic cleft of glutamate since they contain high affinity glutamate transporters [14]. Intracellular glutamate within the astrocyte is metabolized to glutamine via the enzyme GS, aminating glutamate to glutamine and removing ammonia. The newly generated glutamine is shuttled back to the neuron allowing it to be metabolized to glutamate and ammonia via glutaminase. This will allow the neuron to replenish the releasable glutamate pool. However, ammonia-induced astrocyte swelling or AT2A may impair this communication between astrocytes and neurons. Inhibition of glutamate transporters in astrocytes will lead to excitotoxicity and possibly cell death [123]. It has been clearly demonstrated that cultured neurons die when exposed to NMDA-induced excitotoxicity [100]. The mechanism underlying

glutamate excitotoxicity is multifactorial but excessive intracellular calcium concentration plays a major role via activation of ionotropic (NMDA and AMPA receptors) and metabotropic glutamate receptors (mGluR), precipitating mitochondrial dysfunction, oxidative stress, and activation of apoptotic pathways [122]. Ammonia toxicity in the astrocyte can lead to astrocytic glutamate release which could be dependent or independent of astrocyte swelling [124]. Studies have shown NMDA antagonism increases survival in rats with acute liver failure [125]. Chronic hyperammonemia has shown to upregulate the gene expression of NMDA (GluN1 subunit) in the hippocampus of cirrhotic-BDL rats with HE [126]. In addition, HE and ammonia toxicity are associated with enhanced glutamate-nitric oxide-cGMP pathway associated with the NMDA receptors [127, 128]. In fact, increased intracellular cGMP has been shown to correlate with neurotoxicity, neuronal degeneration, and neuronal death [129, 130]. Additionally, ammonia toxicity has been shown to impact on glutamate levels leading to a depletion of intracellular glutamate and eventually neuronal death (glutamatergic cells) [81]. For instance, cirrhotic patients who died from hepatic coma had reduced glutamate concentration in brain regions associated with HE [123, 131]. Similarly, studies in cirrhotic-BDL rats have shown that glutamate concentration depletion in the hippocampus was correlated with systemic ammonia levels [132]. Overall, disrupted glutamate homeostasis has been well documented in HE, however the implications of glutamate excitotoxicity in neuronal cell death remains poorly defined. However, it is clear that healthy astrocytes are vital for optimal neuronal functioning. *In vitro* experiments show that co-incubating astrocytes with neurons prevents neurodegenerative effects (cell death, free radical production, and mitochondria membrane impairment) when exposed to ammonia (5 mM NH_4Cl for 48 h). This suggests that astrocytes protect neurons from ammonia toxicity [88]. Experiments in hyperammonemic TAA rats showed that ammonia toxicity on astrocytes is linked to neuronal integrity impairment, particularly affecting synaptic and neuronal function [113]. Furthermore, Kril and Butterworth, clearly demonstrated in brains from patients who died in grade 3-4 hepatic coma that cerebellar degeneration, characterized by loss of Purkinje cells was accompanied with AT2A in the Bergmann glia layer [76]. As mentioned above, it has been clearly demonstrated that brain edema (possibly low-grade edema) is due to astrocyte swelling [133, 134] which can affect function. Therefore, astrocyte swelling/dysfunction significantly impairs astrocyte-neuron communication, resulting in neuronal dysfunction, neurological decline and eventually neurodegeneration (Fig. 2).

Conclusions

In as much as HE is defined as a reversible syndrome, there are increasing studies demonstrating that this may not be the case. Most evidence stems from the incidences of neurological complications detected in patients after LT. Whether the observed neurological complications and cognitive dysfunction post-LT are residual of HE (present before LT) and/or develop during the intra-operative procedures and/or post-LT, is difficult to determine and causes remains unclear. The brain during peri-operative conditions and post-LT management confronts a number of insults and factors that could be detrimental to proper brain function. However, since the majority of patients following LT succeed with positive neurological outcome, it is suggested that the status of the brain leading up to LT could impact neurological outcome post-LT. There is increasing evidence showing that an episode (or multiple episodes) of overt-HE induces permanent cell damage (persistent HE) in which patients are unresponsive to treatment. In addition, HE may render the brain sensitive to intra-operative and/or post-LT insults and conditions which in turn could cause newly or additional neurological impairments. Further studies are warranted investigating the impact of not only the number of episodes but also the frequency and intensity of episodes on neurological function and brain integrity. Duration of episodes should also be considered since it was reported that longer times spent in an overt-HE episode (>48 h) increases mortality [135].

It is clear that ammonia neurotoxicity not only impinges on astrocytes but can directly impact neurons as well. Ammonia toxicity affects astrocyte structure (AT2A, astrocyte swelling, senescence), altering function leading to astrocyte-neuron miscommunication and neurological impairment. Ammonia has also been shown to precipitate neuronal cell death. However, more studies are needed to thoroughly evaluate the extent of ammonia neurotoxicity while taking into consideration the concentration as well as the duration of ammonia exposure. Elevated blood ammonia has been shown to have prognostic value in patients with CLD [136, 137] and has shown to predict HE-related hospitalizations [138]. In addition, neuronal degeneration has been documented in animal models with chronic hyperammonemia [82–86]. Since the correlation between severity of HE and degree of hyperammonemia is weak, chronic elevated levels of blood ammonia could play an integral part in provoking neuronal injury and cell loss. Elevated

blood ammonia has also been shown to be toxic to other organs [139] therefore monitoring ammonia is critical to help improve management in patients with CLD [8].

Considering the goal of LT is not only to extend the life span of patients with end-stage liver disease but also to improve the patients' quality of life, HE should be considered during transplant criteria. Specifically, the Model for End-Stage Liver Disease (MELD) score system should include HE for an improving organ allocation [140].

An interesting line of research is understanding the role of neurodegeneration in the onset of HE since the metabolic component of HE frequently reverses after LT, whereas the structural component, underlying neurodegeneration, may persist [141].

In conclusion, the impact of HE not only leads to permanent cell damage under certain conditions but also renders the brain susceptible to intra-operative insults and post-LT management representing an increased risk of neurological complications post-LT. 30-45% of patients develop an episode of overt-HE while on the waiting list for a LT [43] and this highlights the importance of treating and managing HE with the goal in reducing the number of episodes of overt-HE. Development of preventive strategies that could improve the patient′s neurological prognosis after LT remain to be considered.

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Conflict of interest

The authors declare that there is no conflict of interest.

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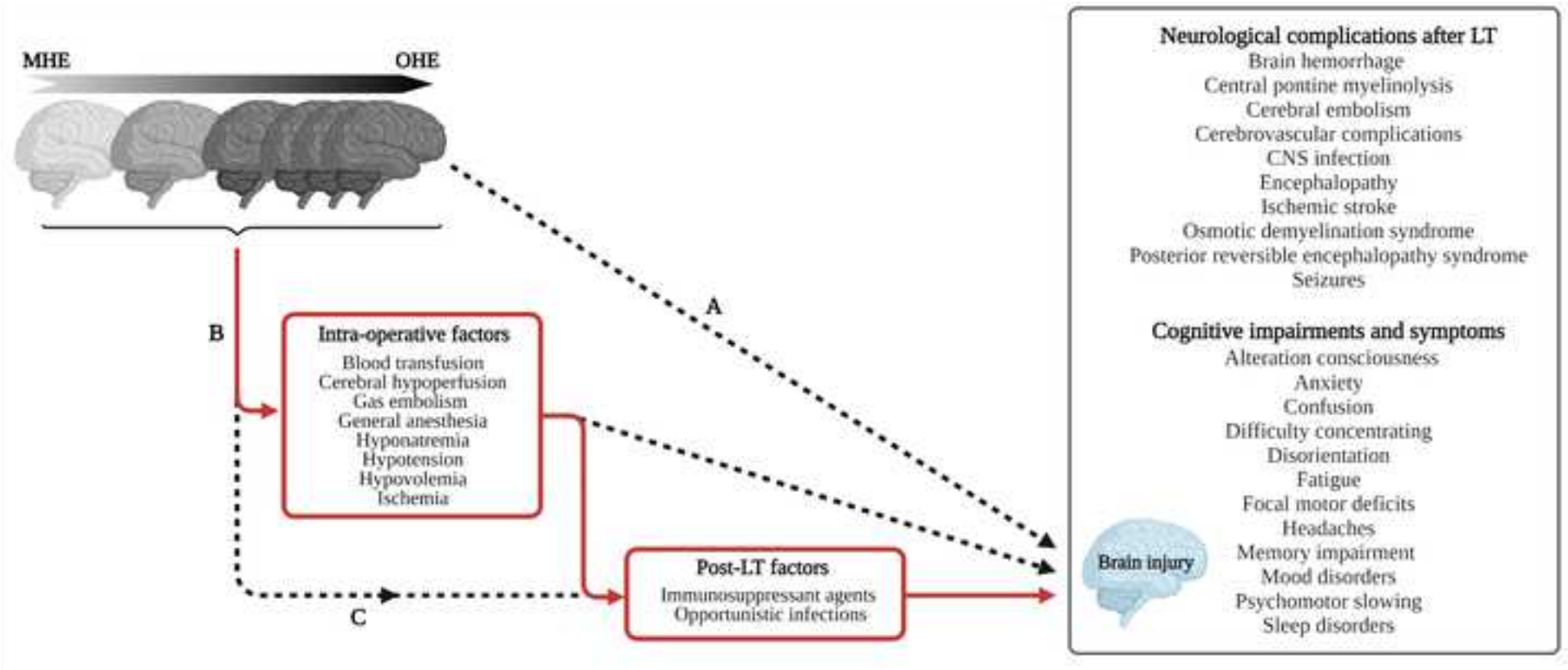
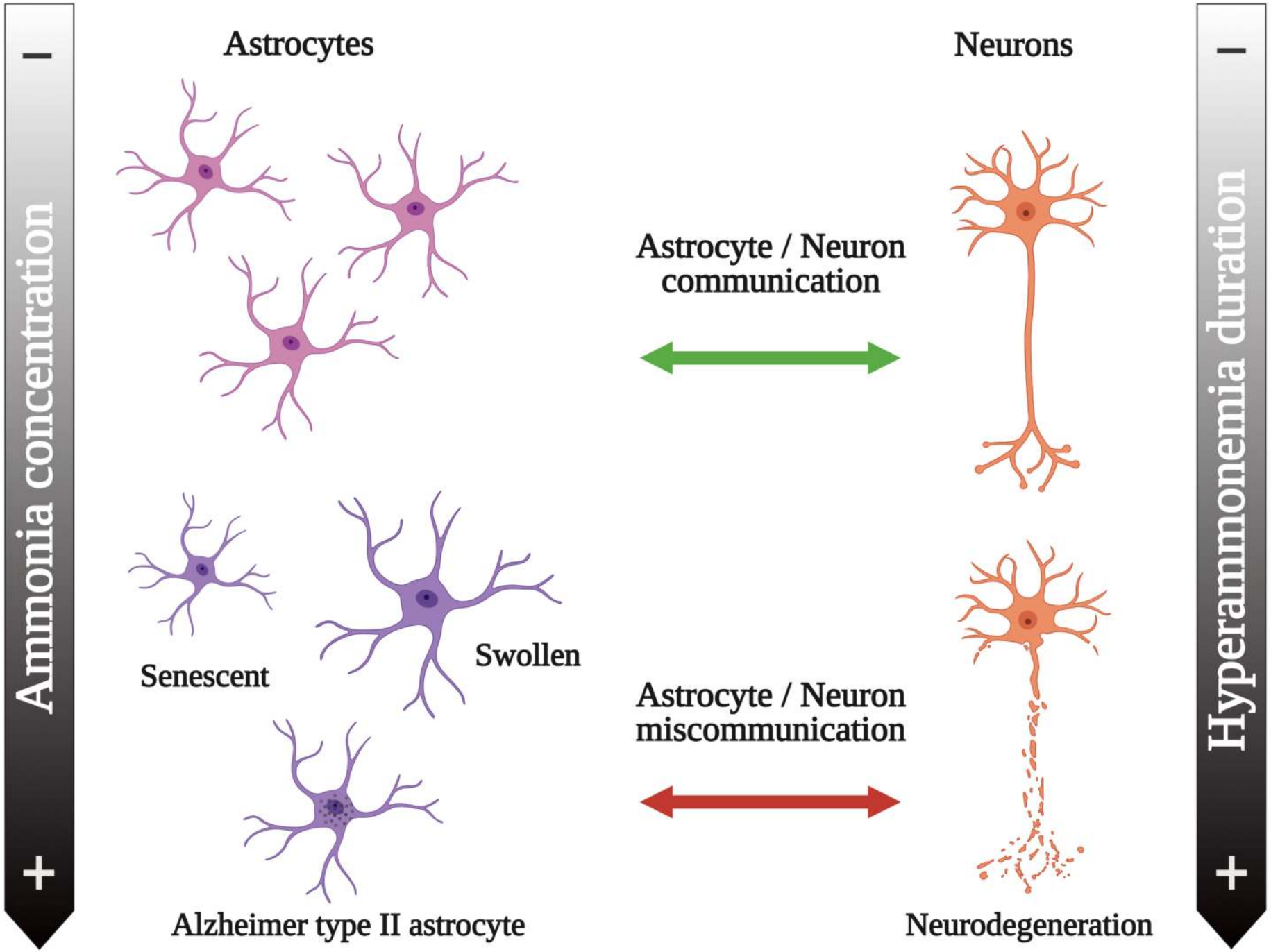
Legends

Fig. 1. The journey of the brain during the progression of liver disease until liver transplantation demonstrating its exposure to numerous factors and insults. The continuum of HE spans the range from normal cognitive function to minimal/covert HE (mHE) to overt HE (OHE). (A) History of HE (episodic, recurrent, permanent) may lead to permanent cell injury and neurodegeneration which will be irreversible and hence lead to residual HE following LT. In addition, an HE brain (B) entering in LT, exposed to intra-operative factors and insults, and/or (C) subjected to post-LT immunosuppression may also lead to irreversible components of brain injury and neurological complications.

Fig. 2. Ammonia concentration and duration leads to Astrocyte-Neuron miscommunication and neurodegeneration. Ammonia toxicity can affect astrocytes causing swelling, Alzheimer type II astrogliosis and/or senescence which in turn affects function and impairs astrocyte-neuron communication which may provoke neuronal cell loss. Ammonia toxicity has also shown to directly impact neurons causing apoptotic cell death. The level of ammonia required to induce cell damage or injury on either astrocytes or neurons remains undefined but toxicity increases with duration and concentration of ammonia.

Figure 1




Ammonia concentration
–
+
Astrocytes
Neurons
Astrocyte / Neuron communication
Astrocyte / Neuron miscommunication
Senescent
Swollen
Alzheimer type II astrocyte
Neurodegeneration
Hyperammonemia duration
–
+