23 Liver Transplantation: The Patient with Severe Co-morbidities, CNS Disease and Increased Intracranial Pressure

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Intracranial Hypertension in Acute Liver Failure

Etiology and Pathophysiology of Encephalopathy and Cerebral Edema in Acute Liver Failure

Intracranial hypertension (ICH) is a common cause of death in acute liver failure (ALF) [1]. The concept cerebral edema and hyperemia as a cause of the acute rise in intracranial pressure (ICP) in ALF is relatively novel and was first described in the early 1970s [2]. ICH is present in up to 75% of ALF patients with grade IV encephalopathy [3] and leads to decreased cerebral perfusion and risk of transtentorial herniation. The onset of ICH in ALF is rapid and allows insufficient time for adaptive processes. The underlying etiology is likely to be multifactorial.

Etiology: Cerebral Cytotoxic Edema

In an analysis of 165 patients with ALF of varying etiology [4], a high arterial ammonia concentration was an independent risk factor for severe encephalopathy and ICH. A level of >100 μmol/L predicts the onset of severe encephalopathy with 70% accuracy, and ammonia levels of >200 μmol/L are associated with the development of ICH and the possibility of herniation. Furthermore, patients who develop ICH tend to have persistently high ammonia levels. Higher MELD (Model for End-Stage Liver Disease) scores, younger age and requirement for vasopressors or renal replacement therapy are additional independent risk factors for hepatic encephalopathy [5].

Ammonia plays a crucial role in the development of cerebral edema because astrocytes take up ammonia produced by bacteria in the bowel and convert it into glutamine, which has considerable osmotic activity. Ammonia also causes additional changes in neurotransmitter synthesis and release, mitochondrial function and neuronal oxidative stress. The net result is astrocyte swelling and cerebral edema [6]. Brain glutamine concentrations are increased in animal models of fulminant hepatic failure (FHF) [7] and also in samples taken post-mortem from patients with FHF [8]. Cerebral microdialysis studies in patients with ALF confirm a strong correlation of arterial ammonia concentrations with brain glutamine content [9]. ICP correlates with brain glutamine, and arterial ammonia levels and persistent elevations of both parameters may identify individuals at risk of ICH (Fig. 23.1).

Gene expression may also be altered in response to the onset of FHF, particularly those genes coding for astrocytic proteins. These proteins have important roles in the regulation of cell volume and in neurotransmission. The expression of the astrocytic/endothelial glucose transporter gene, the aquaporin-4 water

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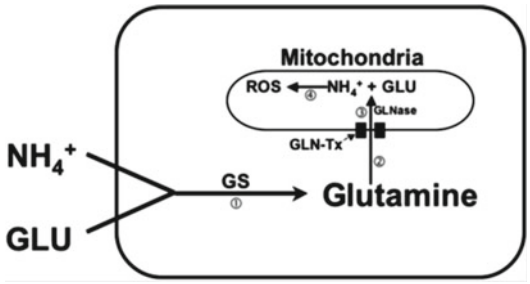

Fig. 23.1 Detoxification of ammonia to glutamine mediated by glutamine synthetase (GS) and subsequent creation of reactive oxygen species (ROS) following transport into the mitochondria. GLN-Tx—glutamine transporter, GLNase—glutaminase

channel and glutamate transporter gene have been specifically studied and demonstrated to be altered in FHF; however, the significance of any of these processes in isolation remains unknown.

Alterations in cerebral hemodynamics are common in acute and FHF and are discussed below. Blood–brain barrier injury, increased cerebral blood flow and hyperemia accompany astrocyte swelling and contribute to the rise of ICP. Blood flow is coupled to cerebral metabolic rate and changes in ventilation and acid–base status, and increases in blood flow can potentiate cerebral edema independently of astrocyte glutamine concentration [10].

In summary, cerebral edema may be vasogenic with inflammatory disruption of the blood–brain barrier, allowing extracellular edema formation (hind > forebrain), or cytotoxic with an increase in intracellular water as a result of defective osmoregulation (mainly forebrain). Evidence of predominant cytotoxic edema formation in ALF is based on findings of diffusion-weighted MRI scanning [11]. The diffusion coefficient that quantifies movement of water molecule across cell membranes is significantly lower in ALF patients with resolution of abnormal findings following recovery of liver failure.

Etiology: Cerebral Blood Flow

FHF is associated with an accumulation of toxic metabolites and a massive systemic inflammatory response with the release of a vast quantity of pro-inflammatory cytokines [12]. Alterations of cerebral blood flow are directly attributable to this inflammatory milieu: Cerebral edema is diminished in anhepatic rats compared with those with experimentally induced FHF [13]. Intrasplenic transplantation of allogeneic hepatocytes prevents development of ICH in pigs with acute ischemic liver failure and transient hepatectomy, and formation of a portacaval shunt has been used successfully in ALF patients with intractable ICH as a bridge to transplantation. The observation that ICH occurs with FHF, but not chronic liver disease, lends further weight to this 'toxic liver hypothesis'. ICP measurements during transplant surgery have demonstrated that ICP increases during the manipulation and dissection of the necrotic liver [14], but then decreases during the anhepatic phase and following graft reperfusion. Evidence from case reports [15] suggests that the levels of pro-inflammatory cytokines are diminished following removal of the toxic liver.

Loss of autoregulation can further lead to increased cerebral blood flow and blood volume and therefore ICH. This concept is supported by findings from animal models and seen in patients with FHF [16]. The loss of autoregulation has been attributed to the effects of nitric oxide (NO) on the cerebral vasculature, but it may be that elevated NO levels only occur secondary to increase in cerebral blood flow rather than as a primary and causative phenomenon [17]. Other pro-inflammatory mediators such as IL-1β, TNFα and IL-6 may also cause cerebral vasodilation and ICH [18].

Pathophysiology of Intracranial Hypertension

Normal ICP is approximately 7–15 mmHg in a supine adult. Definitions of ICH vary, but a pressure of >20 mmHg for a period of 20 min or more can be considered as an episode of significant ICH. Accurate measurement of ICH requires the insertion of an ICP monitor. The US ALF group recommends ICP monitoring for patients with advanced hepatic encephalopathy who are awaiting OLT and osmotic therapy for ICP ≥25 mmHg [19].

According to Monro and Kellie, the cranial compartment is essentially an incompressible

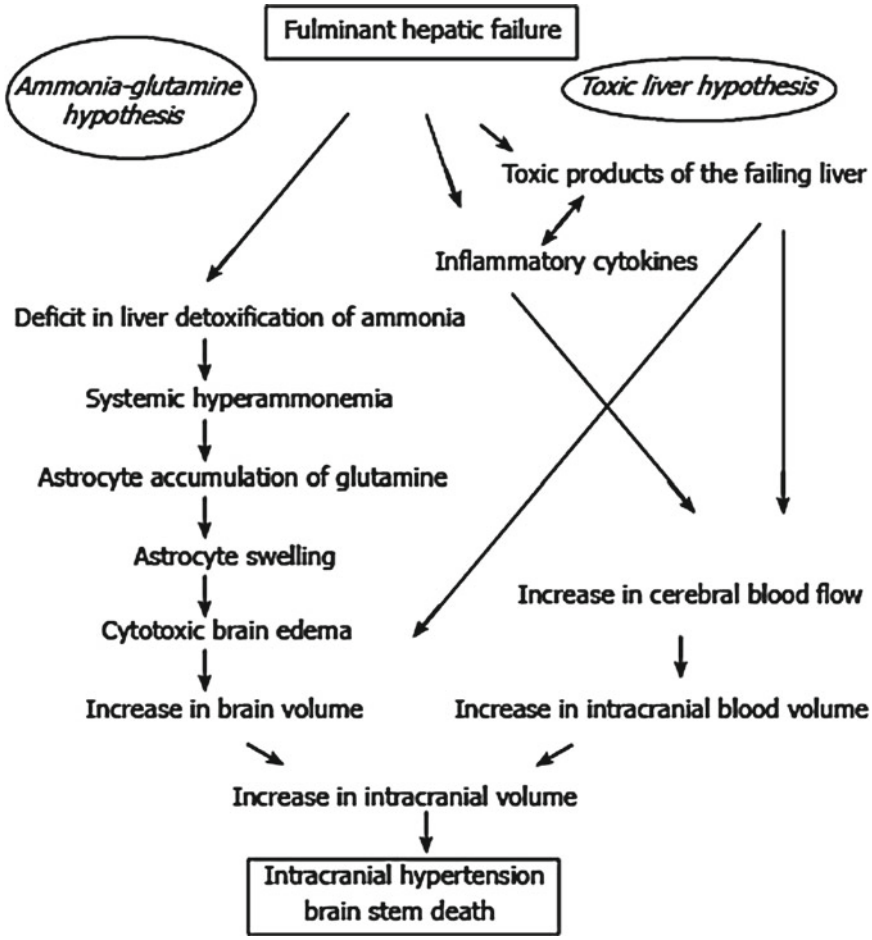

Fig. 23.2 Etiology of ICH. Uptake and detoxification of ammonia to osmotically active glutamine by astrocytes, leading to cerebral edema (the ammonia-glutamine hypothesis). Loss of cerebral autoregulation leading to increased CBF secondary to circulating inflammatory mediators (the toxic liver hypothesis), with disruption of the blood–brain barrier and vasogenic edema formation

box with a fixed internal volume. Blood, CSF and brain tissue (~90% of the total) exist in a state of volume equilibrium and are relatively incompressible, such that any increase in the volume of one of the cranial constituents must be compensated for by a decrease in the volume of another.

CT studies [20] in FHF have demonstrated that ventricular spaces are either unchanged or compressed, and therefore, the expansion of the CSF component is not responsible for rises in ICP. Rather, the radiological appearances are consistent with acute cerebral edema. Brain edema has been demonstrated in rabbits with galactosamine-induced fulminant hepatitis [21] and ammonia-induced cerebral edema in rats. Hyperemia due to defective autoregulation or circulating inflammatory mediators may further compound the rise in ICP. The main complication of profound ICH is diencephalic transtentorial herniation, causing:

- Posterior cerebral artery insufficiency with temporal, thalamic and occipital infarction
- Compression of the cerebral aqueducts and subarachnoid space with resultant obstructive hydrocephalus
- Brain stem compression, ischemia and death

To summarise, two predominant mechanisms are thought to underpin the rise in ICP seen in FHF [22] (Fig. 23.2):

- The uptake and detoxification of ammonia to osmotically active glutamine by astrocytes, leading to cytotoxic cerebral edema (the ammonia-glutamine hypothesis)
- The loss of cerebral autoregulation leading to increased CBF secondary to circulating inflammatory mediators (the toxic liver hypothesis) with disruption of the blood–brain barrier and vasogenic edema formation

Monitoring

Cerebral Perfusion Pressure

ICH compromises cerebral perfusion pressure (CPP) given their relationship: CPP = MAP – ICP (MAP—mean arterial pressure).

A sustained decrease of CPP to less than 40 mmHg for 2 h or more is associated with a poor outcome, although there are reports of complete neurological recovery despite prolonged periods of perfusion pressure below this threshold [23]. Whilst every attempt should be made to maintain cerebral perfusion within well-defined limits in our own experience, a transient decrement in cerebral perfusion should not be interpreted in isolation as a marker of poor prognosis.

Diagnosis and Multimodality Monitoring

ICH should be suspected in any patient who presents with hepatic encephalopathy in the context of acute or fulminant liver failure and/or significantly elevated arterial ammonia levels. Usually patients with ALF and rapidly evolving encephalopathy will require endotracheal intubation with subsequent sedation and mechanical ventilation. Under these circumstances, the only reliable early monitor of raised ICP—the patient's own conscious level—has been lost, although clonus, hypertonicity and decerebrate posturing may still be detected. Pupillary changes, systemic hypertension and reflex bradycardia are late changes, and radiographic changes are non-specific. A relatively 'tight' brain is often seen on CT imaging but correlates poorly with severity of cerebral edema or the presence of ICH.

ICP Monitoring

Insertion of an ICP monitor (after correction of coagulopathy) and jugular bulb oximetry readings allow for continuous monitoring of ICP and give an indication of the cerebral oxygen supply/demand relationship. ICH may develop rapidly and is subject to flux. Inadequate sedation, seizure activity and worsening edema/hyperemia can cause sudden and potentially dangerous surges in ICP. Continuous monitoring enables rapid detection of ICH and allows the physician to target therapy accordingly. ICP monitoring further allows estimates of the likely neurological outcome. In practice, clinical signs do not adequately quantify ICP. Similar to trials of traumatic brain injury (TBI), evidence from randomised controlled studies were not able to demonstrate a clear survival benefit of ICP monitoring in patients with ALF. In addition, the procedure carries an, although in expert hands small, yet significant bleeding risk [24]. Furthermore, a lack of consensus over the therapeutic goals has done little to promote the role of ICP monitoring in ALF. A recent study of 332 patients with ALF reported the experience with ICP monitoring in 24 centres [25]. ICP monitoring was used in only 92 patients (28% of the cohort), and 10% of these experienced intracranial hemorrhage. The 30-day survival for liver transplantation recipients was similar in both monitored and unmonitored groups (85% vs. 85%). A retrospective analysis of over 200 patients in our institution demonstrated much lower rates of associated hemorrhage of 0.8% [26].

Monitoring modalities differ between centres: Extradural monitoring is less accurate and associated with significant baseline drift, but penetration of the dura is associated with higher rates of bleeding. Patients whose ICP is monitored undergo more treatment interventions, but it is not clear whether these interventions are associated with better neurological outcomes.

Jugular Bulb Oximetry

Blood from the cerebral venous sinuses drains into the internal jugular vein. Monitoring of oxygen saturation in the jugular bulb allows an estimation of the balance of global oxygen supply vs. demand ratio and hence of cerebral metabolism.

Both intermittent sampling and continuous monitoring may be used, although the latter requires the insertion of a fibre optic catheter. The normal range for jugular venous oxygen saturations ($SjvO_2$) is 60–75%. Desaturations to less than 55% are indicative of cerebral hypoperfusion due to inadequate CPP or a sign of increased cerebral oxygen uptake as seen with seizure activity. High saturations >80% are found during cerebral hyperemia or with inadequate neuronal metabolism/neuronal cell death, respectively. High jugular venous saturations are equally associated with poor outcome as low values [27]. The major drawback of $SjvO_2$ is that it provides an estimate of global oxygenation and metabolism, and smaller areas of critical ischemia may not affect overall cerebral venous oxygen content. However, rises in ICP, effect of hyperventilation therapy, hypotension and cerebral vasospasm may all be detected with $SjvO_2$.

$SjvO_2$ is reduced in the following clinical scenario:

- Cerebral vasoconstriction (e.g. as a result of hyperventilation and hypocarbia)
- Hypoxemia
- Anemia
- Diminished CPP
- Inappropriately high CPP and vasoconstriction induced by exogenous vasoconstrictor
- Seizure activity

SjO_2 is elevated in:

- Hyperemia
- Vasodilation (e.g. as a result of hypoventilation and hypercarbia)
- Brain death

Transcranial Doppler

Transcranial Doppler ultrasound (TCD) is a simple and non-invasive method of quantifying blood flow velocities in the basal cerebral arteries (most commonly the middle cerebral artery). Cerebral blood flow is calculated from the mean flow velocity if the cross-sectional area of the targeted artery is known; thus,

$$\text{CBF} = \text{mean flow velocity} \times \text{area of artery} \times \text{cosine angle of insonation}$$

Successive measures of CBF are only comparable if the angle of insonation and the diameter of the target vessel remain the same. Varying vessel diameters with vasospasm are a potential source of error. An increase in flow velocities is seen with hyperemia and increased cerebral blood flow and during episodes of cerebral vasospasm. In order to differentiate between these two very different phenomena, the ratio of middle cerebral artery to extracranial internal carotid artery flow can be determined. The MCA velocity is normally about 60–70 cm/s with an ICA velocity of 40–50 cm/s. The MCA/ICA ratio is therefore 1.76 ± 0.1. An MCA velocity >120 cm/s is considered significantly elevated and when accompanied by a high MCA/ICA ratio likely due to vasospasm. If MCA/ICA ratios are lower, hyperemia is the more likely diagnosis.

Non-invasive Monitoring of ICP

Non-invasive monitoring of ICP with computed tomography, MRI, PET scanning or transcranial Doppler is inaccurate, noncontinuous and often impractical in advanced stages of ALF. Tympanic tonometry has been demonstrated to be inaccurate compared with direct ICP measurement but may be useful in detecting changes in ICP. The optic nerve sheath distends when CSF pressure is elevated. Measurement of optic nerve sheath diameter may therefore be an acceptable surrogate for the measurement of raised ICP. MRI and ocular sonography following TBI have demonstrated a correlation between nerve sheath diameter and presence of ICH. This method of assessment is user dependent but non-invasive and can be performed at the bedside. At present, its use in ICH related to FHF has not been fully

evaluated; it may be a useful adjunct if the indications for ICP monitoring are unclear, or in quantifying the risk of ICH and identifying those patients who are most likely to benefit from direct monitoring.

Preoperative Management

Accepted strategies for the reduction of ICH include specific therapies targeting ICP and the reduction of the volume of brain tissue, as well as general measures to protect against secondary brain damage following the primary insult (Rosner's conjecture). This should embrace all the factors responsible for causing secondary insult via cerebral ischemia.

Medical management thus falls under a number of broad titles:

- General supportive measures
- Prevention and treatment of raised ICP
- Achieving an appropriate CPP
- Specific medical therapies
- Anticipation and management of complications

An ICP >15 mmHg is considered abnormally high. Various authors have suggested different thresholds for treatment under different circumstances. The Brain Trauma Foundation [28] suggests a treatment threshold of 20 mmHg, whilst the US Acute Liver Failure Study Group [19] suggests treating ICP of 25 mmHg and above. The limits within which CPP should be maintained are also not clearly defined.

ICP-Targeted Therapies

The majority of treatment strategies are similar to those described in the neurosurgical literature, but many of the pathophysiological mechanisms of cerebral edema in ALF are unique and not applicable to other patient groups.

Positioning and Environment

The head of the bed should be elevated at ~30° to facilitate venous and CSF drainage. Further elevations have been shown to potentially cause paradoxical increase in ICP. Surgical tape should be used to secure endotracheal tubes (in a non-circumferential fashion) or tube ties loosened. The head and neck are kept in a neutral position, approximating the midline. Environmental stimulation is kept to a minimum.

Table 23.1 West Haven criteria for semiquantitative grading of mental state (encephalopathy grades)

Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade 2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behaviour
	Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

With permission from Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716–21

Ventilation

Encephalopathy is usually graded using the West Haven criteria for encephalopathy (Table 23.1). Endotracheal intubation is performed for airway protection in advanced grade III/IV encephalopathy, to facilitate the control of ICP (cerebral blood flow is coupled to cerebral metabolic rate and to paO_2 and $paCO_2$) and for the treatment of respiratory failure. Induction of anesthesia should aim to attenuate surges in ICP on laryngoscopy and intubation whilst maintaining CPP within acceptable limits. There is no general consensus regarding the mode of ventilation to be used. Given that acute respiratory distress syndrome (ARDS) may accompany the systemic inflammatory response of FHF (particularly with the development of

raised ICP), a protective ventilatory strategy should be adopted where possible (limiting tidal volumes to ~6 mL/kg and plateau pressure to <30 cm H_2O). Permissive hypercapnia is poorly tolerated as any rise in $paCO_2$ will be associated with a concomitant rise in ICP. High levels of positive end-expiratory pressure (PEEP) can diminish venous return and reduce hepatic blood flow; at the same time, PEEP levels up to 15 cm H_2O have been used safely in patients with TBI and ARDS. A 'best PEEP' strategy (choosing PEEP levels that will provide maximal recruitment whilst avoiding alveolar overdistension to optimise oxygen delivery) is advisable.

Hypoxia and hypercapnia cause CBF (and therefore ICP) to increase. Prophylactic hyperventilation may reduce brain edema and has been shown to delay the onset of brain herniation [29]; however, it can result in unwanted cerebral vasoconstriction which may be detrimental for oxygen delivery to marginal/at-risk areas of brain tissue. The Brain Trauma Foundation recommends the use of hyperventilation as a temporising measure only and suggests that it should be avoided during the first 24 h after TBI. In the setting of ALF, controlled studies have failed to show any benefit, with no reduction in the number of episodes of raised ICP [29]. Hyperventilation should be guided by jugular bulb oximetry or other forms of monitoring of adequacy of cerebral oxygen supply; as with TBI, it should only be used for the emergency rescue of imminent diencephalic herniation.

Temperature

In general, normothermia should be maintained. Fever needs to be treated aggressively because it stimulates cerebral metabolism and consequently induces vasodilatation. Cooling blankets and paracetamol are both suitable for this purpose. As many patients will require extracorporeal renal replacement therapy, low-temperature control can be easily maintained on extracorporeal circuits.

Glycemic Control

Hyperglycemia may exacerbate secondary brain injury (Rosner's conjecture) and exacerbate ICH [30]. A landmark single-centre clinical trial has shown an outcome benefit with tight glycemic control in critically ill surgical patients [31]. The same group failed to demonstrate a mortality benefit in a medical cohort [32]. In TBI, tight glycemic control can lead to critical brain tissue hypoxia and has been associated with poor ICP control, higher incidence of bacteremia and worsened survival [33]. ALF is associated with a propensity towards hypoglycemia, and there is no compelling evidence that tight glycemic control is beneficial in this population. ALF induces a systemic inflammatory response and hypermetabolic state. Catabolism predominates with a negative nitrogen balance and immunodeficiency. The energy expenditure even in the resting state is considerable, and early nutritional support is therefore recommended, although there is little evidence of benefit in this patient population.

Infection Prophylaxis

Infection is a frequent complication of ALF. In a recent study by the US Acute Liver Failure Study Group (US-ALFSG), the progression of hepatic encephalopathy was associated with sepsis, especially in patients with acetaminophen-induced ALF [34]. Respiratory tract infection, including ventilator-associated pneumonia is most prevalent although line-related sepsis, urinary sepsis, abdominal sepsis secondary to bacterial translocation and de novo septicemia are also common. Gram-positive cocci (*Staphylococci*, *Streptococci*) and enteric Gram-negative bacilli are the most frequently isolated organisms. Fungal infections are also common and may occur in a third of ALF patients [35]. It is routine practice to treat early and aggressively with antifungal therapy. Intravenous catheters should be monitored on a regular basis, changed routinely and removed where possible to avoid infectious complications.

Antibiotic prophylaxis is instituted as a matter of routine in all patients with advanced encephalopathy and when infection seems likely on the basis of clinical and laboratory investigations. US-ALFSG guidelines state that

> There are insufficient data to recommend the routine use of antibiotic prophylaxis in all patients with ALF, particularly those with early stage

hepatic encephalopathy….empirical administration of antibiotics is recommended in the following circumstances….

- surveillance cultures reveal significant isolates
- progression of, or advanced stage (III/IV), hepatic encephalopathy
- refractory hypotension
- presence of SIRS

Empirical antibiotics (antibacterial and antifungal agents) also are recommended for patients listed for OLT, because developing infection often results in delisting and immunosuppression is imminent, acknowledging that specific data to support this practice do not exist. It should be recognised that the risk of developing infection with resistant organisms will increase with longer waiting times.

Antimicrobial coverage should encompass commonly responsible organisms given the likely site of infection, the known bacterial flora of the intensive care unit at the time and the results of blood, urine and sputum cultures, chest radiographs and other surveillance modalities. Further details about infections and antibiotic treatment in liver disease and transplantation can be found elsewhere (Chapter 33) in this book.

Sedation and Neuromuscular Blockade

Sedation should be maintained in a continuous manner and be maintained at a depth that will prevent straining or coughing against the ventilator. BIS monitoring to evaluate depth of sedation is not routinely used and recommended. Intravenous anesthetic agents (with the exception of ketamine) decrease cerebral metabolism and reduce CBF via flow-metabolism coupling. Propofol is a widely used agent in this context and may attenuate CBF more effectively than benzodiazepines. Cerebral metabolic rate ($CMRO_2$) is elevated with inadequate anesthesia and will often be reflected by a low $SjvO_2$. Infusion of an opiate such as fentanyl is commonplace for synergistic sedative effect, to facilitate endotracheal tube tolerance, as an anti-tussive agent, to attenuate surges in ICP. Opiates themselves have little effect on cerebral metabolism and blood flow. Neuromuscular blockade is rarely required when adequate sedation and analgesia are used. Neuromuscular blocking agents mask seizure activity and may be associated with the development of critical care polyneuromyopathy. Their routine use cannot be recommended, although practice varies between centres. They are generally used to prevent coughing, straining and ventilator dyssynchrony and associated surges in ICP. Lidocaine can be administered intravenously or via the tracheal tube prior to the application of tracheal suction to attenuate coughing but is not necessarily common practice.

Seizure Prophylaxis

Grade III/IV encephalopathy is associated with a high incidence of non-convulsive seizure activity. Commonly used sedative agents such as propofol and benzodiazepines are well established in the treatment of epilepsy and provide some degree of prophylaxis/protection of the sedated and ventilated ALF patient. The prophylactic use of other anti-epileptics is not recommended. If BIS monitoring is used to assess the depth of sedation, then discordant readings may prompt further evaluation with EEG. The latter should also be considered for neurological deteriorations and to assess burst suppression when barbiturate coma is induced to treat refractory ICH.

Ammonia-Reducing Strategies

Considering the strong correlation between elevated arterial ammonia levels and the development of encephalopathy and ICH, ammonia-reducing strategies may be useful; however, there is no level 1 evidence to support this practice. Many of the agents that are regarded effective in chronic liver disease have no sufficient data to support their use in ALF.

There are no randomised controlled trials of lactulose administration in ALF, and it is often poorly tolerated in critically ill patients receiving high-dose sedation and analgesia, as reduced gut motility frequently leads to worsening gaseous distension. The routine use of lactulose is therefore not recommended. Neomycin, rifaximin and other non-absorbable antibiotics, such as metronidazole, oral vancomycin, paromomycin and oral quinolones, are administered to patients with chronic cirrhosis in an effort to decrease the colonic concentration of ammoniagenic bacteria.

There is also no strong evidence base supporting the use of these non-absorbable antibiotics in ALF.

L-Ornithine-L-aspartate (LOLA) reduces the hyperammonemia of hepatic encephalopathy [36] by increasing ammonia detoxification in the muscle although overall; however, there is no evidence of an outcome benefit. A placebo-controlled blinded study [37] randomised 201 patients with ALF to either placebo or LOLA infusions (30 g daily) for 3 days. Arterial ammonia was measured at baseline and then daily for 6 days. There was no reduction in mortality with LOLA treatment and no difference between the two groups in the improvement in encephalopathy grade, consciousness recovery time, survival time or complications like seizures and renal failure. CVVHD is indicated for acute renal failure, oligo-anuria and acidemia and has been demonstrated to reduce circulating levels of NH_4; part of the effect can be explained by temperature control and reduction in NH_4 production. There is no evidence that prophylactic use of CVVHD in the absence of other indications for renal replacement therapy improves outcome in patients with ALF and encephalopathy.

Fluid Management and Osmotherapy

Fluid management should be directed towards the provision of adequate hydration and treatment of hypovolemia. The blood–brain barrier will allow the passage of fluids and electrolytes along their osmotic gradients, and hypotonic fluids should therefore not be used as they have a tendency to exacerbate cerebral edema.

Osmotherapy is effective in attenuating cerebral edema. Mannitol and hypertonic saline are both recommended for this purpose. Mannitol elicits a classically described biphasic response [38]: There is an early fall in ICP as blood rheology improves. The improved blood flow enhances oxygen delivery and, via flow/metabolism coupling, results in cerebral vasoconstriction. A subsequent decrement in ICP is observed approximately 30 min later as mannitol increases plasma osmolality and draws brain water across the blood–brain barrier down its osmotic gradient. Mannitol also acts as an oxygen free-radical scavenger. Plasma osmolality should not exceed 320 mosmol/kg.

Hypertonic saline includes any concentration >0.9% NaCl, but solutions used for osmotherapy in ALF are commonly 2.7–30%. The indications for hypertonic saline are similar to those of mannitol. It also acts by establishing an osmotic gradient across the blood–brain barrier [39] with a subsequent reduction in brain water as water is drawn out of the brain parenchyma down its osmotic gradient. There is a biphasic reduction in ICP, similar to that of mannitol.

Serum sodium levels of 145–155 mmol/L are commonly used as a target and reduce the incidence of ICP rise above 25 mmHg [40]. In practice, patients with FHF are often anuric and require continuous renal replacement therapy, so serum sodium levels rarely exceed these values even with prolonged infusion.

The osmotic-reflection coefficient across the intact blood–brain barrier is higher (i.e. the BBB is less permeable) for hypertonic saline than for mannitol. It is therefore less likely to accumulate significantly in the brain parenchyma and, in theory, should be a more effective osmotic agent. It has been postulated that rebound ICH may be smaller with hypertonic saline than with mannitol. Hypertonic saline also causes effective volume expansion without a secondary diuresis.

Plasma osmolality is nominally kept below 320 mosmol/L, although this threshold has recently been questioned and poorer outcomes have only been associated with very high serum sodium levels and corresponding plasma osmolalities of 335–345 mosmol/L. Complications of hypertonic saline relate to the administration (tissue necrosis, thrombophlebitis) and metabolic side effects (hyperchloremic acidosis, hypokalemia, hypocalcemia). Osmotic myelinolysis may be precipitated if serum sodium concentrations are corrected too rapidly.

Therapies targeting cerebral perfusion pressure (CPP)

Under normal conditions, autoregulatory mechanisms ensure that CBF remains constant at approx-

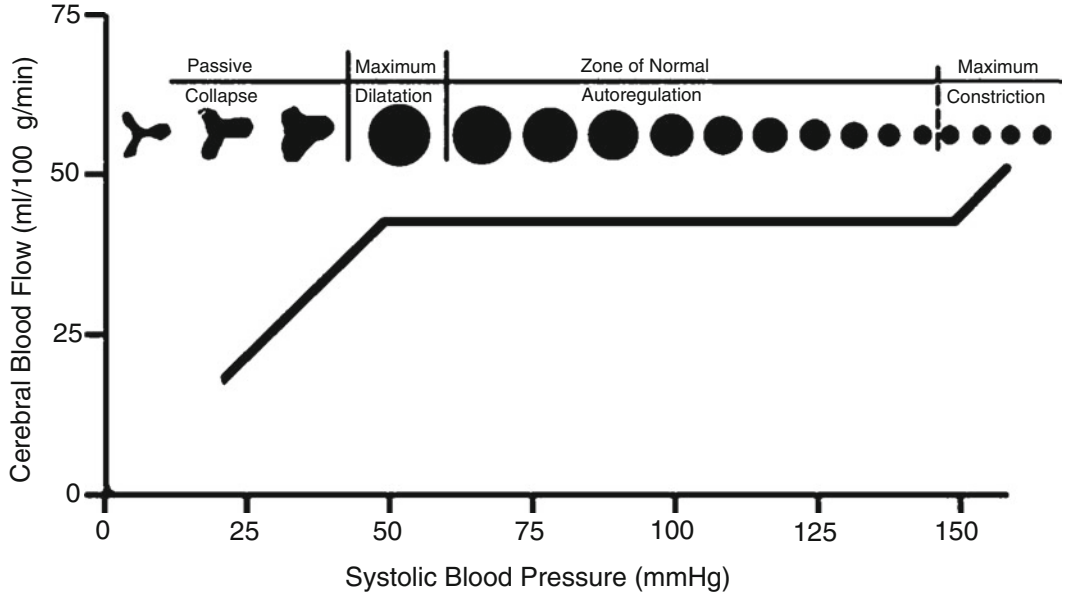

Fig. 23.3 The relationship between systolic blood pressure (SBP) and cerebral blood flow (CBF) in the uninjured brain. The ability to autoregulate blood flow may be lost in brain injury, and flow may become pathologically dependent on pressure

imately 50 mL/100 g/min within a CPP range 50–150 mmHg. In the injured brain, the relationship between CPP and CBF changes—the autoregulation curve tends to shift to the right, so that a CPP > 50 mmHg may be required to maintain flow and normal autoregulation may be disrupted, such that CBF becomes proportional to CPP. General principles of fluid management apply, and fluid therapy is perhaps best guided by the appropriate use of cardiac output monitoring that can provide dynamic measures of preload responsiveness and indicate whether or not stroke volume improves in response to filling. Injudicious use of fluids may worsen cerebral edema and associated lung injury. If hemodynamic optimisation with fluid therapy alone fails to achieve adequate mean arterial pressures in the face of systemic vascular resistance, vasopressors may be required to augment the CPP.

Increasing CPP may increase CBF, particularly in injured regions of the brain, but this will only occur if CPP has fallen below the autoregulation threshold or if autoregulatory mechanisms have failed altogether and CBF is proportional to the CPP. This may be desirable, but risks exacerbating ICH through increased cerebral blood flow and blood volume and worsening cerebral edema (increased hydrostatic pressures). Increasing CPP can also cause cerebral vasoconstriction (thus lowering the ICP) if autoregulation is intact (Fig. 23.3).

The target CPP has been the subject of some controversy. In polytrauma cases at risk of raised ICP, a MAP of 90 mmHg has traditionally been targeted in patients without ICP monitoring. In patients with ICP monitoring, a target CPP of 70 mmHg was originally recommended by the Brain Trauma Foundation in 1995. A contrasting view is that setting a higher CPP target will worsen brain edema by increasing the hydrostatic pressure gradients across tissue beds. There is also some evidence that targeting higher CPPs may promote the development of ARDS [41], although the underlying mechanism is unclear. This led to the Brain Trauma Foundation lowering the target CPP to 60 mmHg in TBI. The brain tissue oxygen partial pressure (PbO_2) may plateau at a CPP of 60 mmHg [42].

Whilst continuing to note the dangers of a CPP >70 or <50 mmHg, a recent recommendation is to monitor markers of cerebral oxygenation and metabolism to adopt an individualised approach to therapy within the CPP range of

50–70 mmHg [43]. Autoregulation thresholds vary over time; hence, CPP goals have to be adapted to changing clinical conditions.

The choice of vasopressor has not been subject of controlled clinical trials. Norepinephrine is the first-line agent, and low-dose vasopressin is increasingly used following trial experience in septic shock and TBI patients. Early concerns regarding increase in cerebral hyperemia with use of vasopressin or vasopressin analogues are probably unfounded. Epinephrine is poorly tolerated due to its effect on aerobic glycolysis and associated worsening of lactic acidosis.

Strategies for Treating Refractory Increases in ICP

Barbiturate Coma

Barbiturates can be titrated to burst suppression of the EEG and decrease cerebral metabolism ($CMRO_2$) and cerebral blood flow by virtue of flow-metabolism coupling. Sodium thiopental can be used as 'rescue therapy' to lower ICP refractory to other measures.

A loading dose of 5–10 mg/kg of sodium thiopental is required, followed by a continuous infusion of 3–5 mg/kg/h. EEG monitoring should be used to guide further therapy. Increasing doses above those required for burst suppression causes unwanted side effects such as arterial hypotension through negative inotropy and a lowering of systemic vascular resistance (dose-dependent) without conferring any additional benefit. Other complications of sodium thiopental therapy include immunosuppression, bronchoconstriction, electrolyte disturbances (notably profound hypokalemia), renal impairment (reduced renal blood flow and increased ADH secretion) and ileus.

After prolonged infusion, the metabolism of sodium thiopental becomes 'zero order'—the hepatic enzyme systems responsible for its metabolism become overwhelmed, and the lipid-soluble drug accumulates in tissues such as fat and muscle. The duration of action is therefore greatly prolonged and 'washout' of the drug takes considerable time. In addition, sodium thiopental is partly metabolised to pentobarbitone, which has a longer half-life than sodium thiopental itself.

Indomethacin

Indomethacin has been used in the treatment of refractory cerebral hyperemia [44, 45]. Doses of 25 mg iv over 1 min may have a vasoconstrictor effect, although in these circumstances, CBF may actually increase (as measured by transcranial Doppler) as ICP is reduced and CPP is restored. Indomethacin has been used more extensively in traumatic ICH, in patients with space occupying lesions and animal models and its use is not widely reported in ALF.

Therapeutic Hypothermia

Cooling the patient's core temperature to as low as 32–33°C reduces otherwise refractory elevation in ICP in patients with ALF [46]. Arterial ammonia levels and cerebral uptake of ammonia are reduced with hypothermia, with a reduction in cerebral edema and hyperemia. CPP improves as a result of diminished ICP. This degree of hypothermia has some deleterious systemic effects, including coagulopathy, immune suppression, insulin resistance and an increased risk in nosocomial infections—particularly ventilator-associated pneumonia. Prolonged hypothermia in patients not progressing to transplantation requires the use of deep sedation and/or paralysis to attenuate shivering. Several animal studies and case series have been published, and a pilot trial was recently completed: The *Hypothermia to Prevent High Intracranial Pressure in Patients with Acute Liver Failure* (Rigshospitalet, Denmark, 2009) is an open, randomised and unblinded study that intends to evaluate the effect of prophylactic hypothermia on preventing high ICP and compromised cerebral oxidative metabolism. It hypothesises that the reduced cerebral metabolic rate and reduced splanchnic ammonia production might contribute to neuroprotection and reduce the risk of cerebral hypertension in patients with ALF. Results from this trial are to be published soon.

Mild to moderate hypothermia, targeting temperatures of 35–36°C, may represent a

reasonable compromise. ICP is reduced, although perhaps not as effectively as with more profound cooling techniques, and ammonia production is less affected, but the deleterious consequences of profound hypothermia are minimized. Allowing a passive decline of core temperature using an extracorporeal circuit is a simple way of inducing and maintaining mild hypothermia.

Hepatectomy

Refractory increases in ICP have been treated by total hepatectomy as a bridge to OLT. Marked reductions in ICP following removal of the toxic liver supports the postulate that pro-inflammatory cytokines are involved in the pathogenesis of cerebral edema and/or hyperemia in ALF. The procedure may be lifesaving for extreme cases but requires the availability of a transplantable organ within a very short time.

Intra-operative Considerations

Patients are at risk of brain herniation intra-operatively as well as during the peri-operative phases. In an analysis of 116 FHF patients, 13 (11.2%) developed brain death during or shortly after OLT [47], and the exact timing of the neurological insult is unclear. Detry et al. [14] observed that of 12 patients transplanted for FHF, the four patients with normal preoperative ICPs maintained normal pressures intra-operatively. Of the 8 patients with preoperative episodes of increased ICP, 4 patients developed 6 episodes of ICH during surgery. The dissection and reperfusion phases were most associated with cerebral insufficiency secondary to surges in ICP and consequent reduction in CPP. The anhepatic phase was associated with a decrease of the ICP. At the end of the anhepatic phase, the ICP was lower than the preoperative ICP in all patients and below 15 mmHg in all but one patient.

This observation is in concordance with a small study of six cases from King's College Hospital which demonstrated higher ICP levels pre-anhepatic and during graft reperfusion and similarly reduced ICP during the anhepatic phase [48]. Lidofsky et al. [49] noted that thiopental treatment was most frequently required during liver dissection, but ICP invariably normalised within 15 min of caval cross-clamping. This group also noted transient rises in ICP at the time of graft reperfusion.

The use of veno-venous bypass during OLT has been advocated to maintain cerebral perfusion. It has been proposed that the lack of adequate collateral venous circulation leads to hemodynamic instability and volume replacement that can exacerbate cerebral edema is subsequently required to maintain target hemodynamic parameters. Furthermore, the release of CO_2 during reperfusion can exacerbate cerebral vasodilatation and raise ICP. However, there is no consensus regarding the efficacy of VVB to ameliorate these effects.

The Neurology of Chronic Liver Disease

Brain edema and ICH are not commonly recognised features of terminal chronic liver failure, although occasional cases have been reported in the literature. Clinical symptoms and cerebral edema are less severe with chronic liver disease compared with ALF since encephalopathy in chronic liver disease progresses more slowly and adaptive responses can develop. The distribution of edema differs in chronic liver disease; excess brain water is mostly intracellular with ALF, whereas with chronic liver disease, it is mostly extracellular. This may result from the loss of organic solute and water from cells with restoration of volume and minimal effect on function.

The Patient with Severe Hyponatremia and CNS Dysfunction

Hyponatremia is common, both in patients with cirrhosis and ALF, and morbidity and mortality are increased in patients with lower serum sodium levels listed for transplant and during the peri-operative phase. Exacerbations of

encephalopathy are increased in frequency, duration and severity in hyponatremic cirrhotics [50]. Hyponatremia in combination with hepatic encephalopathy leads to a clinical picture of confusional syndrome and is similar to other metabolic encephalopathies. The severity of neurological symptoms correlates with the speed and severity of the decrease of serum sodium levels. A gradual drop, even to very low levels, may be tolerated well if it occurs over several days or weeks. Serum sodium levels of <120 mmol/L can significantly lower the seizure threshold, and serum sodium concentration is an independent predictor of EEG abnormalities in patients with HE. Lethargy, seizures and coma may be seen with variable frequency with a slower decrease of serum sodium levels to <110 mmol/L. The osmotic disequilibrium resulting from hyponatremia causes astrocyte swelling. The generation of the action potential and synaptic transmission are also dependent on ionic gradients and the movement of sodium down its electrochemical gradient through Na-specific voltage-gated ion channels.

The resolution of hyponatremia in cirrhotics leads to improvement in related neurological symptoms. To avoid hyponatremia, causes such as diuretic use, infusion of hypotonic fluids and gastrointestinal losses due to diarrhea or medication (lactulose, enema) should be considered. It is important to distinguish between hypovolemic and hypervolemic hyponatremia, as this will determine whether saline infusion or fluid restriction is the appropriate treatment. In ALF, osmotherapy with hypertonic saline infusion increases serum sodium to levels of 145–155 mmol/L and is associated with a reduction in the incidence and severity of episodes of ICH. In chronic cirrhotics with hepatic encephalopathy and hyponatremia, saline infusions may be administered if signs of hypovolemia or recent diuretic use are evident. Under these circumstances, paracentesis may be the preferred treatment modality for resistant ascites [51]. Sodium levels should be normalised prior to liver transplantation in hyponatremic patients to avoid rapid sodium shifts during surgery. Occasionally pre- and intra-operative ultrafiltration therapy is indicated to prevent postoperative neurological complications.

The rapidity of correction of hyponatremia is based on the speed of onset. If the speed is not known, slow rise in serum sodium concentration at a rate of <0.5 mmol/L/h is advisable. Rapid rises in serum sodium concentration can precipitate osmotic myelinolysis that can cause profound and often permanent neurological deficits. Severe damage of the myelin sheath of nerve cells in the corticobulbar and corticospinal tracts of the brainstem may cause quadriparesis, dysphagia, dysarthria, diplopia, loss of consciousness and locked-in syndrome.

The MRI in Fig. 23.4 is of a patient who went to OLT with serum sodium 128 mmol/L. Subsequent to OLT, the serum sodium rose to 135 mmol/L. The patient extubated successfully but underwent re-laparotomy the following day for ongoing blood loss with consequent infusion of colloid, packed cells and blood products. The day following re-laparotomy, the serum sodium had risen to 142 mmol/L, and there was an associated deterioration in respiratory function and GCS (Fig. 23.4).

Neurological Outcomes After Liver Transplantation

Neurological complications are common following liver transplantation (13–43%) [52], in part due to co-morbidities present at the time of surgery (HE, hepatitis C, alcohol, arterial hypertension, etc.). Other factors to consider include effects of calcineurin inhibitors, other drug effects, cerebrovascular accidents (CVA), anxiety, metabolic disorders, CNS infection, rapid shifts of plasma sodium levels, systemic inflammation and infection and persisting portosystemic shunts.

In those with marked encephalopathy prior to transplantation, neurological outcome is in general favourable, with eventual improvement of cognitive function in the majority of patients; however, resolution of neurological symptoms may be slow in some and persist in a minority. The most tangible radiological evidence for the

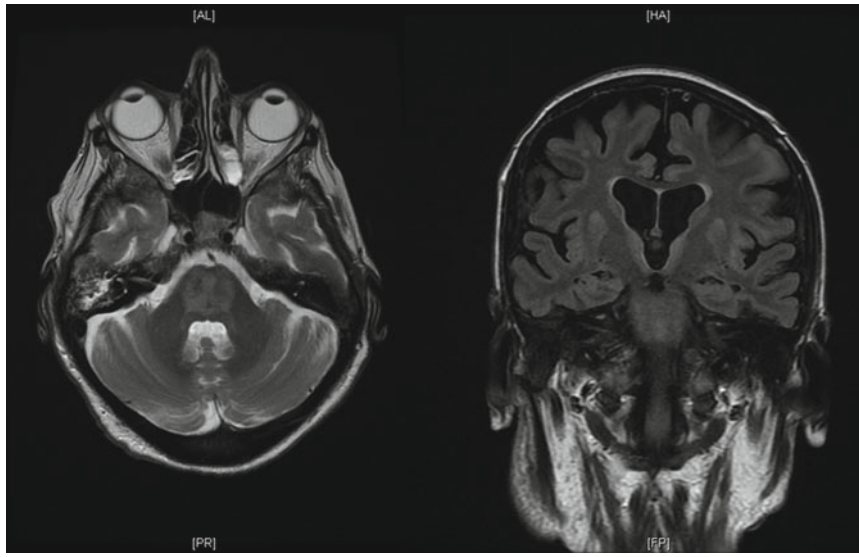

Fig. 23.4 There is a large central area of high T2 signal abnormality in the pons consistent with osmotic pontine myelinolysis

resolution of cerebral edema comes from magnetic resonance imaging that demonstrates an increase in the volume of the ventricles in association with an improvement in neurological and cognitive function after liver transplantation (and is therefore unlikely due to an absolute loss of brain parenchyma). These subtle radiological changes may take months to become evident.

A number of studies have documented an improvement in cognitive function following OLT and an improvement in quality of life index markers. This is not always the case and for a significant number of patients, cognitive deficits persist long into the postoperative period. The etiology for this is likely to be multifactorial but include the presence of hepatic encephalopathy pre-transplant, subsequent neuronal loss, brain atrophy (commonly seen in cirrhosis), presence of cerebral small vessel disease pre-transplant, peri-operative vascular complications, immunosuppression (calcineurin inhibitors) and the persistence of portosystemic collaterals that take time to resolve. Persisting cognitive dysfunction is associated with co-morbidities such as diabetes mellitus, arterial hypertension, hyperlipidemia and increasing age (all associated with other causes of neuronal loss such as small vessel disease).

Other Hepatic Diseases with Cerebral Manifestation: Wilson's Disease and Acquired Hepatocerebral Degeneration

Wilson's disease is an autosomal recessive disorder of chromosome 13 that results in defective biliary copper excretion and copper accumulation in the tissues. It was first described by Dr. Samuel Alexander Kinnier Wilson, a professor of neurology at King's College Hospital. Most of the symptoms are attributable to the deposition of copper through the body. Patients present early with liver disease or late with the neurological syndrome which consists of neuropsychiatric symptoms and movement disorders.

Acquired (non-Wilsonian) hepatocerebral degeneration (AHD) is a chronic progressive neurological syndrome in patients with portosystemic shunts characterised by dementia, dysarthria, ataxia of gait, intention tremor and choreoathetosis (i.e. neuropsychiatric and extrapyramidal symptomatology). AHD and Wilson's disease are often mistaken—the diagnosis depends on age of onset (Wilson's usually presents <30 years), serum caeruloplasmin concentration and the presence of Kayser-Fleischer rings. The disease is associated with multiple metabolic insults and has

been variously linked to the failure of clearance of toxins such as ammonia and manganese. Microscopically, there is patchy cortical necrosis, diffuse proliferation of Alzheimer type II glial cells and neuronal loss.

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