Neurochemistry International 60 (2012) 736–742

Contents lists available at SciVerse ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Review

Neurological complications of acute liver failure: Pathophysiological basis of current management and emerging therapies

Liliane Mpabanzi [a,b,c], Rajiv Jalan [c,*]

[a] Department of Surgery, Maastricht University Medical Centre, and NUTRIM School of Nutrition, Toxicology and Metabolism, Maastricht University, P.O. Box 5800, Maastricht, The Netherlands
[b] Hepato-Pancreato-Biliary and Liver Transplant Surgery, Royal Free Hospital, University College London, Pond Street, London NW3 2QG, United Kingdom
[c] Liver Failure Group, UCL Hepatology, Royal Free Hospital, University College London, Pond Street, London NW3 2QG, United Kingdom

ARTICLE INFO

Article history:
Available online 13 November 2011

Keywords:
Intracranial pressure
Cerebral blood flow
Ammonia
Hepatic encephalopathy
Acute liver failure

ABSTRACT

One of the major causes of mortality in patients with acute liver failure (ALF) is the development of hepatic encephalopathy (HE) which is associated with increased intracranial pressure (ICP). High ammonia levels, increased cerebral blood flow and increased inflammatory response have been identified as major contributors to the development of HE and the related brain swelling. The general principles of the management of patients with ALF are straightforward. They include identifying the insult causing hepatic injury, providing organ systems support to optimize the patient's physical condition, anticipation and prevention of development of complications. Increasing insights into the pathophysiological mechanisms of ALF are contributing to better therapies. For instance, the evident role of cerebral hyperemia in the pathogenesis of increased ICP has led to a re-evaluation of established therapies such as hyperventilation, N-acetylcysteine, thiopentone sodium and propofol. The role of systemic inflammatory response in the pathogenesis of increased ICP has also gained importance supporting the concept that antibiotics given prophylactically reduce the risk of developing sepsis during the course of illness. Moderate hypothermia has also been established as a therapy able to reduce ICP in patients with uncontrolled intracranial hypertension and to prevent increases in ICP during orthopic liver transplantation. Ornithine phenylacetate, a new drug in the treatment of liver failure, and liver replacement therapies are still being investigated both experimentally and clinically. Despite many advances in the understanding of the pathophysiological basis and the management of intracranial hypertension in ALF, more clinical trials should be conducted to determine the best therapeutic management for this difficult clinical event.

1. Introduction

Acute liver failure (ALF) is a rare but severe clinical event often resulting in death. Though mortality rates have decreased in the last 20 years from over 80% to 40–50%, depending on the etiology and the units in which the patient is treated, ALF is still a highly challenging clinical status (Bernal et al., 2010). The causes of ALF are multiple ranging from toxic, viral, vascular to metabolic injury to the liver (Bernal et al., 2010). Its clinical course is characterized by a progressive dysfunction of multiple organ systems. The features of ALF may initially be non-specific with symptoms such as abdominal pain, fatigue and fever before progressing to hepatic encephalopathy (HE) (Shakil et al., 2000). The development of HE in patients with acute liver injury is defining in their prognosis (Ascher et al., 1993; Hoofnagle et al., 1995; Makin et al., 1995; O'Grady et al., 1989). HE, in ALF, is associated with a raised intracranial pressure (ICP) which is a major cause of mortality due to subsequent brain herniation (Clemmesen et al., 1999). The pathophysiology of this elevated ICP is still not completely understood but is believed to be multifactorial (Blei and Larsen, 1999; Larsen and Wendon, 2002). A series of consecutive hits, namely sudden elevation of ammonia levels, increased systemic inflammatory response and changes in cerebral blood flow (CBF) are considered key events in the development of HE, the associated brain edema and increased ICP (Blei, 2004; Jalan, 2003; Butterworth, 2002; Bernal et al., 2007; Rolando et al., 2000). The circulatory disturbances in ALF progressively deteriorate and are marked by splanchnic vasodilatation resulting in increased cardiac output, reduced systemic vascular resistance and hypotension (Bihari et al., 1985, 1986). In addition to cerebral and vascular complications, patients with ALF develop severe coagulopathy and have an increased susceptibility to infections. In the last 20 years, emergency orthotopic liver transplantation (OLT) has emerged as the 'only' therapeutic option

Abbreviations: ALF, acute liver failure; ICP, intracranial pressure; CBF, cerebral blood flow; OLT, orthotopic liver transplantation.

* Corresponding author. Tel.: +44 20 74 33 27 92; fax: +44 20 74 33 28 71.
E-mail address: r.jalan@ucl.ac.uk (R. Jalan).

0197-0186/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuint.2011.10.014

of proven benefit for patients with advanced ALF (Bernal and Wendon, 2004). All other therapies aim at optimizing the prognosis by stabilizing the condition until liver regeneration or graft availability.

The focus of the present review will be the neurological complications of ALF, the current and emerging therapies of the neurological complications of ALF.

2. General management of ALF

It is imperative to begin the management of patients with acute liver injury as soon as the patients present. Early referral to an experienced liver unit is essential as it affects the outcome of the patient (Ananthakrishnan et al., 2008; Bernuau, 2004). Moreover, time is of the essence in this patient population as ALF is characterized by a rapid deterioration. Therefore close clinical monitoring and correction of glucose levels, to prevent cerebral and systemic effects of hypoglycemia, are the important first steps (Jalan, 2005; Larsen and Bjerring, 2011). Additionally, metabolic acidosis and arterial hypotension need to be corrected using aggressive volume expansion with colloids, crystalloids and fresh frozen plasma in case of ooze bleeding (Larsen and Bjerring, 2011). Hyperthermia should be prevented as it worsens intracranial hypertension (Munoz et al., 1993).

2.1. N-Acetylcysteine (NAC)

As an early antidote after a paracetamol overdose, NAC is extremely effective at replenishing hepatic glutathione stores and preventing severe hepatotoxicity and liver failure (Heard, 2008). However, evidence for the use of NAC in established ALF is weaker. Initial studies suggested that NAC improved oxygen delivery and consumption in ALF (Harrison et al., 1990; Keays et al., 1991), but this position has later been challenged (Harrison et al., 1991). Moreover, prolonged NAC therapy was recently shown to impair murine liver regeneration and worsen outcome following paracetamol poisoning (Yang et al., 2009). However in recently published trials, the use of NAC has again been encouraged. In a study with 47 patients, of which the majority suffered from HE grade 3–4, continuous infusion of NAC for 72 h led to improvement in survival (Mumtaz et al., 2009). The largest clinical trial, included 173 patients and showed that intravenous NAC improved transplant-free survival in patients with early stage of ALF but that patients with advanced coma grades do not benefit from NAC (Lee et al., 2009). According to these data, the use of NAC in ALF is strongly recommended.

3. Neurological management of ALF

The most important neurological feature of ALF is the development of HE. Evidence of HE should lead to management in an intensive care environment to ensure appropriate monitoring and treatment awaiting decisions regarding OLT. The pathogenesis of HE in ALF is only partly understood but clinical and experimental data suggests an important role of circulating neurotoxins, especially ammonia (Bjerring et al., 2009).

3.1. HE, increased ICP and brain water

3.1.1. HE in ALF

Beyond the aforementioned initial steps, it is important to record the mental status and close attention should be paid to the pupillary size and reaction to light. Once the patient progresses to grade 3 HE (using the West Haven criteria) (Conn et al., 1977) intubation, mechanical ventilation and sedation should be applied. Fever, psychomotor agitation and arterial hypertension often precede severe intracranial hypertension (Jalan, 2003, 2005).

3.1.2. Monitoring ICP

The symptoms and physical signs of increased ICP and brain edema such as headache, vomiting, confusion or hyperreflexia are not sensitive enough to detect changes in ICP (Rabinstein, 2010). Brain imaging may be more reliable but is not recommended as moving patients with ALF and severe encephalopathy risks exacerbating elevated ICP. The use of invasive continuous ICP monitoring is preferred to non-invasive techniques by many liver units mainly because of a better sensitivity (Munoz et al., 1991; Keays et al., 1993). However, clear cut criteria for the placement of an invasive ICP monitoring device remain a matter of debate (Cordoba and Blei, 1995; Kanazi et al., 1993). ALF patients have a severe coagulopathy which results in increased risk of bleeding. Consequently, the risks of insertion have to be acceptable and alternative methods to monitor ICP need be considered. Generally, the risk of bleeding is acceptable if coagulopathy is corrected prior to the procedure. It has been shown in a cohort of 332 ALF patients with grade 3–4 HE that rates of intracranial hemorrhages can reach 10% but only half of those lead to neurological decline (Vaquero et al., 2005).

3.1.3. Ammonia reducing therapies

Since ammonia is considered the most important neurotoxin in the pathophysiology of HE, it is only logical that many therapies are directed at lowering its levels. In chronic liver failure, many ammonia lowering drugs such as lactulose, branched amino acids or non-absorbable antibiotics have proven to be of added value in the prognosis of patients (Butterworth, 2002). They help modulate the production and absorption of nitrogenous moieties that contribute to HE. However, there are currently no randomized controlled clinical trials using the aforementioned ammonia reducing strategies in ALF patients. Their use can therefore not be recommended. Moreover, a retrospective study with 117 ALF patients compared 70 ALF patients who received lactulose to 47 patients who did not receive lactulose and it was shown that there was no difference between the groups in the severity of HE (Alba et al., 2002).

3.1.4. L-Ornithine L-aspartate (LOLA)

LOLA is a mixture of two amino acids. LOLA has been shown in controlled clinical trials to reduce blood ammonia concentrations by increasing ammonia detoxification in the muscle and reducing the severity of HE in cirrhosis (Kircheis et al., 1997). Despite the above mentioned promising results in cirrhosis and in experimental models of ALF (Ytrebo et al., 2009; Rose et al., 1999), a recently published randomized controlled trial showed no effect of LOLA in ALF patients regarding ammonia levels and survival (Acharya et al., 2009). However, it has been argued that the dose used in the trial was sub-optimal leading to a lack of change in ammonia values. Systemic ammonia concentrations can only be reduced either by decreasing its production or by enhancing its removal from the body. LOLA provides glutamate to muscle, therefore increasing the substrate, which should detoxify ammonia into glutamine. However, the glutamine produced can be converted back into glutamate and ammonia by the enzyme glutaminase present in many organs. This effect of LOLA has been shown in patients with liver failure who developed a rebound hyperammonemia following treatment with LOLA (Jalan and Lee, 2009). Routine use of LOLA in ALF patients is therefore not recommended.

3.1.5. Ornithine phenylacetate (OP)

OP is a novel ammonia lowering therapy that is currently being investigated. The hypothesis behind the working mechanisms of