Brain edema in acute liver failure

R F BUTTERWORTH

Neuroscience Research Unit, Hôpital Saint-Luc du CHUM, University of Montreal, Montreal, Quebec, Canada

Brain edema and consequent increase in intracranial pressure is a major complication of acute liver failure (ALF) and is a major cause of death in this condition. Rapid accumulation of ammonia in brain has been implicated in the pathogenesis of brain edema in ALF. Increased brain ammonia may cause brain swelling via the osmotic effects of an increase in astrocytic glutamine concentration or by inhibition of glutamate removal from brain extracellular space. Acute liver failure results in altered expression of several genes in the brain, some of which code for proteins involved in central nervous system function such as the glutamate transporter GLT-1, the astrocytic structural protein, glial fibrillary acidic protein, and the water channel protein, aquaporin IV. Loss of expression of GLT-1 results in increased extracellular brain glutamate. Therapeutic measures currently used to prevent and treat brain edema in acute liver failure include mannitol; strategies aimed at lowering of gut ammonia production are generally ineffective. Studies in experimental animals suggest that mild hypothermia or the use of L-ornithine-L-aspartate may be useful in the prevention of brain edema in these patients.

Keywords: Astrocytes, hypothermia, L-ornithine-L-aspartate

Acute (or fulminant) liver failure (ALF) may result from viral infections or from ingestion of toxins such as acetaminophen. It is characterized by a rapidly progressive deterioration in hepatic function and, neurologically, by impaired cognitive and motor skills progressing to stupor and coma within days. The major cause of death in ALF is brain herniation, which occurs as a consequence of raised intracranial pressure due to cerebral edema.

Cerebral edema associated with ALF is cytotoxic in nature and the cellular element undergoing swelling is the astrocyte. There is little convincing evidence to suggest the presence of vasogenic brain edema associated with breakdown of the blood-brain barrier, in ALF.

Neurochemistry of acute liver failure

Role of ammonia

While the precise mechanisms responsible for cerebral edema in ALF have not been completely elucidated, there is a re-emergence of interest in ammonia. In experimental animal models of ALF, concentration of ammonia in blood, cerebrospinal fluid (CSF) and brain is significantly increased and, at coma/edema stages of encephalopathy, brain ammonia concentrations are in the 1-5 mM range. Further support to ammonia as the cause of cerebral edema in ALF are reports of significant cerebral edema in other hyperammonemic conditions such as the urea cycle enzymopathies and Rye's syndrome, in which arterial ammonia concentration may reach millimolar levels. More recently, Clemens et al. studied arterial ammonia concentrations in patients with ALF awaiting liver transplantation; patients who subsequently died of brain herniation had significantly higher arterial ammonia concentrations compared to those who survived. Brain ammonia flux in ALF may be up to 45-fold higher than that in normal subjects (Table).

Brain energy failure

For several decades it was assumed that the central nervous system (CNS) manifestations of ALF were a consequence of brain energy failure. However, precise biochemical and magnetic resonance spectroscopic techniques have failed to find any significant primary alterations of brain energy metabolism. Consequently, attention has been focused on alterations in neurotransmitter function, rather than brain energy failure.

Pathophysiology of brain edema in ALF

Glutamine hypothesis

It has been proposed that glutamine accumulation, resulting from ammonia detoxification by glutamine synthetase, is the primary cause of astrocytic swelling (cytotoxic brain edema) in ALF.

Brain glutamine production is increased several hundred-fold in ALF; this alteration is limited to astrocytes, the primary site of edema in this disorder. Partial protection against brain edema provided by pre-treat-

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<th>Table: Brain ammonia flux, brain glutamine production and muscle ammonia production in liver failure</th>
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<td>Normal</td>
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<td>Brain ammonia flux (nmol/g/min)</td>
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<td>Brain glutamine production (nmol/100 g/min)</td>
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<td>Muscle glutamine production (nmol/100 g/min)</td>
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*13.5-fold increase; **45-fold increase, p<0.01
ment with methionine sulfoximine, an inhibitor of glutamine synthetase, in some animal models of ALF further supports the ‘glutamine hypothesis’.7

Alterations of gene expression in brain in ALF

As liver fails, the brain responds rapidly by altering the expression of genes that code for various proteins whose role is critical to CNS function, including the maintenance of cell volume integrity and neurotransmission. Using the technique of differential display-RT PCR, and brain extracts from animals with experimental ALF resulting from (surgical) hepatic devascularization, it was recently shown that the expression of several genes was altered (Fig). Since astrocytes are the primary site of edema and are the cells responsible for ammonia removal, it is not surprising that alterations in gene expression affect proteins involved in astrocytic (rather than neuronal) function, viz., the forebrain astrocytic glutamate transporter GLT-1,8 the astrocytic structural protein known as glial fibrillary acidic protein (GFAP),9 and aquaporin IV,10 a protein implicated in astrocytic water channels.

Astrocytic glutamate transporter

ALF in hepatic devascularization animal model results in loss of expression of GLT-18 and concomitant rise in extracellular concentrations of glutamate in the brain.11 Increased extracellular glutamate may be involved in the pathogenesis of hyperexcitability and seizures, which are sometimes encountered in ALF. In addition, increased extracellular glutamate could be implicated in the pathogenesis of brain edema in ALF in view of the reports that exposure of astrocytes to glutamate results in significant cell swelling.

GFAP

GFAP is a structural astrocytic protein often used as a marker of astrocytic integrity in immunohistochemical studies. Experimental ALF results in a reduction in expression of GFAP, which correlates with the degree of astrocytic swelling and severity of brain edema.9

Prevention and treatment of brain edema in ALF

Many treatment strategies like lactulose, neomycin and branched-chain amino acids have been used in patients with ALF and brain edema, though none of these have proved to be successful in controlled trials. Mannitol may be effective but requires adequate renal function. Treatment of end-stage ALF continues to rely heavily on liver transplantation. Prevention of brain edema has therefore become a challenge particularly in those patients who are awaiting liver transplant. Two new experimental therapeutic approaches, i.e., mild hypothermia and L-ornithine-L-aspartate,12,13 have been proposed based upon studies in animal models of ALF.

Mild hypothermia (of the order of 35°C) has proven to be effective in the attenuation of brain damage in cerebrovascular disorders (stroke) and neurotrauma. In rats with ALF resulting from hepatic devascularization, mild hypothermia has been shown to consistently increase the time to onset of severe encephalopathy and prevent brain edema.12,13 Prevention of brain edema was accompanied by a decrease in CSF (but not blood) concentration of ammonia, suggesting that one of the beneficial actions of mild hypothermia was a reduction in blood-to-brain transfer of ammonia.13 This effect was accompanied by a prevention in the rise of extracellular brain concentrations of glutamate in hypothermic animals with ALF, underscoring the important causative role of failed astrocytic glutamate transport in CNS manifestations of ALF.

Following these findings in experimental animals, mild hypothermia was tried in 7 patients with ALF awaiting liver transplantation.14 Hypothermia successfully lowered intracranial hypertension in these patients; this was accompanied by decreased cerebral ammonia utilization rates. More controlled clinical trials on the use of mild hypothermia in the prevention of brain edema in ALF are currently ongoing.

L-ornithine-L-aspartate administered intravenously to rats with ALF resulting from hepatic devascularization prevents the progression of brain edema and results in a significant lowering of circulating ammonia in these animals.15 In contrast to mild hypothermia, the effect of L-ornithine-L-aspartate on plasma ammonia appears to be mediated at a peripheral level, by removal of ammonia in the muscle (Table).5 Expression and activity of glutamine synthetase in muscle of rats with ALF show a significant post-translational increase fol-

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Fig: Gene expression in brain in acute liver failure. 1: control; 2: acute liver failure, precoma; 2: acute liver failure, coma
lowing treatment with L-ornithine-L-aspartate, consistent with an ammonia-lowering effect of this drug. To date, studies using L-ornithine-L-aspartate for the treatment of the CNS manifestations of ALF in humans have not been performed.

References